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The rational use of antipsychotics outside severe mental illness

Literature review: full report

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1 Abbreviations

AD: Alzheimer’s disease

AHRQ: Agency for Healthcare Research and Quality

AP: antipsychotic(s)

BEHAVE-AD: Behavioral Pathology in Alzheimer's Disease Rating Scale;

BMI: body mass index

BPRS: Brief Psychiatric Rating Scale

BPSD: behavioral and psychological symptoms of dementia

BZ: benzodiazepine

BZRA: benzodiazepine receptor agonist

CBT-I: cognitive behavioral therapy for insomnia

CI: confidence interval

CGI: Clinical Global Impression Scale

CVA: cerebrovascular accident

CMAI: Cohen-Mansfield Agitation Inventory

EPS: extrapyramidal symptoms

FAST: Functional Assessment Staging scale

FGA: first generation antipsychotic(s)

GDG: guideline development group

HRQoL: health-related quality of life

ICU: intensive care unit

ISRS : inhibiteur sélectif de la recapture de la sérotonine

ITT: intention to treat analysis

LTC: long-term care

MA: meta-analysis

MD: mean difference

MMSE: Mini Mental Status Exam

n: number of patients

N: number of studies

NHS: National Health Service

NMS (SMN): neuroleptic malignant syndrome (syndrome malin des neuroleptiques)

NNH: number needed to harm

NNT: number needed to treat

NPI: neuropsychiatric inventory

NPI-NH: Neuropsychiatric Inventory, Nursing Home

NPS: neuropsychiatric symptoms

NR: not reported

NS: not statistically significant

PSS: personal social service

RCT: randomized controlled trial

ROB: Risk Of Bias

SGA: second generation antipsychotic(s)

SMD: standard mean difference

SPC: summary of product characteristics

SS: statistically significant

2 Methodology

2.1 Introduction

This systematic literature review was conducted in preparation of the consensus conference "**The rational use of antipsychotics outside severe mental illness**", which will take place on the 25th of November 2021.

2.2 Questions to the jury

The questions to the jury, as they were phrased by the organising committee of the RIZIV/INAMI are:

1. **Algemene inleiding over de antipsychotica:**
    1) Wat zijn de farmacologische eigenschappen van typische (eerste generatie) en atypische (tweede generatie) antipsychotica?
    2) Zijn er relevante onderlinge verschillen binnen de atypische antipsychotica?
    3) Wat zijn de belangrijkste groepen van ongewenste effecten met klinische relevantie?
1. **Introduction générale aux antipsychotiques :**
    1) Quelles sont les propriétés pharmacologiques des antipsychotiques typiques (première génération) et atypiques (deuxième génération) ?
    2) Y a-t-il des différences pertinentes entre les antipsychotiques atypiques ?
    3) Quels sont les principaux groupes d'effets indésirables ayant une pertinence clinique ?

2. **Gedrags- en psychologische symptomen ten gevolge van dementie (BPSD):**
    1) Doeltreffendheid :
        a. Wat is de plaats van de typische antipsychotica binnen de aanpak van BPSD?
        b. Wat is de plaats van de atypische antipsychotica binnen de aanpak van BPSD?
    2) Veiligheid:
        a. Wat zijn de ongewenste effecten van typische antipsychotica binnen de aanpak van BPSD?
        b. Wat zijn de ongewenste effecten van atypische antipsychotica binnen de aanpak van BPSD?
    3) Bestaan er specifieke aanbevelingen rond de deprescribing van antipsychotica binnen de aanpak van BPSD?
    4) Is er, wat de antipsychotica betreft, een voorkeursbehandeling (product, toedieningsweg) binnen de aanpak van BPSD?
2. **Symptômes psychologiques et comportementaux de la démence (SPCD) :**
    1) Efficacité :
        a. Quelle est la place des antipsychotiques typiques dans le traitement des SPCD ?
        b. Quelle est la place des antipsychotiques atypiques dans le traitement des SPCD ?
    2) Sécurité :
        a. Quels sont les effets indésirables des antipsychotiques typiques dans le traitement des SPCD ?
        b. Quels sont les effets indésirables des antipsychotiques atypiques dans le traitement des SPCD ?
    3) Y a-t-il des recommandations spécifiques sur la déprescription d'antipsychotiques dans le traitement des SPCD ?
    4) En ce qui concerne les antipsychotiques, y a-t-il un traitement préférentiel (produit, voie d'administration) dans le traitement des SPCD ?
3. **Delirium en agitatie:**

1) Doeltreffendheid :
    a. Wat is de plaats van typische antipsychotica binnen de aanpak van delirium?
    b. Wat is de plaats van atypische antipsychotica binnen de aanpak van delirium?
    c. Wat is de plaats van typische antipsychotica binnen de aanpak van agitatie?
    d. Wat is de plaats van atypische antipsychotica binnen de aanpak van agitatie?
2) Veiligheid:
    a. Wat zijn de ongewenste effecten van typische antipsychotica binnen de aanpak van delirium?
    b. Wat zijn de ongewenste effecten van atypische antipsychotica binnen de aanpak van delirium?
    c. Wat zijn de ongewenste effecten van typische antipsychotica binnen de aanpak van agitatie?
    d. Wat zijn de ongewenste effecten van atypische antipsychotica binnen de aanpak van agitatie?
3) Is er, wat de antipsychotica betreft, een voorkeursbehandeling (product, toedieningsweg)
    a. binnen de aanpak van delirium?
    b. binnen de aanpak van agitatie?

3. Délire et agitation :

1) Efficacité :
    a. Quelle est la place des antipsychotiques typiques dans le traitement du délire ?
    b. Quelle est la place des antipsychotiques atypiques dans le traitement du délire ?
    c. Quelle est la place des antipsychotiques typiques dans le traitement de l'agitation ?
    d. Quelle est la place des antipsychotiques atypiques dans le traitement de l'agitation ?
2) Sécurité :
    a. Quels sont les effets indésirables des antipsychotiques typiques dans le traitement du délire ?
    b. Quels sont les effets indésirables des antipsychotiques atypiques dans le traitement du délire ?
    c. Quels sont les effets indésirables des antipsychotiques typiques dans le traitement de l'agitation ?
    d. Quels sont les effets indésirables des antipsychotiques atypiques dans le traitement de l'agitation ?
3) En ce qui concerne les antipsychotiques, y a-t-il un traitement préférentiel (produit, voie d'administration)
    a. dans le traitement du délire ?
    b. dans le traitement de l'agitation ?

4. Insomnia:

1) Doeltreffendheid :
    a. Wat is de plaats van typische antipsychotica binnen de aanpak van insomnia?
    b. Wat is de plaats van atypische antipsychotica binnen de aanpak van insomnia?
    c. Aanbevelingen rond duur van behandeling voor insomnia?
    d. Aanbevelingen rond desprescribing in het kader van een behandeling van insomnia?
2) Veiligheid:
    a. Wat zijn de ongewenste effecten van typische antipsychotica binnen de aanpak van insomnia?
    b. Wat zijn de ongewenste effecten van atypische antipsychotica binnen de aanpak van insomnia?

3) Wat is de plaats van antipsychotica versus andere therapeutische klassen binnen de medicamenteuze aanpak van insomnia?
4) Is er, wat de antipsychotica betreft, een voorkeursbehandeling (product, toedieningsweg) voor de medicamenteuze aanpak van insomnia?

4. Insomnie :

1) Efficacité :
    a. Quelle est la place des antipsychotiques typiques dans le traitement de l'insomnie ?
    b. Quelle est la place des antipsychotiques atypiques dans le traitement de l'insomnie ?
    c. Recommandations sur la durée du traitement de l'insomnie ?
    d. Recommandations sur la déprescription dans le cadre du traitement de l'insomnie ?
2) Sécurité :
    a. Quels sont les effets indésirables des antipsychotiques typiques dans le traitement de l'insomnie ?
    b. Quels sont les effets indésirables des antipsychotiques atypiques dans le traitement de l'insomnie ?
3) Quelle est la place des antipsychotiques par rapport aux autres classes thérapeutiques dans le traitement médicamenteux de l'insomnie ?
4) En ce qui concerne les antipsychotiques, y a-t-il un traitement préférentiel (produit, voie d'administration) pour le traitement médicamenteux de l'insomnie ?

5. Veiligheid kinderen en jongeren:

1) Wat zijn de indicaties van antipsychotica bij kinderen en jongeren (tot 16 jaar)?
2) Bestaan er specifieke veiligheidsaspecten bij kinderen en jongeren (tot 16 jaar)?
3) Welke monitoring is er nodig bij kinderen en jongeren?

5. Sécurité des enfants et des jeunes:

1) Quelles sont les indications des antipsychotiques chez les enfants et les jeunes (jusqu'à 16 ans) ?
2) Y a-t-il des aspects spécifiques de sécurité chez les enfants et les jeunes (jusqu'à 16 ans) ?
3) Quel monitoring est nécessaire chez les enfants et les jeunes?

6. Monitoring:

1) Welke medische parameters moeten worden opgevolgd?
    a. Enkel klinisch of ook door middel van technische (labo) onderzoeken?
2) Hoe frequent moet dergelijke opvolging uitgevoerd worden?
3) Wat is de rol van de verschillende gezondheidszorgberoepen in de opvolging van dergelijke behandeling met antipsychotica?

6. Monitoring :

1) Quels sont les paramètres médicaux à surveiller ?
    a. Seulement cliniques ou aussi à l'aide d'examens techniques (en laboratoire) ?
2) Quelle devrait être la fréquence de ces monitorings ?
3) Quel est le rôle des différentes professions en soins de santé dans le suivi de ces traitements avec les antipsychotiques ?

7. Bestaat er een verschil in de aanpak van patiënten in de thuissituatie versus in een woonzorgcentrum?

1) Bij gedrags- en psychologische symptomen ten gevolge van dementie (BPSD)?
2) Bij delirium?
3) Bij agitatie?

4) Bij insomnia?

7. Y a-t-il une différence entre la prise en charge des patients à domicile et en maison de repos ?

1) En cas de symptômes psychologiques et comportementaux de la démence (SPCD)?
2) En cas de délire ?
3) En cas d'agitation ?
4) En cas d'insomnie ?

2.3 Research task of the literature group

The organising committee has specified the research task for the literature review as follows:

- To discuss **selected guidelines**.
  - See 2.3.1 for guideline inclusion criteria.
- To perform a literature review:
  - To search and report relevant **RCTs or systematic reviews/meta-analyses of RCTs** to provide an answer to certain research questions.
  - See 2.3.2 for information on study type inclusion criteria and 2.3.3 for search details.
- To search and report **observational studies** for selected safety endpoints.
  - See 2.3.2 for inclusion criteria for observational studies and 2.3.3 for search details.
  - To discuss information from **additional sources** for information on safety, contra-indications, specific subgroups, precautions and monitoring.
- See section "11 Additional safety information from other sources".

In the table below, we provide an overview of the research task of the literature group per jury question. We also indicate in what chapter the results can be found.

Question 1 – Introduction
• This question will be answered by an expert-speaker.
Question 2 - BPSD
• The literature group will discuss the selected **guidelines**. BPSD will be discussed in chapter 5.1 and deprescribing of antipsychotics in chapter 5.2. • The literature group will perform a literature search of **RCTs or systematic reviews/meta-analyses** of RCTs. The results of the literature search can be found in chapter 6.1 - 6.7 and details in appendix 11 to 17. Deprescribing can be found in chapter 6.8 and details in appendix 11.11. • The literature group will provide additional information from **observational studies** for the outcome diabetes (see 2.3.3.1.4). **Additional sources** (see 2.3.2) will also be consulted for safety outcomes. The results of additional sources can be found in chapter 10. • An expert speaker will provide comments and additional information.
Question 3 – Delirium and agitation
• The questions about agitation will be answered by an expert-speaker. The task of the literature group is limited to delirium. • The literature group will discuss the selected **guidelines**. This discussion can be found in chapter 5.3.

• The literature group will perform a literature search of **RCTs or systematic reviews/meta-analyses** of RCTs. The results of the literature search can be found in chapter 7 and details in appendix 18. • The literature group will provide additional information from **additional sources** (see 2.3.2) for safety outcomes. The results of additional sources can be found in chapter 10. • An expert speaker will provide comments and additional information.
Question 4 – Insomnia
• The literature group will discuss the selected **guidelines**. This discussion can be found in chapter 5.4. • The literature group will perform a literature search of **RCTs or systematic reviews/meta-analyses** of RCTs. The results of the literature search can be found in chapter 8 and details in appendix 19. • The literature group will provide additional information from **additional sources** (see 2.3.2) for safety outcomes. The results of additional sources can be found in chapter 10. • An expert speaker will provide comments and additional information.
Question 5 – Safety children
• The literature group will perform a literature search of **RCTs, systematic reviews/meta-analyses** of RCTs and **observational studies**. The results of the literature search can be found in chapter 9 and details in appendix 21. • **Additional sources** (see 2.3.2) will also be consulted. The results of additional sources can be found in chapter 10.6. • An expert speaker will provide comments and additional information.
Question 6 - Monitoring
• The literature group will discuss the selected **guidelines**. This discussion can be found in chapter 5.6. • An expert speaker will provide comments and additional information.
Question 7 – Home situation versus residential care
• The literature group will discuss the selected **guidelines**. This discussion can be found in chapter 5.7. • An expert speaker will provide comments and additional information.

2.3.1 Guidelines

Guidelines will be selected and agreed upon through discussion with the organising committee, based on relevance for the Belgian situation and certain quality criteria:

- Publication date: only guidelines from 2014 onwards are to be selected.
- Quality assessment: Only guidelines that report levels of evidence/recommendation are to be selected.
- Systematic review: the guideline needs to be based on a good systematic search and review of the literature.

In order to make an assessment on the rigour of development of the guidelines, guidelines will be scored according to Agree II score, for the domain “Rigour of development”. More information can be found on http://www.agreetrust.org/. [1]

This table gives an overview of the items assessed in this domain according to the Agree II score.[1]

No.	**Description of the item**
7	Systematic methods were used to search for evidence
8	The criteria for selecting the evidence are clearly described
9	The strengths and limitations of the body of evidence are clearly described
10	The methods for formulating the recommendations are clearly described
11	Health benefits, side effects, and risks have been considered in formulating the recommendations.
12	There is an explicit link between the recommendations and the supporting evidence.
13	The guideline has been externally reviewed by experts prior to its publication
14	A procedure for updating the guideline is provided

Table: Items assessed by the domain "Rigour of development" in Agree II score.

Domain scores are calculated by summing up all the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain. The domain score "Rigour of development" can be used to assess the process used to gather and synthesize the evidence, the methods to formulate the recommendations, and to update them, though be careful with the interpretation because this scoring is also subjective and the resulting scores can thus be disputable.

In the chapter about the guidelines, the Domain scores as assessed by the literature group, are given for each guideline.

The literature group will also report whether the guideline was developed together with other stakeholders (other healthcare professionals: pharmacists, nurses,… or patient representatives) and whether these guidelines are also targeting these groups.

Similarities and discrepancies between guidelines are to be reported.

2.3.2 Study types

We will look at meta-analyses, systematic reviews, RCTs and observational (cohort) studies.

To be included in our review, the selected studies need to meet certain criteria.

Meta-analyses and systematic reviews

- Research question matches research question for this literature review
- Systematic search in multiple databases
- Systematic reporting of results
- Inclusion of randomised controlled trials (or observational studies for certain research questions)
- Reporting of clinically relevant outcomes (that match our selected outcomes)
- Only direct comparisons (no network meta-analyses)

If some of the included studies in a meta-analysis do not match all the inclusion criteria for our Consensus Conference literature review (for example: it may include some studies with a small sample size, or studies with drugs that are not on the Belgian market), this meta-analysis may be included in our review if judged to be sufficiently relevant. In this case, the discrepancies with our inclusion criteria will be discussed clearly.

RCT's

- Research question matches research question for this literature review
- Blinding: unblinded (open-label) studies will not be included
- Minimum number of participants: 40 per study-arm. For studies with multiple treatment arms, we will look at the number of participants in comparisons relevant to our search.
- For studies evaluating deprescribing of antipsychotics, we did not exclude studies with sample sizes smaller than 40 patients.
- Phase III trials (no phase II trials)
- Post hoc (subgroup) analyses are excluded.

Observational (cohort) studies

- Observational studies will only be searched for the outcome diabetes in patients with BPSD and for harms in children and youth.
- Prospective or retrospective **cohort** studies with a control arm
- Minimum number of participants: 100

Other sources for safety, contra-indications, specific subgroups, precautions and monitoring

- Belgisch Centrum voor Farmacotherapeutische Informatie (BCFI) / Centre Belge d'Information Pharmacothérapeutique (CBIP)
  - *Gecommentarieerd geneesmiddelenrepertorium(1)/ Répertoire Commenté des Médicaments*
  - *Folia Pharmacotherapeutica*
- Martindale: The complete drug reference, 39th edition(2)

Some publications will be excluded for practical reasons:

- Publications unavailable in Belgian libraries
- Publications in languages other than Dutch, French, German and English
- Unpublished studies

2.3.3 Specific search criteria

2.3.3.1 Antipsychotics and BPSD

2.3.3.1.1 Populations

The following populations are to be discussed:

- Patients with BPSD

Exclusions:

- Patients with schizophrenia or bipolar disorder
- Patients with Parkinson's disease

2.3.3.1.2 Interventions

The following medications, available in Belgium, are to be reported from RCTs (or systematic reviews/meta-analyses of RCTs):

FGA	haloperidol
SGA	aripiprazole
	asenapine
	clozapine
	olanzapine
	paliperidone
	quetiapine
	risperidone
	sertindole
	cariprazine

Excluded from the literature review are

- Pharmaceutical formulations that are not available on the Belgian market.

2.3.3.1.3 Comparisons

The following comparisons will be studied:

- SGA vs placebo
- SGA vs haloperidol
- SGA vs SGA

For withdrawal of antipsychotics the following comparison will be studied:

- Withdrawal vs continuation of antipsychotics

2.3.3.1.4 Endpoints

The following endpoints are to be reported from RCTs or systematic reviews/meta-analyses of RCTs:

Efficacy
Response Quality of life Success of withdrawal from antipsychotics
Safety

Adverse events with a specific focus on - Cerebrovascular accidents - Mortality - Extrapyramidal symptoms - Falls - Endocrine adverse events (diabetes, hyperprolactinemia) - Urinary tract infections

The following safety endpoints are to be reported from systematic reviews of observational studies and individual cohort studies:

- Diabetes

2.3.3.2 Antipsychotics and treatment of delirium

2.3.3.2.1 Populations

The following populations are to be discussed:

- adults with delirium

Exclusions:

- Prevention of delirium
- Critically ill patients: e.g. ICU patients, mechanically ventilated patients
- Patients in postoperative care
- Patients with Parkinson's disease
- Patients with schizophrenia, bipolar disorder, agitation or aggression
- Alcohol or substance-related delirium

2.3.3.2.2 Interventions

The following medications, available in Belgium, are to be reported from RCTs (or systematic reviews/meta-analyses of RCTs):

FGA	haloperidol
SGA	aripiprazol
	asenapine
	clozapine
	olanzapine
	paliperidon
	quetiapine
	risperidon
	sertindol
	cariprazine

Exclusions:

- Pharmaceutical formulations that are not available on the Belgian market.

2.3.3.2.3 Comparisons

The following comparisons will be studied:

- Antipsychotics vs nonantipsychotics/placebo
- SGA vs FGA
- SGA vs SGA

2.3.3.2.4 Endpoints

The following endpoints are to be reported from RCTs or systematic reviews/meta-analyses of RCTs:

Efficacy
Treatment response Hospital length of stay Quality of life Use of physical restraints
Safety
Clinically important adverse events Sedation Extrapyramidal symptoms Mortality

2.3.3.3 Antipsychotics and insomnia

2.3.3.3.1 Populations

The following populations are to be discussed:

- Adults with insomnia

Exclusions:

- Patients with psychiatric comorbidity
- Patients with schizophrenia or bipolar disorder
- Patients with substance abuse
- Patients with post-traumatic stress disorder

2.3.3.3.2 Interventions

The following medications, available in Belgium, are to be reported from RCTs (or systematic reviews/meta-analyses of RCTs):

FGA	Haloperidol
SGA	Quetiapine
	Olanzapine
	Risperidone
	Cariprazine

Excluded from the literature review are

- Pharmaceutical formulations that are not available on the Belgian market.

2.3.3.3.3 Comparisons

The following comparisons will be studied:

- Haloperidol vs placebo/active comparator
- Quetiapine vs placebo/active comparator
- Olanzapine vs placebo/active comparator
- Risperidone vs placebo/active comparator

2.3.3.3.4 Endpoints

The following endpoints are to be reported from RCTs or systematic reviews/meta-analyses of RCTs:

Efficacy
Sleep parameters Success of withdrawal of antipsychotics
Safety
Adverse events

2.3.3.4 Safety of antipsychotics in children and youth

The AHRQ 2017 review(3) was used to answer the research questions concerning harms of antipsychotics in children and youth. The AHRQ 2017 combined data from all study designs irrespective of indication. Children and young adults (<24 year) were included. However, our own search for new studies published after the search date of the AHRQ 2017 was limited to RCT's and prospective cohort studies in children <18 year. Studies in the ICU setting were excluded in this additional search for children <18 years old. The inclusion criteria for RCT's and observational studies can be found in the section "2.3.2 Study types".

2.3.3.4.1 Populations

The following populations are to be discussed:

- Children
- Patients with all conditions

Exclusions:

- Prenatal exposure of antipsychotics

2.3.3.4.2 Interventions

The following medications, available in Belgium, are to be reported from RCTs (or systematic reviews/meta-analyses of RCTs):

FGA	haloperidol
SGA	aripiprazol
	asenapine
	clozapine
	olanzapine
	paliperidon
	quetiapine
	risperidon
	sertindol
	cariprazine

Excluded from the literature review are

- Pharmaceutical formulations that are not available on the Belgian market.

2.3.3.4.3 Comparisons

The following comparisons will be studied:

- FGA vs placebo/no treatment
- SGA vs placebo/no treatment
- SGA vs FGA
- SGA vs SGA

2.3.3.4.4 Endpoints

The following endpoints are to be reported from RCTs or systematic reviews/meta-analyses of RCTs or observational studies:

Efficacy
NA
Safety
Adverse events with a specific focus on • Mortality (sudden cardiac death) • Cardiac arrhythmias • Metabolic (weight gain, diabetes, hyperprolactinemia, dyslipidemia, hypertension) • Extrapyramidal symptoms • Sedation, somnolence • Intoxications (intentional and unintentional)

2.4 Search strategy

2.4.1 Principles of systematic search

*Relevant RCTs, meta-analyses and systematic review*s were searched in a stepwise approach.

As a start we have searched for large systematic reviews from reliable EBM-producers (NICE, AHRQ, the Cochrane library, systematic reviews for included guidelines) that answer some or all of our research questions. One or more systematic reviews were selected as our basic source. From these sources, all references of relevant publications were screened manually.

In a second step, we conducted a systematic search in the Medline (PubMed) electronic database for randomised controlled trials (RCTs), meta-analyses, systematic reviews (and sometimes observational studies) that were published after the search date of our selected systematic reviews.

Guidelines were searched through the link "evidence-based guidelines" on the website of CEBAM (www.cebam.be). These contain links to the national and most frequently consulted international guidelines, as well as links to 'guideline search engines', like G-I-N.

2.4.2 Source documents

The following systematic reviews were selected as source documents and starting points to find relevant publications for our literature review:

Topic	Source document
Antipsychotics and BPSD	Yunusa I, Alsumali A, Garba AE, et al. Assessment of Reported Comparative Effectiveness and Safety of Atypical Antipsychotics in the Treatment of Behavioral and Psychological Symptoms of Dementia: A Network Meta-analysis. JAMA Netw Open. 2019 Mar 1;2(3):e190828.(4)
Antipsychotics and delirium	Kishi T, Hirota T, Matsunaga S, Iwata N. Antipsychotic medications for the treatment of delirium: a systematic review and meta-analysis of randomised controlled trials. J Neurology, Neurosurgery, & Psychiatry 2016;87:767–74.(5)
Antipsychotics and insomnia	no source document was selected
Safety of antipsychotics in children	Pillay J, Boylan K, Carrey N, et al. First- and Second-Generation Antipsychotics in Children and Young Adults: Systematic Review Update. Comparative Effectiveness Review No. 184.(3)

For all these research questions, a search string was developed to search Medline via Pubmed from the research date of the selected source document up until 20th December 2019 for BPSD, insomnia,

and delirium and up until 24th January 2020 for safety of children. If no source document could be found, a search of Medline without a starting date was performed.

Due to the COVID-19 pandemic and the subsequent postponement of the consensus conference, an additional literature search was performed on the 15th of January 2021. Studies published after the search date of the original search were included. Because cariprazine was available at the Belgian market, which was not the case during the first search, a separate search was done with cariprazine for every topic. None of the studies with cariprazine met our inclusion criteria. Furthermore, a new search resulted in the identification and addition of an Irish guideline for patients with dementia.

Due to a second postponement of the consensus conference, an additional literature search was performed on the 15th of July 2021. One observational study was added as a result of this second update in chapter 9 Safety of antipsychotics in children.

2.4.3 Search strategy details

The full search strategies can be found in chapter 21.

2.5 Selection procedure

Selection of relevant references was conducted by two researchers independently. Differences of opinion were resolved through discussion. A first selection of references was done based on title and abstract. When title and abstract were insufficient to reach a decision, the full article was read to decide on inclusion or exclusion.

In - and exclusion criteria of the different types of studies are found in "2.4.3. Specific search criteria" with relevant populations, interventions, endpoints and study criteria. The selection of the studied drugs was based on discussions with experts of the organisation committee. Commonly used antipsychotics and antipsychotics for which there might be evidence available were included in the search.

The list of articles excluded after reading of the full text can be found in chapter 22.

2.6 Assessing the quality of available evidence

To evaluate the quality of the available evidence, the GRADE system was used. In other systems that use 'levels of evidence', a meta-analysis is often regarded as the highest level of evidence. In the GRADE system, however, only the quality of the original studies is assessed. Whether the results of original studies were pooled in a meta-analysis is of no influence to the quality of the evidence.

The GRADE-system is outcome-centric. This means that quality of evidence is assessed for each endpoint, across studies.

The GRADE system assesses the following items:

Study design	+ 4	RCT
	+ 2	Observational
	+ 1	Expert opinion

Study quality		- 1	Serious limitation to study quality
		- 2	Very serious limitation to study quality
Consistency		- 1	Important inconsistency
Directness		- 1	Some uncertainty about directness
		- 2	Major uncertainty about directness
Imprecision		- 1	Imprecise or sparse data
Publication bias		- 1	High probability of publication bias
For observational studies	Evidence of association	+ 1	Strong evidence of association (RR of >2 or <0.5)
		+ 2	Very strong evidence of association (RR of >5 or <0.2)
	Dose response gradient	+ 1	Evidence of a dose response gradient (+1)
	Confounders	+ 1	All plausible confounders would have reduced the effect
SUM		4	HIGH quality of evidence
		3	MODERATE quality of evidence
		2	LOW quality of evidence
		1	VERY LOW quality of evidence

Table. Items assessed by the GRADE system

In this literature review the criteria 'publication bias' has not been assessed.

In assessing the different criteria, we have applied the following rules:

Study design

In this literature review RCT's and observational studies are included. RCTs start out as high quality of evidence (4 points), observational studies start out as low quality of evidence (2 points). Points can be deducted for items that are assessed as having a high risk of bias.

Study quality

To assess the methodological quality of RCT's, we considered the following criteria:

- **Randomization**: If the method of generating the randomization sequence was described, was it adequate (table of random numbers, computer-generated, coin tossing, etc.) or inadequate (alternating, date of birth, hospital number, etc.)?
- **Allocation concealment:** If the method of allocation was described, was it adequately concealed (central allocation, …) or inadequate (open schedule, unsealed envelopes, etc.)?
- **Blinding**: Who was blinded? Participants/personnel/assessors. If the method of blinding was described, was it adequate (identical placebo, active placebo, etc.) or inadequate (comparison of tablet vs injection with no double dummy)?
- **Missing outcome data:** Follow-up, description of exclusions and drop-outs, ITT
- **Selective outcome reporting**

If a meta-analysis or a systematic review is used, quality of included studies was assessed. It is not the quality of the meta-analysis or systematic review that is considered in GRADE assessment, but only the quality of RCTs that were included in the meta-analysis/systematic review.

Application in GRADE:

Points were deducted if one of the above criteria was considered to generate a high risk of bias for a specific endpoint.

For example:

> Not blinding participants will not decrease validity of the results when considering the endpoint 'mortality', but will decrease validity when considering a subjective endpoint such as pain, so for the endpoint pain, one point will be deducted.
> A low follow-up when no ITT analysis is done, will increase risk of bias, so one point will be deducted in this case.

Consistency

Good "consistency" means that several studies have a comparable or consistent result. If only one study is available, consistency cannot be judged. This will be mentioned in the synthesis report as "NA" (not applicable).

Consistency is judged by the literature group and the reading committee based on the total of available studies, whilst taking into account:

- Statistical significance
- Direction of the effect if no statistical significance is reached. E.g. if a statistically significant effect was reached in 3 studies and not reached in 2 others, but with a non-significant result in the same direction as the other studies, these results are considered consistent.
- Clinical relevance: if 3 studies find a non-significant result, whilst a 4th study does find a statistically significant result, that has no clinical relevance, these results are considered consistent.
- For meta-analyses: Statistical heterogeneity.

Directness

Directness addresses the extent in which we can generalise the data from a study to the real population (external validity). If the study population, the studied intervention and the control group or studied endpoint are not relevant, points can be deducted here. When indirect comparisons are made, a point is also deducted.

Imprecision

A point can be deducted for imprecision if the 95%-confidence interval crosses both the point of appreciable harm AND the point of appreciable benefit (e.g. RR 95%CI ≤0.5 to ≥1.5).

Additional considerations for observational studies

For observational studies, when no points are deducted for risk of bias in one of the above categories, a point can be added if there is a large magnitude of effect (high odds ratio), if there is evidence of a dose-response gradient or (very rarely) when all plausible confounders or other biases increase our confidence in the estimated effect.

Application of GRADE when there are many studies for 1 endpoint:

Points are only deducted if the methodological problems have an important impact on the result. If 1 smaller study of poor quality confirms the results of 2 large good quality studies, no points are deducted.

More information on the GRADE Working Group website: http://www.gradeworkinggroup.org

2.7 Synopsis of the study results

The complete report contains:

- (Comprehensive) summary of selected guidelines.
- Evidence tables (English) of systematic reviews or RCTs on which the answers to the study questions are based.
- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system (English).

The synopsis report contains:

- (Brief) summary of selected guidelines.
- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system.

The conclusions of this report have been discussed and adjusted through discussions between the authors of the literature search and the reading committee of the literature group.

3 Critical reflections of the reading committee and the literature group

3.1 Review scope

Indications for antipsychotics include schizophrenia and bipolar disorders but antipsychotics are used for a large number of off-label indications as well. In general, the main focus of this report is the safe use of antipsychotics in the primary care setting. Not considering our review of antipsychotics in children, patients with severe mental illness (e.g. schizophrenia, bipolar disorders) were excluded. To allow a systematic literature search and a comparison of guidelines for a specific pathology, we had to limit the studied topics.

The use of antipsychotics in the following populations are studied:

- patients with behavioral and psychological symptoms of dementia (BPSD)
- patients with insomnia without psychiatric comorbidity
- patients who are not critically ill with delirium

Finally, we focus on the use of antipsychotics in children for multiple (off-label) indications. Treatment with antipsychotics in this population is usually initiated by medical specialists and treatment guidelines are consequently generally not intended for general practitioners (GP's). For this reason, we did not perform a search for guidelines.

Given the specialist care setting, we did not perform a literature search to evaluate the efficacy of antipsychotics for all possible conditions in children. However, GP's care for these patients as well and, after started by a specialist, also prescribe antipsychotics for this population. For this reason, we performed a literature search for adverse events of antipsychotics in children irrespective of the indication.

In general we searched for studies comparing second generation antipsychotics (SGA) with placebo, SGA with haloperidol, and SGA with SGA. We refer to the methodology section for other included comparisons per indication and other details. The selection of the studied drugs was based on discussions with experts of the organisation committee. Commonly used antipsychotics and antipsychotics for which there might be evidence available were included in the search. Non-pharmacological interventions were not studied for this report.

Since we focused more on the harms of antipsychotics, one might wonder why we did not study all adverse events combined irrespective of the condition. The risk of adverse events related to antipsychotics differs depending of the population. For example, contrary to other patients the risk of cerebrovascular accidents and mortality is increased in patients with dementia; critically ill patients might have an increased risk for certain harms compared to other populations; children seem to have a higher risk than adults for experiencing adverse events such as weight gain and metabolic effects. At least a distinction should be made between more homogenous populations. Such evaluations with separate analyses for SGA in children, adults, and the elderly irrespective of the condition are available in the literature for off-label indications.(6) However, some other factors like the dosage should be considered which may vary depending on the condition or population.

In this report, we assess adverse events for children irrespective of the condition and for elderly (i.e. patients with BPSD) separately. We do not report a separate comprehensive evaluation for adults since we only focused on adults with insomnia and non-critically ill patients with delirium.

3.2 Guidelines

We searched for guidelines published in the last 5 years for the treatment of BPSD, insomnia, and delirium. It is important to note that we only select guidelines that report levels of evidence in their recommendations and that are based on a good systematic search and review of the literature.

Four guidelines were selected for information on antipsychotics for BPSD(7),(8),(9), (10) and three other guidelines for insomnia(11),(12),(13). An additional guideline was selected that was specifically developed for deprescribing antipsychotics in BPSD and insomnia. Finally, three guidelines were selected for the treatment of delirium in non-critically ill patients.(14),(15),(16).

The selected guidelines provide little information concerning the monitoring of antipsychotics. This might be expected since guidelines of off-label indications for antipsychotics are reviewed here. Because of this, we decided to perform an additional search for guidelines published more than 5 years ago that specifically focus on monitoring and follow-up of patients on antipsychotics. A systematic review of De Hert et al. 2011 evaluated the quality of 18 guidelines for cardiovascular risk in people with schizophrenia.(17) The authors concluded that 4 guidelines were of good quality. From these 4 guidelines, we selected 1 guideline of good quality according to our criteria (e.g. systematic search, GRADE evaluation).(18) Although already published in 2011, this guideline for monitoring safety of second generation antipsychotics (SGA) in children and youth was the only guideline from our (not exhaustive) search providing recommendations for laboratory tests with recommendation grades. The lack of adequate cardiometabolic monitoring which could lead to cardiovascular disease is a known problem in children and youth on SGA.

3.3 Behavior and Psychological Symptoms of Dementia (BPSD)

3.3.1 Efficacy

First, we assessed SGA compared to placebo for overall BPSD, psychosis, and agitation. We found moderate quality of evidence for an effect of aripiprazole and olanzapine for overall BPSD and agitation in patients with BPSD but not for psychosis. No significant effect was found for quetiapine for any of the three studied outcomes (moderate quality evidence). Low to moderate quality of evidence was found for an effect of risperidone for the three outcomes. We found no data for the other studied SGA.

Secondly, we compared the efficacy of SGA with haloperidol. We found very low to low quality of evidence showing no difference between SGA as a group and haloperidol for overall BPSD and agitation.

Finally, we compared SGA with each other based on data from head-to-head trials. There was low quality of evidence showing no difference between risperidone and olanzapine or quetiapine for any of the studied outcomes.

The AHRQ 2011 (6) review covering the off-label use of atypical antipsychotics was used as one of our main sources. One of the reasons for selecting this comprehensive analysis in patients with BPSD was the separate analysis for overall BPSD, psychosis, and agitation. A surveillance report of May 2016 by the AHRQ stated that the report is partly out of date and that some conclusions may not be current. This is however not pertaining to the efficacy analysis for BPSD. The surveillance report did mention an additionally found RCT(19) in patients with comorbid Parkinson's disease or parkinsonism, a population excluded from our analysis.

Scales to evaluate BPSD in RCT's evaluating antipsychotics differ between studies. For some analyses pooling was done across several scales for which standard mean differences (SMD) were calculated. Only small effects for efficacy were observed. A SMD of 0.20 or smaller were considered small, sizes of 0.50 and greater were considered large, and those between were considered moderate.(6)

As pointed out by the authors of the AHRQ 2011 review, differences between studies in disease severity and permission to treat with psychotropic medicines during the study restrict the interpretation of the results. Furthermore, there were limited trials per comparison, most included RCT's used flexible dosing resulting in patients taking a wide range of doses, and high dropout rates were reported.

Some recent publications from the same group raise some questions about the quality of RCT's evaluating antipsychotics for BPSD. This also raises the question whether our rating of the quality of evidence should be further downgraded. One study evaluated the run-in periods of 35 placebo controlled trials, some of which are included in our review as well.(20) Run-in periods are used to identify placebo-responders and for washout. This study concluded that the use of run-in in trials might have led to overestimated efficacy and especially underestimated risks of side effects of antipsychotics compared with placebo in dementia. Another analysis of 23 placebo controlled trials, again some of which are included in our review, shows baseline imbalances that were associated with higher efficacy and lower risk of extrapyramidal symptoms for SGA.(21) The third study tackles the issue of subjective scales used in antipsychotics trials. The authors show that according to objective measures antipsychotics do not effectively reduce neuropsychiatric symptoms in dementia, and increase the risk of side effects.(22) They included 38 placebo-controlled trials with SGA and conventional antipsychotics to compare subjective scales with objective outcomes.

First generation antipsychotics (FGA) (e.g. haloperidol) are associated with significant adverse effects (e.g. extrapyramidal symptoms). SGA are considered to have less neuromotor side effects but are associated with an elevated risk for cardiometabolic adverse effects. Furthermore, the extent of adverse events between SGA may vary as well. We found few head-to-head trials and few trials that compared SGA with haloperidol in patients with dementia. Network meta-analyses, combining data from many BPSD studies, have been published that rank antipsychotics for efficacy and safety. (4) These results should be considered exploratory in nature due to the use of direct and indirect comparisons, and the increased risk of bias in network meta-analyses compared to traditional pair-wise meta-analyses. Network meta-analyses were excluded in our literature search.

3.3.2 Safety

The systematic review from Ma 2014(23) contained more detailed information in their meta-analyses for adverse events than AHRQ 2011 and was therefore used for placebo controlled trials. All included studies in the analysis for adverse events in Ma 2014 were included in AHRQ 2011.

Similarly to our review of efficacy, we evaluated preselected harms of antipsychotics in studies comparing SGA with placebo, haloperidol, and SGA in patients with BPSD. We studied cerebrovascular accidents (CVA), mortality, extrapyramidal symptoms, falls, endocrine adverse events, and urinary tract infections. We refer to the efficacy section for general limitations of the quality of the included studies, since the same RCT's were used.

The quality of evidence for the risk of CVA from SGA was very low to low across the comparisons. In the individual comparisons, only risperidone showed an increased risk for CVA compared to placebo.

However, SGA as a class had an increased risk as well. We found no comparisons with haloperidol and the few data from head-to-head trials showed no difference.

The quality of evidence for mortality in placebo-controlled trials was low for aripiprazole and moderate for the other SGA. The individual comparisons with SGA showed no increased risk, but SGA pooled together showed an increased risk for mortality. We found very low quality of evidence for no difference in morality risk between olanzapine and haloperidol, and between risperidone and olanzapine.

The quality of evidence for the risk of extrapyramidal symptoms from SGA was very low to low across the comparisons. We found no increased risk for aripiprazole and quetiapine and an increased risk for olanzapine, risperidone, and SGA pooled together compared to placebo. We found insufficient evidence to assess the risk of SGA compared to haloperidol or other SGA.

The quality of evidence for the risk of falls from SGA was very low to moderate across the comparisons. We observed no increased risk in any of the comparisons between SGA and placebo, haloperidol, and SGA.

We found few data for the risk of diabetes. There was very low quality of evidence for no increased risk of risperidone compared to placebo and for olanzapine compared to haloperidol. We performed an additional search for observational studies but no eligible studies were identified.

We found low to moderate quality of evidence for no increased risk of urinary tract infections from studies comparing individual SGA with placebo. We observed an increased risk for SGA pooled together (low quality of evidence). Low quality of evidence showed no difference in risk between quetiapine and haloperidol. There was insufficient evidence for the comparison SGA versus SGA.

3.3.3 Deprescribing of antipsychotics

The Cochrane review from Van Leeuwen 2018 studied the discontinuation of long-term antipsychotic use in older patients with dementia. Their primary outcome was success of withdrawal defined as the ability to complete the study (i.e. no dropout due to worsening of neuropsychiatric symptoms (NPS) or no relapse to antipsychotic drugs use during the trial). Since this was not reported in any of the included studies, the authors used the difference between groups in the number of non-completers of the study as a proxy. Data from the primary outcome could not be pooled. Therefore, a critical interpretive synthesis of data from individual studies was performed. Reported data were predominately from studies at low or unclear risk of bias.

As discussed by Van Leeuwen 2018 “We found low-quality evidence that long-term use of antipsychotics can be successfully and safely discontinued in most adults aged 65 and older with dementia and BPSD without an important effect on behavioral and psychological symptoms. This is consistent with the observation that most behavioral complications of dementia are intermittent and often do not persist for longer than 3 months. Possibly, some adults aged 65 and older with more severe BPSD (NPI >14) or psychosis, aggression, or agitation may benefit from continuing their antipsychotic medication. Nevertheless, in these older adults with severe BPSD, discontinuation is still possible but the potential benefits of discontinuation should be carefully weighed against the potential risks of antipsychotic treatment.”

We included a guideline in this report from Canada that provides guidance in deprescribing antipsychotics in patients with BPSD.(24)

3.3.4 Additional comments of the reading committee

Members of the reading committee would also like to point out these points:

In most studies, the study duration was too short to detect any differences for some long-term outcomes, and sometimes the selected outcomes were inappropriate. Given the important adverse effects with the longterm use of antipsychotics in older patients, studies with antipsychotics should evaluate outcomes such as sarcopenia, which could lead to falls and fractures. The outcome malnutrition as a consequence of dysphagia should be evaluated as well, considering the increased risk of dysphagia (and aspiration pneumonia) with the use of antipsychotics.

In clinical practice, antipsychotics are often started in crisis situations and are not discontinued afterwards. Before considering starting antipsychotics, it is important to assess the underlying cause of the BPSD (organic disease, infection, environmental stimuli, etc.). Preferably, this assessment should be done by a multidisciplinary team. To ensure safe deprescribing of antipsychotics, good collaboration between secondary and primary care is required. The need of well-trained caregivers in residential care should also be emphasized.

3.4 Insomnia

Antipsychotics are sometimes used off-label in clinical practice to treat insomnia. As this report shows, there is no evidence from RCT's to support the use of antipsychotics for insomnia in the absence of psychiatric conditions. Furthermore, multiple guidelines do not recommend the use of antipsychotics for insomnia.

We found no studies that evaluated the withdrawal of antipsychotics that was started for insomnia. However, we included a guideline in this report from Canada that provides guidance in deprescribing antipsychotics in patients with BPSD and insomnia.(24)

3.5 Delirium

The question to the jury for this consensus conference involves the use of antipsychotics for delirium and agitation. However, the task for the literature group was limited to delirium.

The majority of recent studies have focused on critically ill patients with delirium. Given our focus on primary care, we limited our literature search to the treatment of delirium in non-critically ill patients. For this population, we found only insufficient poor quality data.

The Cochrane review from Burry 2018(25) identified a total of nine trials in non-ICU patients comparing antipsychotics versus non-antipsychotics/placebo or comparing haloperidol versus SGA. There were issues in most of these studies with short duration resulting in low to very low quality of evidence. Important outcomes such as duration of delirium, length of hospital stay, or quality of life were not available in the current literature. Except for one study(26), none of the studies factored in nonpharmacological treatment strategies that already have been shown to be helpful in this population to clarify if an antipsychotic alters delirium outcomes.(25) Also, differences in rescue

therapies for agitation between studies, which was not consistently reported, might have introduced bias.

From the poor quality data available, antipsychotics did not reduce delirium severity, resolve symptoms, or alter mortality compared to non-antipsychotics/placebo. There was also no difference for these outcomes between haloperidol and SGA. There was no difference in the frequency of extrapyramidal symptoms in both comparisons.

Adverse event reporting was limited and measured with inconsistent methods. No RCT's, included in Burry 2018, reported on QTc prolongation or sudden cardiac death. Good quality data in this regard is needed given that in this population patients will often already have multiple risk factors for QTc prolongation and Torsades de Pointes. A search for observational studies for this outcome was not included in our literature search.

Delirium is common in older patients or patients with dementia. Burry 2018 had planned subgroup analyses for these populations to determine if there were differences in effect or safety, but such analyses were not possible due to lack of data.

In their discussion, Burry 2018(25) compare their results with a review by Kishi 2016(5) who included ICU and non-ICU populations. In a subgroup analysis, Kishi 2016(5) found a superior effect of antipsychotics compared to placebo or nonantipyschotics for response rate in non-ICU patients. Antipsychotics had also a small effect for delirium severity compared to no antipsychotics in the total sample.

However, four of the studies included were unpublished or in abstract form only; these were excluded by Burry 2018(25). Furthermore, Burry 2018(25) included two additional trials for the analysis of delirium severity.

The literature does not provide evidence to support the use of antipsychotics for treatment of delirium in non-ICU patients. Although beyond the scope of our review, we also note that a comprehensive AHRQ review by Neufeld 2019(27) found no evidence to support the use of antipsychotics for the treatment of delirium in any population.

Additional comments of the reading committee

There is insufficient data available to draw firm conclusions about the efficacy of antipsychotics in delirium. The relevant study populations (age, comorbidities), clinical context, measurements and outcome measures are also heterogeneous. When dealing with few and poor quality data, it cannot be stated with a high reliability that there is no effectiveness whatsoever in any population or in any clinical condition. Caution is therefore advised in the interpretation of the results and the need for additional research should be emphasized, as is also concluded in most meta-analyses and reviews. However, there are no initiatives from the industry regarding additional research.

Despite a lack of evidence, antipsychotics are often prescribed in clinical practice because delirium does not immediately improve or because of high levels of disstress (agitation, aggression). Other reasons include the high workload for caregivers, the few alternatives and other options (such as non-drug interventions) are often not feasible in clinical practice (especially in primary care). In addition, these patients with delirium can show prominent psychotic symptoms, as well as agitation, which are indications for antipsychotics.

Members of the reading committee also wanted to add some comments regarding the risk of QTc prolongation:

- The risk of QTc prolongation and monitoring for this risk are important factors to consider when prescribing antipsychotics. Besides QTc prolonging medication, other risk factors for QTc prolongation should be considered including cardiac comorbidities, electrolyte imbalance, age, gender, etc.

-The distinction between the FGA and SGA also deserves a little more attention in that regard. The efficacy of haloperidol is not superiour to SGA and haloperidol potentially has a higher incidence of certain adverse events (such as QTc prolongation and extrapyramidal symptoms). Although the latter should be put into perspective with a low dosage and short duration of treatment during hospitalization; furthermore there appear to be few differences between FGA and SGA in the current literature review. However, in primary care it is more difficult to provide a follow-up and monitoring, so these aspects may be relevant after all. QTc prolongation can occur rapidly after administration and must be followed up correctly. It should also be noted that the FGA (except haloperidol) are generally less well researched and documented in terms of safety than the SGA.

-Some potential side effects (such as effect on QTc, sedation, extrapyramidal symptoms) are more important in delirium than other side effects reported in this report (such as metabolic side effects), because antipsychotics are usually prescribed for a short period of time and in a low dose.

3.6 Safety of antipsychotics in children

It is difficult to draw conclusions from adverse events reported in RCTs, since they are usually set up in a way to minimize adverse events.

Some adverse events are rare occurrences. The less common they are, the longer and/or larger the studies need to be to identify a difference between active and control group.

To assess rare adverse events, we included observational studies (cohort studies). An observational study cannot prove a causal link, it can merely establish an association between the treatment and a specific outcome. The quality of evidence in the GRADE approach for observational studies is LOW by default, although upgrading or downgrading according to certain rules is possible.

Results from observational studies are very sensitive to hidden bias. Results are generally statistically adjusted to correct for confounders, but not all possible confounders are known or measured.

For adverse events in children and young adults, we reported many meta-analyses from the AHRQ 2017(3) report. These meta-analyses combine results from RCTs and cohort study designs. The authors of the AHRQ 2017 report cite following reasons for combining these study designs:

1. *"empirical evidence has found no difference in estimates of harms between meta-analyses of RCT and cohort study designs(28)"*
2. *"a major contributor to bias on harms from observational studies is confounding by indication (e.g., differential prescriptions based on beliefs/knowledge about factors related to development of harms) which we did not believe was an important threat in studies examining unanticipated harms in (mostly) treatment naïve children"*
3. *"cohort studies are commonly recognized as contributing valuable, relatively high-quality evidence applicable to real-world settings."*

We mention here some of the results mainly based on the analysis of AHRQ 2017. Most of the evidence is of low quality. Information on outcomes not mentioned here and more detailed results can be found in "9. Safety of antipsychotics in children".

Antipsychotics in general are associated with increased mortality and unexpected deaths compared to control medications (ADHD medication, antidepressants and mood stabilizers). SGA are associated with increased risk of cardiovascular events, diabetes, weight measurements (weight, BMI, >7% weight increase), total cholesterol, triglycerides, extrapyramidal symptoms, akathisia (long-term), sedation, and somnolence (short-term) compared to placebo. FGA are associated with less weight gain than SGA.

Quetiapine was associated with a longer QTc compared to aripiprazole.

Aripiprazole was associated with less weight gain and a lower risk for (some) other weight measurements compared to olanzapine, paliperidone, and quetiapine. Olanzapine was associated with an increase of some weight measurements compared to quetiapine and risperidone.

Aripiprazole was associated with fewer patients with hyperprolactinemia compared to paliperidone, less increase of blood pressure, total cholesterol, and triglycerides compared to quetiapine.

Quetiapine was associated with fewer extrapyramidal symptoms compared to risperidone.

Aripiprazole was associated with fewer patients with akathisia, but more sedation compared to quetiapine.

In chapter 10 "Additional safety information from other sources", we report information from BCFI/CBIP sources and from Martindale (39th) edition as an addition to the information that was reported in the observational studies included in our review.

<u>Additional comments of the reading committee</u>

As this report includes trials that included children and young adults until the age of 24 years, the wide age range might have masked some effects or side effects of antipsychotics. It could be questioned whether the endocrine effects (prolactin, diabetes, metabolic syndrome) are the same for a population of 2-6 years olds and a population of 12-16 years olds.

Furthermore, pooling all SGA together might bias the results for the outcome hyperprolactinemia. No difference was found between SGA and placebo for this outcome despite some relevant differences in the pharmacological profile among the SGA. An analysis with the separate drugs is expected to lead to other findings. Hyperprolactinemia would be expected for certain SGA (e.g. risperidone, paliperidone) but not for others (aripiprazole, cariprazine).

4 General information on selected guidelines

4.1 Selected guidelines

The selected guidelines and their abbreviations as used in this report can be found in Table 1 to Table 5.

Antipsychotics for BPSD

Abbreviation	Guideline
APA 2016	Reus VI, Fochtmann LJ, Eyler AE, et al.; The American Psychiatric Association practice guideline on the use of antipsychotics to treat agitation or psychosis in patients with dementia.(7)
AUS 2016	Guideline Adaptation Committee; Clinical; Practice Guidelines and Principles of Care for People with Dementia.(8)
NICE 2018	Dementia: assessment, management and support for people living with dementia and their carers; NICE guideline NG97.(9)
IRE 2019	Department of Health; Appropriate prescribing of psychotropic medication for non-cognitive symptoms in people with dementia (NCEC National Clinical Guideline No. 21). (10)

Table 1: Selected guidelines and their abbreviations as used in this report.

Antipsychotics for the treatment of delirium

Abbreviation	Guideline
SIGN 2019	Scottish Intercollegiate Guidelines Network (SIGN); Risk reduction and management of delirium; SIGN publication no. 157.(14)
NICE 2010/upd 2019	DELIRIUM: diagnosis, prevention and management; NICE guideline CG103.(15)
NHG 2014	Eizenga WH, Dautzenberg PLJ, Eekhof JAH et al.; NHG-Standaard Delier.(16)

Table 2: Selected guidelines and their abbreviations as used in this report.

Antipsychotics for insomnia

Abbreviation	Guideline
EUR 2017	Riemann D, Baglioni C, Bassetti C, et al.; European guideline for the diagnosis and treatment of insomnia.(11)
WOREL 2018	Cloetens H, Declercq T,Habraken H, Callens J et Van Gaste A ; Prise en charge des problèmes de sommeil et de l'insomnie chez l'adulte en première ligne.(12)
USA 2016	Qaseem A, Kansagara, Forciea MA, Cooke M, and Denberg TD, for the Clinical Guidelines Committee of the American College of Physicians; Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians.(13)

Table 3: Selected guidelines and their abbreviations as used in this report.

Discontinuation of antipsychotics

Abbreviation	Guideline
Canada 2018	Bjerre LM, Farrell B, Hogel M et al.; Deprescribing antipsychotics for behavioural and psychological symptoms of dementia and insomnia.(24)

Table 4: Selected guidelines and their abbreviations as used in this report.

Monitoring of antipsychotics

Abbreviation	Guideline
CAMESA 2011	Pringsheim T, Panagiotopoulos C, Davidson J,Ho J for the CAMESA guideline group. Evidence-Based Recommendations for Monitoring Safety of Second Generation Antipsychotics in Children and Youth.(18)

Table 5: Selected guidelines and their abbreviations as used in this report.

4.2 Grades of recommendation

Grades of recommendation and levels of evidence as defined in each guideline, can be found in table Table 6 to Table 17.

APA 2016		
Grades of recommendation:	"recommendation" (denoted by the numeral 1)	confidence that the benefits of the intervention clearly outweigh the harms.
	"suggestion" (denoted by the numeral 2)	indicates uncertainty (i.e., the balance of benefits and harms is difficult to judge, or either the benefits or the harms are unclear)
Levels of evidence	High (denoted by the letter A)	High confidence that the evidence reflects the true effect.
	Moderate (denoted by the letter B)	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
	Low (denoted by the letter C)	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.

Table 6: Grades of recommendation and Level of evidence of the APA 2016 guideline.

<table>
<tr><th colspan="3">AUS 2016</th></tr>
<tr><td rowspan="2">Grades of recommendation:</td><td>Strong recommendations expressed in the wording of the recommendation using the term ‘should’ or ‘should not’.</td><td>A strong recommendation implies that most or all individuals will be best served by the recommended course of action.</td></tr>
<tr><td>Weak recommendations use expressed in the wording of the recommendation using the term ‘should/could be considered’ or ‘suggested’ or “may be offered”.</td><td>A weak recommendation implies that not all individuals will be best served by the recommended course of action and there is a need to consider individual patients’ circumstances, preferences and values.</td></tr>
<tr><td rowspan="4">Levels of evidence</td><td>Evidence-based recommendation (EBR)</td><td>Recommendation formulated after a systematic review of the evidence, with a rating of the overall quality of the evidence and supporting references provided.</td></tr>
<tr><td colspan="2">Strengths of EBR have been evaluated according to GRADE procedure (assessment of risk of bias, directness, consistency and precision of the estimates):
<table>
<tr><td>High</td><td>Further research is very unlikely to change our confidence in the estimate of effect</td></tr>
<tr><td>Moderate</td><td>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate</td></tr>
<tr><td>Low</td><td>Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change, the estimate</td></tr>
<tr><td>Very Low</td><td>Any estimate of effect is very uncertain</td></tr>
</table></td></tr>
<tr><td>Consensus based recommendation (CBR)</td><td>Recommendation formulated in the absence of adequate evidence, when a systematic review of the evidence has failed to identify sufficient studies meeting the inclusion criteria for that clinical question to inform a recommendation.</td></tr>
<tr><td>Practice point (PP)</td><td>A recommendation that is outside the scope of the search strategy for the systematic evidence review, or for which a systematic review was not conducted, and is based on expert opinion.</td></tr>
</table>

Table 7: Grades of recommendation and Level of evidence of the AUS 2016 guideline.

NICE 2018		
Grades of recommendation:	Interventions that must (or must not) be used worded as such in the text.	Generally used if there is a legal duty to apply the recommendation. But used as well if the consequences of not following the recommendation could be extremely serious or potentially life threatening.
	Intervention that should (or should not) be used are worded in the text using the term “offer”, “refer”, “advise” or similar…	There is clear evidence of benefit. We are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective.
	Intervention that could (or could not) be used are worded in the text using the term “consider”	Reflects a recommendation for which the evidence of benefit is less certain. We are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient’s values.
Levels of evidence	While levels of evidence have been evaluated using described procedures (GRADE, CASP RCT, cohort study, case-control checklists, CERQual) NICE does not explicitly attribute strength levels to each particular recommendation.	

Table 8: Grades of recommendation and Level of evidence of the NICE 2018 guideline.

IRE 2019		
Grades of recommendation:	Strong: worded as such in the text	Most individuals should receive the recommended course of action.
	Weak or conditional: worded as such in the text	Different choices will be appropriate for different patients. Practitioner must help each patient arrive at a management decision consistent with her or his values and preferences.
Levels of evidence	High	Very confident that the true effect lies close to the estimated effect
	Moderate	Moderately confident in the effect estimate. The true effect probably lies close to the estimated effect, but the possibility exists that it differs substantially from it.

	Low	Limited confidence in the effect estimate. The true effect can differ substantially from the estimated effect.
	Very Low	Very little confidence in the effect estimate The true effect probably differs substantially from the estimated effect.

Table 9: Grades of recommendation and Level of evidence of the IRE 2019 guideline.

SIGN 2019		
Grades of recommendation:	Strong	Interventions that "should" (or "should not") be used. The guideline development group is confident that, for the vast majority of people, the intervention(s) will do more good than harm (or more harm than good).
	Conditional	Interventions that should be "considered". The guideline development group is confident that the intervention will do more good than harm for most patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.
Levels of evidence	1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
	1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias.
	1–	Meta-analyses, systematic reviews, or RCTs with a high risk of bias.
	2++	High-quality systematic reviews of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
	2+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
	2–	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.
	3	Non-analytic studies, eg case reports, case series.

	4	Expert opinion.

Table 10: Grades of recommendation and Level of evidence of the SIGN 2019 guideline.

NICE 2011/upd 2019		
Grades of recommendation:	Interventions that must (or must not) be used worded as such in the text.	Generally used if there is a legal duty to apply the recommendation. But used as well if the consequences of not following the recommendation could be extremely serious or potentially life threatening.
	Intervention that should (or should not) be used are worded in the text using the term “offer”, “refer”, “advise” or similar…	There is clear evidence of benefit. We are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective.
	Intervention that could (or could not) be used are worded in the text using the term “consider”	Reflects a recommendation for which the evidence of benefit is less certain. We are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient’s values.
Levels of evidence	While levels of evidence have been evaluated using described procedures (GRADE, CASP RCT, cohort study, case-control checklists, CERQual) NICE does not explicitly attribute strength levels to each particular recommendation.	

Table 11: Grades of recommendation and Level of evidence of the NICE 2011/upd2019 guideline.

NHG 2014		
Grades of recommendation:	Strong: expressed in the wording of the recommendation	/
	Weak: expressed in the wording of the recommendation	This often means there is not enough evidence to recommend a specific option and that medical professionals, together with their patient, make a choice from different options.
Levels of evidence	High	The true effect lies close to the estimated effect

	Moderate	The true effect probably lies close to the estimated effect, but the possibility exists that it differs substantially from it.
	Low	The true effect can differ substantially from the estimated effect.
	Very Low	The true effect probably differs substantially from the estimated effect.

Table 12: Grades of recommendation and Level of evidence of the NHG 2014 guideline.

EUR 2017		
Grades of recommendation: According to GRADE	Strong	The desirable effects of the intervention clearly outweigh the undesirable effects, or clearly do not.
	Weak	Evidence suggest that desirable and undesirable effect are closely balanced.
Levels of evidence According to GRADE	High	Further research is very unlikely to change our confidence in the estimate of effect.
	Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
	Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
	Very Low	Any estimate of effect is uncertain.

Table 13: Grades of recommendation and Level of evidence of the EUR 2017 guideline.

WOREL 2018		
Grades of recommendation:	1 exprime une recommendation forte	Les avantages sont nettement supérieurs aux inconvénients ou aux risques
	2 exprime une recommendation faible	Équilibre entre les avantages et les inconvénients ou risques
	Recommandation du groupe de développement (« GPP »)	Inspiré des « GPP » (« Good Practice Points ») de certains GPC anglophones dont SIGN, et qui équivaut à une recommandation basée sur l'expérience clinique du groupe de développement et/ou figurant comme tel dans nos GPCs de référence.

Levels of evidence	A	RCT sans limitations ou preuves très convaincantes issues d'études observationnelles
	B	RCT avec limitations ou preuves très convaincantes issues d'études observationnelles
	C	Études observationnelles ou études de cas

Table 14: Grades of recommendation and Level of evidence of the WOREL 2018 guideline.

USA 2016		
Grades of recommendation:	Strong	A strong recommendation means that benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits.
	Weak	When benefits are finely balanced with risks and burden or appreciable uncertainty exists about the magnitude of benefits and risks, a recommendation is classified as weak. Patient preferences may strongly influence the appropriate therapy.
Levels of evidence	High	Evidence is considered high quality when it is obtained from 1 or more well-designed and well-executed randomized, controlled trials (RCTs) that yield consistent and directly applicable results. This also means that further research is very unlikely to change our confidence in the estimate of effect.
	Moderate	Evidence is considered moderate quality when it is obtained from RCTs with important limitations. Evidence from well-designed controlled trials without randomization, well-designed cohort or case–control analytic studies, and multiple time series with or without intervention are in this category. Moderate-quality evidence also means that further research will probably have an important effect on our confidence in the estimate of effect and may change the estimate.
	Low	Evidence obtained from observational studies would typically be rated as low quality because of the risk for bias. Low-quality evidence means that further research is very likely to have an important effect on our confidence in the estimate of effect and will probably change the estimate.
	Insufficient	When the evidence is insufficient to determine for or against routinely providing a service, we grade the

		recommendation as “insufficient evidence to determine net benefits or risks.” Evidence may be conflicting, of poor quality, or lacking, and hence the balance of benefits and harms cannot be determined. Any estimate of effect that is very uncertain as evidence is either unavailable or does not permit a conclusion.

Table 15: Grades of recommendation and Level of evidence of the USA 2016 guideline.

Canada 2018		
Grades of recommendation:	Strong (phrased as “we recommend ...”)	All or most patients should receive the intervention or all patients in the given situation would want the recommended course of action, and only a small proportion would not.
	Weak (phrased as “we suggest ...”)	Different choices will be appropriate for individual patients. Most patients would wish to follow the recommendation, but some patients would not. Clinicians must help patients and caregivers make treatment decisions consistent with patients’ values and preferences.
Levels of evidence	High	According to GRADE (assessment of risk of bias, inconsistency, indirectness, and imprecision).
	Moderate	
	Low	
	Very Low	

Table 16: Grades of recommendation and Level of evidence of the Canada 2016 guideline.

CAMESA 2011		
Grades of recommendation:	1 = strong	Strong recommendation, can apply to most patients in most circumstances without reservation or, for low quality of evidence, may change when higher quality evidence becomes available.
	2 = weak	Weak recommendation, best action may differ depending on circumstances. Clinical significance of test is questionable, or there is conflicting evidence between studies.
	3 = weak recommendation, no evidence, consensus based.	Weak recommendation, best action may differ depending on circumstances. No data from RCTs or observational studies to support presence of specific side effect recommended on the basis of expert opinion.
Levels of evidence Modifications to the GRADE system were made to reflect that while there is good evidence that specific side effects occur with the use of SGAs, there is no evidence on the outcome of monitoring for these side effects	A	RCTs without important limitations.
	B	RCTs with important limitations, or exceptionally strong evidence from observational studies.
	C	Observational studies or case series

Table 17: Grades of recommendation and Level of evidence of the Canada 2016 guideline.

4.3 Agree II score

Information about the Agree II score can be found in the section “Methodology”.

A summary of the assessment by the literature group of the individual items of the domain score for each guideline can be found in Table 18. The total domain score is also reported in this table.

Rigour of development item	7	8	9	10	11	12	13	14	Total	Domain score
APA 2016	6	6	6	7	7	5	5	3	**45**	**80,4**
AUS 2016	6	7	7	5	5	6	5	5	**46**	**82,1**
NICE 2018	7	7	7	4	7	7	5	5	**49**	**87.5**
IRE 2019	7	7	4	6	6	7	6	6	**49**	**87.5**
SIGN 2019	7	6	6	6	5	6	7	6	**49**	**87.5**
NICE 2010/upd 2019	7	7	7	4	7	7	5	5	**49**	**87.5**
NHG 2014	7	4	4	5	6	7	6	3	**42**	**75.0**
EUR 2019	5	5	5	6	5	4	5	1	**36**	**64.3**
WOREL 2018	3	3	5	4	6	6	5	5	**37**	**66.1**
USA 2016	7	7	7	4	6	7	5	1	**44**	**78.6**
Canada 2018	2	2	5	4	7	6	6	2	**34**	**60.7**
CAMESA 2011	3	5	6	7	4	3	4	2	**34**	**60.7**

Table 18: AGREE score of selected guidelines on item “Rigour of development”, see methodology for a description of the items.

4.4 Included populations – interventions – main outcomes

In the following tables, the populations, interventions and main outcomes considered in the selected guidelines are represented.

APA 2016	
Population	Patients with dementia who are exhibiting agitation or psychosis.
Interventions	Antipsychotics
Outcomes	Overall BPSD Agitation Psychosis Adverse effects

Table 19: Included population, intervention and main outcomes of the APA 2016 guideline.

AUS 2016	
Population	People with behavioral and psychological symptoms of dementia (BPSD) including Alzheimer's disease, vascular dementia, dementia with Lewy Bodies, subcortical dementia, frontotemporal dementias, mixed dementias, and dementia encountered in the course of Parkinson's Disease. However, dementia in Huntington's chorea is considered out of scope.
Interventions	Antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone, haloperidol)/placebo or placebo plus non pharmacological intervention.
Outcomes	Overall BPSD (as well agitation psychosis and aggressive behavior) Secondary outcomes (Quality of life of the person with dementia, Institutionalization) Adverse effects

Table 20: Included population, intervention and main outcomes of the AUS 2016 guideline.

NICE 2018	
Population	Persons aged 40 and over living with dementia or suspected dementia (including Alzheimer's disease), excluding people with a confirmed diagnosis of mild cognitive impairment and people with juvenile onset dementia.
Interventions	All setting for support and person-centred care including medication, care coordination and staff training.
Outcomes	Possible clinical benefits and adverse effects, diagnostic, resource use and costs.

Table 21: Included population, intervention and main outcomes of the NICE 2018 guideline.

IRE 2019	
Population	Adults (18 and more) with dementia of any age, and of any type, and in any setting including people with an intellectual disability and dementia. However most evidence is based on common dementia types, particularly Alzheimer's dementia. This guideline is not intended to guide the treatment of delirium.
Interventions	Medication categories within the scope of this guideline are: antipsychotic medications (excluding lithium); antidepressant medications; anticonvulsant medications; benzodiazepines; hypnotics and sedatives including z-drugs, benzodiazepine-derivative and melatonin ; acetylcholinesterase inhibitors and memantine, when used for non-cognitive symptoms; compared to placebo, other phamrmacological intervention(s) or non pharmacological intervention(s). Non-pharmacological interventions are not within the scope of this guideline.
Outcomes	Any patient/ healthcare outcomes: • Morbidity • Mortality • Quality of life • Satisfaction • Cost and resource use • Adverse events/efficacy

Table 22: Included population, intervention and main outcomes of the IRE 2019 guideline.

SIGN 2019	
Population	Adults at risk of delirium, with suspected delirium or with delirium. The guideline excludes delirium secondary solely to alcohol and illicit substances use. It also excludes delirium in children.
Interventions	Assessment tools. Multicomponent interventions, non-pharmacological and pharmacological interventions compared to usual care or between therapies.
Outcomes	• Risk evaluation: Incidence of delirium (hospital acquired), prevalence of delirium (community acquired), duration of delirium, severity of delirium. • Treatment evaluation: Mortality, duration of delirium, severity of delirium, distress in delirium, length of hospital stay, loss of independent living/new institutionalization, reduction in depression and anxiety, reduced dementia risk, worsening of dementia, reduction in long-term effects, reduction in falls, cost effectiveness.

Table 23: Included population, intervention and main outcomes of the SIGN 2019 guideline.

NICE2011/upd 2019	
Population	People aged 18 and over in hospital and in long-term residential care or a nursing home. It also covers identifying people at risk of developing delirium in these settings and preventing onset. This guideline does not cover children and young people (under the age of 18 years), people receiving end-of-life care, people with intoxication and/or withdrawing from drugs or alcohol, and people with delirium associated with these states.
Interventions	• Pharmacological and non-pharmacological interventions. • Pharmacological interventions were: Haloperidol Olanzapine Amisulpride Quetiapine
Outcomes	The guideline addresses: • modifiable risk factors to identify people at risk of developing delirium; diagnosis of delirium in acute, critical and long-term care. • Regarding the pharmacological interventions, evaluated outcomes were recovery from delirium (complete response), duration of delirium and severity of delirium.

Table 24: Included population, intervention and main outcomes of the NICE2011/upd 2019 guideline.

NHG 2014	
Population	Ouderen en patiënten in de palliatieve fase. Delier bij jongere en niet-kwetsbare patiënten valt buiten het bestek van deze standaard.
Interventions	Niet-medicamenteuze adviezen, medicamenteuze behandeling van de symptomen van delier.
Outcomes	signalering en diagnose van een delier, therapeutisch beleid bij een delier, preventie van een recidief delier.

Table 25: Included population, intervention and main outcomes of the NHG 2014 guideline.

USA 2016	
Population	The study population included adults (aged ≥18 years) with chronic insomnia disorder (insomnia definitions that match diagnostic criteria for insomnia disorder).
Interventions	• Psychological therapies, including CBT-I, multicomponent behavioral therapy or BBT for insomnia, stimulus control, relaxation strategies, and sleep restriction. • Pharmacologic therapies, including doxepin, triazolam, estazolam, temazepam, flurazepam, quazepam, zaleplon, zolpidem, eszopiclone, ramelteon, suvorexant, off-label use of drugs (such as antidepressants and antipsychotics), and melatonin. • Complementary and alternative approaches, including acupuncture and Chinese herbal medicine.
Outcomes	Evaluated outcomes included global outcomes assessed by questionnaires (such as treatment response), patient-reported and intermediate sleep outcomes, and harms

Table 26: Included population, intervention and main outcomes of the USA 2016 guideline.

EUR 2017	
Population	Adult patients with insomnia as defined by ICD-10/ICSD-3 (defined as difficulties in initiating or maintaining sleep, or early morning awakening associated with impaired daytime functioning).This includes all subtypes of insomnia, for example, non-organic insomnia and insomnia co-morbid with somatic or mental disorders.
Interventions	Pharmacological and non-pharmacological therapies
Outcomes	Diagnosis and treatment of insomnia is the main focus of this guideline. In addition, the etiology and pathophysiology, diagnostic procedure, epidemiology, health risks, and costs of insomnia are also summarized.

Table 27: Included population, intervention and main outcomes of the EUR 2017 guideline.

WOREL 2018	
Population	Ce guide de pratique clinique s'applique aux adultes (à partir de 18 ans) se plaignant de leur sommeil et/ou insomniaques.
Interventions	Interventions non médicamenteuses et médicamenteuses.
Outcomes	Les résultats recherchés n'ont pas toujours été clairement mentionnés. Toutefois le diagnostic ainsi que les résultats sur la durée d'endormissement, la qualité du sommeil, le fonctionnement diurne et les effets secondaires sont discutés de façon récurrente.

Table 28: Included population, intervention and main outcomes of the WOREL 2018 guideline.

Canada 2018	
Population	Elderly patients taking antipsychotics for the purpose of treating BPSD, for treating primary insomnia, or for treating secondary insomnia when the underlying comorbidities are managed. This guideline does not apply to patients taking antipsychotics for the treatment of schizophrenia, schizoaffective disorder, bipolar disorder, acute delirium, Tourette syndrome or tic disorders, autism, mental retardation or developmental delay, obsessive-compulsive disorder, alcoholism, cocaine abuse, or Parkinson disease psychosis; to those taking them as an adjunct for the treatment of depression; or if psychosis in patients with dementia has been treated for less than 3 months' duration.
Interventions	Deprescribing/continuation of antipsychotic Atypical antipsychotics/placebo
Outcomes	Important patient outcomes (benefits and harms): • medication withdrawal, a change in BPSD, the presence or absence of withdrawal symptoms, a change in the adverse effects of antipsychotics, a change in quality of life, and mortality. • total sleep time, latency to sleep, and sleep satisfaction.

Table 29: Included population, intervention and main outcomes of the Canada 2018 guideline.

CAMESA 2011	
Population	This guideline applies to children and youth 18 years of age and younger who have been prescribed a second generation antipsychotic medication for the treatment of a mental health disorder.
Interventions	Second generation antipsychotics
Outcomes	Metabolic and neurological side effects as well as the monitoring of metabolic and neurological side effects. It should be noted that the performance of electrocardiograms, absolute neutrophil counts and slit lamp eye examinations as a part of monitoring were considered out of scope for this guideline.

Table 30: Included population, intervention and main outcomes of the CAMESA 2011 guideline.

4.5 Members of development group – target audience

Members of the development group that produced the guidelines, and the target audience for whom the guidelines are intended, can be found in the following tables.

APA 2016	
Development group	The Guideline Writing Group was diverse and balanced and composed of eight psychiatrists with general research and clinical expertise and of some experts from other disciplines (i.e., nursing, neurology, and geriatrics).
Target audience	The guideline applies to generalist and specialist clinicians care providers as well as individuals with dementia in all settings of care. Recommendations are not intended to apply to individuals who are receiving antipsychotic medication for another indication (e.g., chronic psychotic illness) or individuals who are receiving an antipsychotic medication in an urgent context.

Table 31: Members of the development group and target audience of the APA 2016 guideline.

AUS 2016	
Development group	The Guidelines were developed by adapting the UK's guidelines for dementia by a committee of experts who had relevant practical experience in the management of dementia, including carers of people with dementia, general practitioners, specialists, scientifics, as well as consumer representatives.
Target audience	Intended users of guideline are medical specialists (general physicians, general practitioners, geriatricians, neurologists, psychiatrists, psychogeriatricians, rehabilitation physicians), nurses, aged care workers and allied health professionals. The Guideline is also relevant to health system planners and managers and administrators whose organizations provide services for people with dementia. The guideline will also be useful for people with dementia and their carer(s)/family.

Table 32: Members of the development group and target audience of the AUS 2016 guideline.

NICE 2018	
Development group	A multidisciplinary guideline committee including practitioners (both specialists in the topic and generalists), service or care providers or commissioners, topic experts, people with personal experience of using health or care services, as well as a subgroup of social care practitioners.
Target audience	This guideline is intended to healthcare and social care professionals caring for and supporting people living with dementia; commissioners and providers of dementia health and social care services; housing associations, private and voluntary organizations contracted by the NHS or social services to provide care for people living with dementia; and people living with dementia, their families and carers.

Table 33: Members of the development group and target audience of the NICE 2018 guideline.

IRE 2019	
Development group	The development group was co-chaired by a Clinical Lead and a Senior Academic Pharmacist ; membership nominations were sought from a variety of clinical and non-clinical backgrounds so as to be representative of all key stakeholders within the acute, community, residential care, and intellectual disability sectors, whilst also being cognisant of geographical spread and urban/rural representation ; members included those involved in clinical practice, education, administration, research methodology, and two persons representing patients and family carers, two persons representing dementia advocacy groups, as well as a person representing a representative organisation for nursing homes, pharmacists, and a regulatory body.
Target audience	These guidelines are relevant to all doctors, nurses, pharmacists, health and social care professionals, healthcare assistants, and general support staff involved in the care of people with dementia (e.g. porters who provide a “specialling service”).

Table 34: Members of the development group and target audience of the IRE 2019 guideline.

SIGN 2019	
Development group	This guideline was developed by multidisciplinary groups of practicing healthcare professionals including a.o. psychiatrists, consultants in geriatric medicine, general practitioners, lead pharmacists, clinical nurses, health economists, AHP Consultants (Dementia), and carer representatives.
Target audience	This guideline will be of interest to primary and secondary healthcare professionals, community and care home staff involved in the care of patients at risk of, or experiencing, delirium, as well as patients and carers. The guideline applies to all settings: home, long-term care, hospital, and hospice.

Table 35: Members of the development group and target audience of the SIGN 2019 guideline.

NICE 2011/upd2019	
Development group	The guideline development group was convened by the NCGC and chaired by Professor John Young in accordance with guidance from NICE. This included a multidisciplinary guideline committee including practitioners (both specialists in the topic and generalists), service or care providers or commissioners, topic experts, people with personal experience of using health or care services, as well as a subgroup of social care practitioners.
Target audience	• NHS staff responsible for patients in hospital (including critical care) and long-term residential care settings (including primary care healthcare professionals). • Adult hospital patients. • Adults in long-term residential care or a nursing home. • Family and carers of people with or at high risk of developing delirium.

Table 36: Members of the development group and target audience of the NICE 2011/upd2019 guideline.

NHG 2014	
Development group	Hierin nemen naast huisartsen ook vertegenwoordigers van andere beroepsgroepen zitting. De werkgroep bestaat uit maximaal acht personen. Een wetenschappelijke medewerker en senior wetenschappelijk medewerker van de NHG-afdeling Richtlijnontwikkeling en Wetenschap begeleiden de werkgroep.
Target audience	De NHG-Standaarden geven richtlijnen voor het handelen van de huisarts.

Table 37: Members of the development group and target audience of the NHG 2014 guideline.

EUR 2017	
Development group	This European guideline was developed by a group of clinically oriented insomnia specialists from several European countries who are members of the European Insomnia Network with different professional backgrounds. Patient groups were not involved in the development of this guideline.
Target audience	The guideline is meant for physicians and clinical psychologists/psychotherapists who diagnose and treat patients with insomnia, and the target patient population (adults with chronic insomnia disorder).

Table 38: Members of the development group and target audience of the EUR 2017 guideline.

WOREL 2018	
Development group	Les auteurs de cette mise à jour du guide de pratique clinique sont : un psychologue, des médecins généralistes, un collaborateur scientifique FARMAKA/CBIP, et un psychiatre.
Target audience	Les utilisateurs visés par ce guide de pratique clinique sont les médecins généralistes actifs dans les soins de santé ambulatoires en première ligne.

Table 39: Members of the development group and target audience of the WOREL 2018 guideline.

USA 2016	
Development group	Members of the Clinical Guidelines Committee are physicians trained in internal medicine and its subspecialties and include clinical experts and experts in evidence synthesis and guideline development.
Target audience	The target audience for this guideline includes all clinicians, health system leaders, policymakers and the target patient population that includes all adults with chronic insomnia disorder.

Table 40: Members of the development group and target audience of the USA 2016 guideline.

Canada 2018	
Development group	The overall team comprised 9 clinicians (1 family physician, 1 family physician specializing in long-term care, 1 geriatric psychiatrist, 2 geriatricians, 4 pharmacists) and a methodologist
Target audience	Canadian primary care and long term care physicians, pharmacists, nurse practitioners, and specialists who care for patients taking antipsychotics.

Table 41: Members of the development group and target audience of the Canada 2018 guideline.

CAMESA 2011	
Development group	The CAMESA guideline group includes: Pediatric Neurologists, Child Psychiatrists, Pediatric Endocrinologists, Consultant, Mental Health Commission of Canada, Pediatric Cardiologist, a General Internist, Clinical Epidemiologists and a Family Physicians.
Target audience	Target users of this guideline include psychiatrists, pediatricians, developmental pediatricians, neurologists, and family practitioners.

Table 42: Members of the development group and target audience of the CAMESA 2011 guideline.

5 Information and recommendations from guidelines

Formal recommendations, that are supplied with grades of recommendations or levels of evidence, are written in bold.

Supplemental information are shown in plain text.

Comments coming from the bibliography group are written in italic.

Although NICE 2018, NICE 2010, and NHG 2014 guidelines use the GRADE methodology they do not explicitly categorize recommendations in strong and weak recommendations. The strengths of the recommendations are expressed in the wording of the recommendations. The levels of evidence of studies from which recommendations are made are succinctly summarized in plain text. Similarly while EUR 2017 guideline assessed the quality of evidence when formulating its recommendations, the levels of evidence of studies from which recommendations are made is succinctly noted in plain text, and the strengths of the recommendations are expressed in the wording of the recommendation.

Overview of the selected guidelines

The 12 guidelines that were selected for this evidence report on antipsychotic uses all have a different focus.

The APA 2016 guideline focuses on the use of antipsychotics to treat agitation or psychosis in patients with dementia while AUS 2016, NICE 2018 and IRE 2019 are more general guidelines on dementia.

The SIGN 2019, NICE 2010 and NHG 2014 focus on delirium; and EUR 2017, USA 2016, and WOREL 2018 are general guideline on the treatment of insomnia.

The Canada 2018 specifically focuses on antipsychotic deprescribing for dementia and insomnia.

The CAMESA 2011 guideline specifically focuses on monitoring of antipsychotics for children.

5.1 Antipsychotics and BPSD

5.1.1 Summary

Efficacy of antipsychotics for BPSD

All the guidelines recommend non-pharmacological approaches and/or reviewing the clinical response to non-pharmacological interventions prior using pharmacological treatment for people with dementia who develop BPSD.

Antipsychotic medication:

- Should only be offered for the treatment of agitation or psychosis in patients with dementia when symptoms are severe, dangerous, and/or causing significant distress to the patient (APA 2016, AUS 2016, NICE 2018, IRE 2019); or if there is an immediate risk of harm for the patients or carers (AUS 2016, NICE 2018, IRE 2019).
- Pharmacological management should complement, not replace, non-pharmacological approach (AUS 2016, NICE 2018, IRE 2019).
- All the guidelines agree that there is evidence of efficacy for positive effects of antipsychotics on BPSD overall, agitation and aggression. However APA 2016 and AUS 2016 point out that the benefits of antipsychotic medication are at best small.
- AUS 2016 recommends that target symptoms should be identified, quantified and documented.
- IRE 2019 states that any use of antipsychotics for the management of certain non-cognitive symptoms such as walking about, hoarding, fidgeting, inappropriate voiding, verbal aggression, screaming, sexual disinhibition and repetitive actions needs to be particularly justified.

Treatment should be initiated at a low dose to be titrated up to lowest effective dose as tolerated. APA 2016 suggests that the starting dose for frail or older patients will be one-third to one-half the starting dose used to treat psychosis in younger individuals or the smallest size of tablet that is available. Factors such as drug-drug interactions, medication half-life, and renal/hepatic function should be taken into consideration during titration.

There are no published studies on the optimal duration of antipsychotic treatment in individuals with dementia. In an effort to reduce the potential harms of treatment:

- IRE 2019 and APA 2016 recommend to taper and withdraw the drug within 3 or 4 months of initiation respectively.
- NICE 2018 states to use them as short as possible.

The different guidelines also recommend to discontinue treatment with antipsychotics if the person is not getting a clear ongoing benefit from taking them within a relatively short timeframe.

- AUS 2016 mentions a timeframe of one to two weeks.
- APA 2016 recommends a 4-week trial of an adequate dose. Further dose titration may be indicated if a partial response to antipsychotic treatment occurs.
- IRE 2019 states to taper and stop antipsychotics where possible; after discussion with the person and/or their relevant carers.

Canada 2018 is a specific guideline on antipsychotic withdrawal and therefore no specific recommendations on BPSD management are provided.

Safety of antipsychotics

All the guidelines warn on the significant adverse events and risks associated with antipsychotic treatment, including mortality. Antipsychotic use in the context of dementia should be limited only to situations where there is an urgent need for treatment.

All the guidelines agree that the choice of antipsychotic should be made after an individual risk–benefit analysis. This should be assessed by the clinician, and discussed with the person with dementia and their carers/family.

- NICE 2018 provides a decision aid in order to support healthcare professionals discussion about benefits and harms of antipsychotics with patients and their family.
- AUS 2016 and IRE 2019 have made formal recommendations to assess and discuss cerebrovascular risk factors, the possible increased risk of stroke/transient ischaemic attack, and possible adverse effects on cognition.

APA 2016 clearly mentions and discusses the following adverse effects:

- Mortality, metabolic effects, pulmonary effects, cognitive worsening, sedation/fatigue, anticholinergic effects, postural hypotension, cardiovascular risk, prolonged QTc intervals, sexual dysfunction, and extrapyramidal symptoms (parkinsonism, dystonia, tardive dyskinesia).
- Cardiovascular risk is increased for all antipsychotics, with the risk being highest early in the treatment, and of a greater risk with risperidone and olanzapine.
- Metabolic effects of antipsychotics (weight gain, diabetes, dyslipidemia, and metabolic syndrome) are not as strong in individuals with dementia as it is in younger adults. This risk seems highest for olanzapine and risperidone and lowest for aripiprazole and high-potency FGAs.
- Antipsychotic treatment in individuals with dementia appears to carry an increased risk for pneumonia and for venous thromboembolism, with no apparent difference between FGAs and SGAs.

IRE 2019 recons that evidence were insufficient to make a recommendation about the risk of cognitive adverse effects. Risk of harm due to stroke or death in a person with dementia is of sufficient concern without additional consideration of whether antipsychotics hastened cognitive decline.

AUS 2016 and IRE 2019 also recommends to not prescribe antipsychotics for people with Alzheimer's disease, vascular dementia or mixed dementias with mild to moderate BPSD because of the increased risk of cerebrovascular adverse events and death.

All the guidelines particularly warn about the risk of worsening motor features and antipsychotic sensitivity reactions in people with Parkinson's disease or dementia with Lewy bodies taking antipsychotics. IRE 2019 has made specific recommendations in this context and advises to contact a specialist team with experience in treating these people.

Preferential antipsychotic treatment

There is a lack of head-to-head comparison data among antipsychotic medication on efficacy and harms that makes it difficult to designate a specific antipsychotic as being most appropriate to use as a first line agent in treating BPSD symptoms (APA 2016).

Differences in efficacy/harms for diverse antipsychotics as discussed by APA 2016, AUS 2016 and IRE 2019:

- Haloperidol:
  - AUS 2016 mentions that haloperidol decreases behavioural symptoms, aggressive behaviour and agitation during BPSD, with no significant difference in the risk of cardiovascular event and death between haloperidol and SGAs; although not disclosing formal recommendation for/against FGAs.
  - APA 2016 mentions that the risk of mortality with FGAs in individuals with dementia is generally greater than the risk with SGAs. APA 2016 recommends not to use haloperidol as a first-line agent in the absence of delirium. On the basis of the available data on harms, it may be preferable to avoid use of other FGAs as well.
- FGAs are deemed not different from SGAs in the management of behavioural symptoms and agitation, and there is lack of evidence to compare the effects of FGAs and SGAs on psychosis (APA 2016).
- IRE 2019 recommends that where an antipsychotic is required, SGAs should be used as they have less risk of extrapyramidal effects.
- Among SGAs:
  - For psychosis: APA 2016 and AUS 2016 state that risperidone has the strongest evidence for treating psychosis although according to APA 2016 evidence for the efficacy of SGAs suggests low utility in the management of psychosis.
  - For agitation: APA 2016 and AUS 2016 report that risperidone and olanzapine have the strongest evidence for treating agitation/aggression, with weaker evidence for aripiprazole.
  - For behavioural symptoms: AUS 2016 mentions that SGAs display significant positive effects on BPSD overall (strongest evidence for risperidone followed by aripiprazole and then olanzapine and quetiapine). IRE 2019 notes that the evidence for olanzapine was not dissimilar to risperidone. APA 2016 meanwhile suggests low utility for SGAs in behavioural/psychological symptoms with the evidence for aripiprazole substantially better than for the class.
  - Quetiapine: According to APA 2016, there is insufficient information to determine whether it is effective in treating either agitation or psychosis, and it appears not better than placebo in treating BPSD overall. IRE 2019 mentioned that quetiapine was far more commonly used in Ireland due to its lower risks of adverse effects (although less effective).
  - On the potential risk of SGAs: APA 2016 reports a greater risk of mortality with the use of SGAs relative to placebo using pooled data, but does not show significant differences in mortality between placebo and individual antipsychotic medications.
  - APA 2016 reports that there is no information about the benefits or harms of asenapine, clozapine, paliperidone or cariprazine (available from 02-2020 in Belgium) as well as for brexpiprazole, iloperidone, lurasidone, ziprasidone (not available in Belgium) in individuals with dementia.

Administration route:

- AUS 2016 recommends that oral medication should be offered before parenteral medication. If parenteral treatment is necessary (i.e. control of violence and extreme agitation) olanzapine and i.m. administration are preferred because it is safer than i.v.

administration. Similar recommendation was made by IRE 2019 regarding general psychotropic medications.

- APA 2016 recommends to not use a long-acting injectable antipsychotics unless it is otherwise indicated for a co-occurring chronic psychotic disorder. In general the potential harms of a long-acting formulation were viewed as greater than the potential benefits.
- APA 2016 also specifies that if i.m. antipsychotic is indicated for short-term use in individuals who are unable to take oral medications or in emergent situations, care should be taken to use a short-acting preparation.
- APA 2016 considers potential benefits of long-acting injectable antipsychotics in some selected circumstances (this may aid adherence and minimize struggles over the taking of oral medications). If used, caution is needed to assure that oral medication is well tolerated before shifting to a long-acting injectable form.

5.1.2 APA 2016

5.1.2.1 Antipsychotic treatment

APA recommends that nonemergency antipsychotic medication should only be used for the treatment of agitation or psychosis in patients with dementia when symptoms are severe, are dangerous, and/or cause significant distress to the patient. (1B-Recommendation with moderate strength of evidence.**)**

Statement based on moderate strength evidence in individuals with dementia that the benefits of antipsychotic medication are small. In addition, consistent evidence, predominantly from large observational studies, indicates that antipsychotic medications are associated with clinically significant adverse effects, including mortality, among individuals with dementia. The overall strength of evidence is graded as moderate on the basis of this balance of benefits and harms.

Expert consensus suggests that use of an antipsychotic medication in individuals with dementia can be appropriate, particularly in individuals with dangerous agitation or psychosis, and can minimize the risk of violence, reduce patient distress, improve the patient's quality of life, and reduce caregiver burden. However, in clinical trials, the benefits of antipsychotic medications are at best small, whether assessed through placebo/controlled trials, head-to-head comparison trials, or discontinuation trials.

If agitation or psychosis results in significant negative consequences to the patient and to his or her quality of life, the potential for benefits of an antipsychotic medication should be weighed against the potential for harmful effects. This is particularly important given the modest benefits and demonstrated risks of antipsychotic treatment in clinical trials and in less rigorous observational and cohort studies. In emergent situations, when there is risk of harm to the patient or others, acute treatment may need to proceed to allow the immediate crisis to be stabilized. However, in other contexts, discussing potential benefits and harms with the patient's family or other surrogate decision makers and eliciting their concerns, values, and preferences are essential in helping them arrive at an informed decision about treatment that will be person-centered and focused on overall quality of life. Patients may also be able to appreciate these factors and offer input on their current and future treatment preferences depending on their level of cognitive impairment. Open-ended questioning and discussion will likely be helpful in identifying potential benefits and side effects of treatment that are most important to the person living with dementia. For example, individuals may be particularly concerned about effects of the medication on their remaining capabilities in terms of cognition and communication. On the other hand, calming effects of medication may be viewed as

particularly helpful if they ease distressing anxiety or suspiciousness or alleviate aggressive episodes, allowing individuals to remain safely in their homes. If medication calms the individual for even a few hours, it can facilitate attendance at an adult day program, giving them pleasure through program activities and granting a caregiver a few hours of respite. In all settings of care, such preferences of patients, family, and other caregivers should be respected, documented, and reviewed in ongoing discussions as part of the treatment planning process

APA recommends reviewing the clinical response to nonpharmacological interventions prior to nonemergency use of an antipsychotic medication to treat agitation or psychosis in patients with dementia. (1C-Recommendation with low strength of evidence.**)**

In statements which address treatment planning and review of response to nonpharmacological interventions, the group chose not to comment on specific psychopharmacological medications other than antipsychotic medications. Although the guideline writing group only reviewed evidence on antipsychotic medications during the development process, available systematic reviews suggested that the harms of nonpharmacological interventions were minimal.

5.1.2.2 Risks and/or adverse effects of antipsychotics

APA recommends that before nonemergency treatment with an antipsychotic is initiated in patients with dementia, the potential risks and benefits from antipsychotic medication be assessed by the clinician and discussed with the patient (if clinically feasible) as well as with the patient's surrogate decision maker (if relevant) with input from family or others involved with the patient. (1C-Recommendation with low strength of evidence**).**

If agitation or psychosis results in significant negative consequences to the patient and to his or her quality of life, the potential for benefits of an antipsychotic medication should be weighed against the potential for harmful effects. With antipsychotic medications, the drugs' potential for harms must be balanced against their modest evidence of benefit. As with any drug, this requires assessing the benefits and harms of prescribing the drug for an individual patient.

No studies are available that assess the harms of withholding or delaying a trial of antipsychotic medication for individuals with agitation or psychosis in association with dementia. However, clinical observations suggest that such delays could lead to poorer outcomes for some individuals, such as physical injury to themselves or others, disruptions of relationships with family or other caregivers, or loss of housing due to unmanageable behavioral and psychological symptoms.

The subtype of dementia is another important factor to establish before the potential benefits and risks of antipsychotic treatment are considered. For example, in individuals with Lewy body dementia and Parkinson's disease dementia, the risks of extrapyramidal side effects of antipsychotic medication and the potential for cognitive worsening will be significantly greater than in individuals with other types of dementia and in some instances have been reported to include irreversible cognitive decompensation or death.

Other benefits and risks of treatment will relate to the individual characteristics and circumstances of the patient. For example, individuals with preexisting diabetes have an increased risk of hospitalization for hyperglycemia with antipsychotic initiation, whereas those with preexisting problems with gait may be at an increased risk for falls if they develop extrapyramidal side effects. Lowering of blood pressure and development of orthostasis can also contribute to falls, particularly

in combination with use of other medications or dehydration. Other co-occurring conditions such as cerebrovascular disease or cardiac disease may also influence the risk of side effects from antipsychotic medications.

The strength of evidence for harms of antipsychotic agents ranges from insufficient to high depending on the specific adverse effect; however, on the whole, there is consistent evidence that antipsychotics are associated with clinically significant adverse effects, including mortality. In addition to mortality, other serious adverse events of antipsychotic medications in individuals with dementia have been reported, including stroke, acute cardiovascular events, metabolic effects, and pulmonary effects. The strength of the evidence is low for stroke, but pooled analyses for risperidone and olanzapine suggest an increase in risk relative to placebo. The strength of the evidence on acute cardiovascular events is also low; however, there is some evidence of increased risk for all antipsychotics, with the risk being highest early in the treatment, and of a greater risk with risperidone and olanzapine than with other agents. Although the evidence on metabolic effects of antipsychotics (including weight gain, diabetes, dyslipidemia, and metabolic syndrome) is not as strong in individuals with dementia as it is in younger adults, the existing evidence is in keeping with what is largely known about this risk: highest for olanzapine and risperidone and lowest for aripiprazole and high-potency FGAs. Antipsychotic treatment in individuals with dementia also appears to carry an increased risk for pneumonia and for venous thromboembolism, but the strength of this evidence is low, with no apparent difference between FGAs and SGAs. Evidence is variable for other adverse effects, including cognitive worsening, sedation/fatigue, anticholinergic effects, postural hypotension, prolonged QTc intervals, sexual dysfunction, and extrapyramidal symptoms (e.g., parkinsonism, dystonia, tardive dyskinesia). However, case reports and observational data suggest a substantial increase in the likelihood of adverse effects when individuals with Lewy body dementia or Parkinson's disease dementia receive antipsychotic treatment. In some instances, these adverse effects have included irreversible cognitive decompensation or death.

5.1.2.3 Antipsychotic dosage

APA recommends that if a risk/benefit assessment favors the use of an antipsychotic for behavioral/psychological symptoms in patients with dementia, treatment should be initiated at a low dose to be titrated up to the minimum effective dose as tolerated. (1B-Recommendation with moderate strength of evidence.**)**

Five published randomized controlled trials (RCTs) assessed differing doses of antipsychotic medications in managing behavioral and psychological symptoms of dementia, but these studies were of varying quality, had inconsistent findings, and often showed no therapeutic benefit at the highest dose.

In terms of decisions about doses of antipsychotic medications, there is strong evidence that SGAs are associated with clinically significant dose-related adverse effects. Thus, if medications are begun at a low dose and increased gradually depending on clinical response, adverse effects may be minimized. On the other hand, it is possible that harms to the patient or others may occur if the response to treatment is delayed by underdosing of medication, particularly in emergency situations.

After a risk-benefit assessment and discussion with the family or other surrogate decision makers, if antipsychotic treatment is clinically indicated on a nonemergent basis, it is important to begin the medication at a low dose. Typical starting doses for frail or older patients will be one-third to one-half the starting dose used to treat psychosis in younger individuals or the smallest size of tablet that is available. Doses should be titrated gradually to the lowest dose associated with clinical response.

Factors such as drug-drug interactions, medication half-life, and renal and hepatic function should be taken into consideration during titration of medications to avoid dose adjustments that are too rapid. Because of variations in the metabolism of antipsychotic medications and variations in the time needed to reach steady-state medication levels, it is not possible to predict the time needed to reach an adequate dose of medication for an individual patient. However, doses used in clinical trials in patients with dementia can serve as a guide to the typical dose of medication required with each agent.

5.1.2.4 Duration of antipsychotic treatment

As a full section on withdrawal of antipsychotics in the context of BPSD has been developed in this document, the detailed discussion of the two following statements has been included in the corresponding section.

APA recommends that in patients with dementia with agitation or psychosis, if there is no clinically significant response after a 4-week trial of an adequate dose of an antipsychotic drug, the medication should be tapered and withdrawn. (1B-Recommendation with moderate strength of evidence.**)**

If there is no clinically significant response within 4 weeks of reaching a typical therapeutic dose of medication, the medication should be tapered and stopped to avoid potential harms of medication treatment without any offsetting benefit.

If a partial response to antipsychotic treatment occurs, further dose titration may be indicated depending on whether side effects are present and on the relative balance of benefits and harms for the patient.

APA recommends that in patients with dementia who show adequate response of behavioral/psychological symptoms to treatment with an antipsychotic drug, an attempt to taper and withdraw the drug should be made within 4 months of initiation, unless the patient experienced a recurrence of symptoms with prior attempts at tapering of antipsychotic medication. (1C-Recommendation with lox strength of evidence.**)**

There are no published studies on the optimal duration of antipsychotic treatment in individuals with dementia, and experts are divided in their opinion on optimal treatment duration.

Even when benefit is apparent, patients' symptoms and need for an antipsychotic medication may change. Consequently, in an effort to reduce the potential harms of treatment, an attempt should be made to taper the antipsychotic medication within 4 months of treatment initiation. However, earlier attempts at tapering the medication may also be warranted given the ongoing risk of harms with continued treatment.

5.1.2.5 Specific antipsychotic medication and administration route

APA recommends that in the absence of delirium, if nonemergency antipsychotic medication treatment is indicated, haloperidol should not be used as a first-line agent. (1B-Recommendation with moderate strength of evidence.**)**

The data on harms in observational and administrative database studies sometimes focused on specific medications and sometimes on the class of FGAs as compared with SGAs. Since haloperidol was the most commonly used agent among FGAs, it was difficult to determine whether other FGAs had a comparable risk of harms. For this reason, the group chose to recommend that haloperidol not be used as a first-line agent, rather than recommending against use of any FGA as a first-line agent. On the basis of the available data on harms, it may be preferable to avoid use of other FGAs as well.

If an antipsychotic medication is being initiated, a number of factors warrant consideration when a specific agent is being selected. For example, patients, surrogate decision makers, or family members may express a preference for a specific medication or note concerns about specific side effects (e.g., weight gain, diabetes, sedation, additional cognitive impairment). Such preferences should be considered in concert with the other factors noted below. Barriers to choice of specific medications are also common and typically involve regulatory stipulations, cost considerations, formulary coverage, or preauthorization requirements.

The side effect profile of a medication is another important factor in selecting a specific agent. Anticholinergic effects of antipsychotic medications can worsen cognition or narrow angle glaucoma as well as contribute to urinary retention and constipation. The frequency of these adverse effects will vary depending on the antipsychotic medication that is chosen. Features that individuals in the expert survey noted may influence their prescribing of specific medications include the long half-life, potential for drug-drug interactions, and partial agonist mechanism of action and rates of akathisia with aripiprazole; greater likelihood of extrapyramidal effects and hyperprolactinemia with risperidone; anticholinergic effects, sedation, metabolic effects, and weight gain with olanzapine; and QTc prolongation and changes in absorption with food for ziprasidone.

As with all medication-related decisions, choice of a medication will also depend on factors such as the patient's prior responses to a specific agent; co-occurring medical conditions; the pharmacokinetic properties of the medication, such as absorption and half-life; and the potential for drug/drug interactions and additive side effects with other medications that the patient is already taking. Some antipsychotic medications have active metabolites of the parent drug that may be relevant in medication selection. For example, nor quetiapine has significantly greater anticholinergic side effects than quetiapine; interactions of other medications with quetiapine's primary metabolic pathway (i.e., cytochrome P450 3A4) can also worsen anticholinergic effects.

FGAs/SGAs

Effect sizes of second generation antipsychotics (SGAs) range from nonsignificant to small depending on symptom domain (agitation, psychosis, and overall behavioral/psychological symptoms) and agent. First-generation antipsychotics (FGAs) are deemed not different from SGAs in the management of agitation and overall behavioral/psychological symptoms, but the strength of the evidence for the comparisons is low, and haloperidol is the predominant agent that has been studied. There is not enough evidence to compare the effects of FGAs and SGAs on psychosis.

The potential side effects of specific medications are also important considerations. In studies using administrative databases that have examined a wide range of antipsychotics, the risk of mortality with an FGA in individuals with dementia was generally greater than the risk with an SGA. Head-to-head comparison data from randomized trials are limited, and the bulk of the available evidence on FGAs relates to haloperidol.

Specific SGA?

On the basis of both strength of the research evidence and effect size (moderate and small, respectively), the best evidence for SGA efficacy is in treatment of agitation, results that are driven by findings with risperidone treatment. Although evidence for the efficacy of SGAs suggests low utility (low strength of evidence for a very small effect) in the management of psychosis, the evidence for risperidone is substantially better than for the class (moderate strength of evidence for a small effect). Likewise, the efficacy evidence for SGAs in the management of overall behavioral/psychological symptoms also suggests low utility (high strength of evidence for a very small effect); the evidence for aripiprazole is substantially better than for the class (moderate strength of evidence for a small effect).

Among the SGAs, the choice of a specific medication involves consideration of a number of factors. As described in the sections "Potential Benefits and Harms" earlier in this guideline and "Review of Supporting Research Evidence" in Appendix A, data from randomized placebo-controlled trials suggest efficacy for risperidone in treating psychosis and for risperidone, olanzapine, and aripiprazole in treating agitation. There was insufficient information from trials of quetiapine to determine whether it was efficacious in treating either agitation or psychosis, and it appeared to be no better than placebo in treating behavioral or psychological symptoms of dementia overall.

In terms of potential risks, the pooled data from randomized trials indicate a greater risk of mortality with use of an SGA relative to placebo but do not show significant differences in mortality between placebo and individual antipsychotic medications. However, the total number of deaths in each study is small. When pooled placebo-controlled RCT data are considered along with data from larger observational cohort studies and research using administrative databases, the evidence suggests that there may be differences in risk between individual antipsychotic agents, but confidence intervals are overlapping and effects are dose dependent. In addition, the number of individuals who had received aripiprazole was very small relative to the number who had received risperidone or olanzapine.

There is no information about the benefits or harms of asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, paliperidone, or ziprasidone in individuals with dementia.

The lack of head-to-head comparison data among antipsychotic medications on efficacy and on harms makes it difficult to designate a specific antipsychotic as being most appropriate to use as a first line agent in treating agitation or psychosis in individuals with dementia.

In individuals with Lewy body dementia or Parkinson's disease dementia, quetiapine and clozapine were noted as the most appropriate medications because of the risk of worsened motor symptoms with the other antipsychotic agents.

Long acting injectable antipsychotics

APA recommends that in patients with dementia with agitation or psychosis, a long acting injectable antipsychotic medication should not be utilized unless it is otherwise indicated for a co-occurring chronic psychotic disorder. (1B-Recommendation with moderate strength of evidence.**)**

No studies have examined the use of long-acting injectable antipsychotic medications in individuals with dementia. However, the longer duration of action of these medications suggests that they would be associated with an increased risk of harm relative to oral formulations or short-acting parenteral formulations of antipsychotic medications, particularly in frail elders.

There was an acknowledgement of potential benefits of a long-acting antipsychotic medication for adherence in some selected circumstances. Nevertheless, for the preponderance of patients, the potential harms of a long-acting formulation were viewed as greater than the potential benefits. However, there was recognition that under selected circumstances, this balance may shift. In particular, some individuals will have had a chronic psychotic disorder, such as schizophrenia, that preceded the onset of dementia, and clinical opinion suggests that these patients may have continuing benefits of long-acting antipsychotic medication.

The available formulations of the antipsychotic may also play a role in the medication selection process. For example, for patients who have difficulty swallowing pills, it would be preferable to choose a medication that is available as a rapidly dissolving tablet or oral concentrate formulation.

If an intramuscular formulation of antipsychotic is indicated for short-term use in individuals who are unable to take oral medications or in emergent situations, care should be taken to use a short acting parenteral preparation.

The long-acting injectable decanoate formulation of haloperidol and other long-acting injectable formulations of antipsychotic medications are likely to carry a greater risk of side effects in individuals with dementia. However, individuals with a chronic psychotic disorder, such as schizophrenia, may benefit from treatment with a long-acting injectable antipsychotic medication if they have a history of poor adherence and have tolerated oral formulations of medication. In other selected circumstances, a low dose of a long-acting injectable antipsychotic may aid adherence and minimize struggles over the taking of oral medications. Individuals with a preexisting chronic psychotic illness may also have adherence enhanced by administering long-acting medication. Nevertheless, if used, caution is needed to assure that oral medication is well tolerated before shifting to a long-acting injectable. Furthermore, care must still be taken in dosing of long-acting intramuscular formulations because of aging-related changes in medication pharmacokinetics, changes in body composition, and impairments in renal or hepatic function.

5.1.3 AUS 2016

People with dementia who develop behavioural and psychological symptoms of dementia should usually be treated using non-pharmacological approaches in the first instance. Pharmacological intervention should usually only be offered first if the person, their carer(s) or family is severely distressed, pain is the suspected cause, or there is an immediate risk of harm to the person with dementia or others (i.e., very severe symptoms). If pharmacological management is used, this should complement, not replace, non-pharmacological approaches. (PP-Practice point.**)**

People with dementia and severe behavioural and psychological symptoms of dementia (i.e., psychosis and/or agitation/aggression) causing significant distress to themselves or others, may be offered treatment with an antipsychotic medication. Risperidone has the strongest evidence for treating psychosis. Risperidone and olanzapine have the strongest evidence for treating agitation/aggression, with weaker evidence for aripiprazole.

The following conditions should also be met:

• There should be a full discussion with the person with dementia and their carers and family about the possible benefits and risks of treatment. In particular, cerebrovascular risk factors should be assessed and the possible increased risk of stroke/transient ischaemic attack and possible adverse effects on cognition discussed.

• Target symptoms should be identified, quantified and documented.

• The effect of comorbid conditions, such as depression, should be considered.

• The choice of antipsychotic should be made after an individual risk–benefit analysis.

• The dose should be initially low and titrated upwards if necessary.

• If there is no efficacy observed within a relatively short timeframe (usually one to two weeks), treatment should be discontinued.

- **…**

(EBR Moderate-Evidence-based recommendation with moderated strength of evidence.**)**

5.1.3.1 Classical antipsychotics

The NICE Guideline Committee considered evidence for haloperidol compared to placebo from five studies of haloperidol for agitation in dementia. No additional studies were identified. Haloperidol decreased behavioural symptoms, aggressive behaviour and agitation. A 2005 meta-analysis of published and unpublished studies showed haloperidol was associated with an increase in the risk of death at a rate similar to that of atypical antipsychotics, although it was not statistically significant. Data from an observational study indicated no significant difference in the risk of cardiovascular events between haloperidol and atypical antipsychotics. The overall quality of evidence was rated as moderate.

5.1.3.2 Atypical antipsychotics

The current review identified a 2011 meta-analysis of 17 trials of atypical antipsychotics conducted over a six to 12 week follow-up. The analysis demonstrated that atypical antipsychotics had small but statistically significant positive effects on behavioural and psychological symptoms of dementia overall, with the strongest evidence for risperidone, moderate evidence for aripiprazole and less evidence for olanzapine and quetiapine. Risperidone had the strongest evidence for decreasing psychosis symptoms. Olanzapine and risperidone had the strongest evidence for a small, but statistically significant improvement in agitation, with less evidence for aripiprazole.

A large study reporting on the quality of life of people with dementia found no difference in carer-rated quality of life for subjects receiving atypical antipsychotic treatment compared to placebo (the Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease, CATIE-AD). No additional studies of atypical antipsychotics for behavioural and psychological symptoms of dementia published to November 2014 were identified.

A 2005 meta-analysis of 15 published and unpublished studies of atypical antipsychotic use in dementia indicated a statistically significant increased risk of mortality (3.5 per cent atypical

antipsychotics vs 2.3 per cent placebo; OR 1.54, 95 per cent CI 1.06 to 2.23).The 2011 review found a statistically significant increased risk of cardiovascular events for olanzapine (OR 2.33, 95 per cent CI 1.08 to 5.61) and risperidone (OR 2.08, 95 per cent CI 1.38 to 3.22), but not quetiapine or aripiprazole.

5.1.3.3 Risks of antipsychotics

People with Alzheimer's disease, vascular dementia or mixed dementias with mild to moderate behavioural and psychological symptoms of dementia should not usually be prescribed antipsychotic medications because of the increased risk of cerebrovascular adverse events and death. (EBR Moderate-Evidence-based recommendation with moderated strength of evidence.**)**

As far as possible, antipsychotics should be avoided in people with Dementia with Lewy Bodies due to the risk of severe untoward reactions, particularly extrapyramidal side effects. Acetylcholinesterase inhibitors could be considered. If antipsychotics are used for severe behavioural and psychological symptoms of dementia, atypical or second generation antipsychotics with low propensity to cause extrapyramidal side effects should be used; quetiapine and olanzapine are considered to have the best tolerability5. Healthcare professionals should use low dosage and closely monitor for adverse effects. (PP-Practice point.**)**

5.1.3.4 Intramuscular atypical antipsychotics

If medications are necessary for the control of violence, aggression and extreme agitation in people with dementia, oral medication should be offered before parenteral medication. (PP-Practice point.**)**

There is a paucity of evidence regarding the efficacy and safety of parenteral medication in behavioural emergencies. However, in certain rare situations, parenteral medication may be required for the management of people with dementia with extreme behavioural and psychological symptoms of dementia. (PP-Practice point.**)**

If parenteral treatment is necessary for the control of violence, aggression and extreme agitation, intramuscular administration is preferable because it is safer than intravenous administration. Intravenous administration should be used only in exceptional circumstances. Vital signs should be monitored after parenteral treatment. Health professionals should be aware that loss of consciousness can be mistaken for sleep. If the person appears to be or is asleep, more intensive monitoring is required because of the risk of loss of consciousness. (PP-Practice point.**)**

If parenteral medication is necessary for the control of violence, aggression and extreme agitation in people with dementia, olanzapine or lorazepam are preferred. Wherever possible, a single agent should be used in preference to a combination. (CBR-Consensus-based recommendation**)**

The NICE Guideline Committee recommended intramuscular olanzapine for behavioural control in

situations where there is a significant risk of harm, based on one trial considered of moderate quality. One additional study of intramuscular aripiprazole was identified in this evidence update. As this antipsychotic is not available in this formulation in Australia, these data were not reviewed.

5.1.4 NICE 2018

Nice 2018 guideline on dementia is an extensive guideline on assessment, management and support for people living with dementia and their carers. The recommendations discussed below concerning the use of antipsychotics are reported from the "Interventions for treating illness emergent non-cognitive symptoms in people living with dementia" subheading of the full length original document. Non-cognitive symptoms in people living with dementia presented in this guideline are anxiety and depression, agitation and aggression, and sleep problems. Pharmacological interventions for treating these non-cognitive symptoms may include: • Antipsychotics • Cholinesterase inhibitors • Memantine • Carbamazepine • Valproate (mood stabilisers) • Antidepressants • Anxiolytics • Propranolol.

Recommendations regarding antipsychotic use more particularly concern agitation, aggression, distress and psychosis as symptom subclass.

There are a range of potential treatments for the non-cognitive symptoms of dementia which can be divided into two groups: pharmacological and non-pharmacological interventions. Pharmacological interventions are targeted to the problematic behaviour of the person with dementia and include the use of antidepressants, antipsychotics, mood stabilisers and drugs to modify sleep patterns. In contrast, non-pharmacological interventions take a wider view and may include approaches aimed at: resetting sleep patterns using bright light therapy or by increasing the activity levels of the person with dementia; calming and distracting an agitated person; and altering the carer's behaviour to better cope with and manage the person with dementia. In addition, anxiety and depression may be treated using cognitive behavioural therapy, multisensory stimulation, relaxation and animal-assisted therapies.

5.1.4.1 Antipsychotics as pharmacological intervention

Antipsychotics quality of evidence: The committee agreed that there were good quality studies with large sample sizes looking at both antipsychotic efficacy and the effects of antipsychotic discontinuation. There were also long-term studies looking at the effects of antipsychotics on mortality, and therefore the committee agreed there was a robust evidence base behind the recommendation made.

Only offer antipsychotics for people living with dementia who are either: at risk of harming themselves or others or experiencing agitation, hallucinations or delusions that are causing them severe distress.

The committee agreed there was a clear pattern in the evidence for antipsychotics. They showed clear evidence of efficacy (reductions in agitation and NPI scores), but also evidence of significant harms, with increase in rates of all types of adverse events, and mortality. The committee agreed that the significant risks of treatment meant their use should be restricted as much as possible, and limited only to situations either where there is an urgent need for treatment to prevent harm to the person living with dementia or others, or where the use is for the treatment of an underlying psychosis, and would be equally appropriate in a person who does not have dementia. The committee also agreed that a specific discussion is necessary with the person living with dementia and their carers/family members about the benefits and harms of treatment.

It was noted that the majority of the included studies were for noncognitive symptoms such as agitation or similar behavioural symptoms, rather than as treatments for psychosis.

Before starting antipsychotics, discuss the benefits and harms with the person and their family members or carers (as appropriate).

In order to support healthcare professionals discussion about benefices and harms of antipsychotic with patients and their family, Nice guideline on dementia provided the following decision aid:

*"*Antipsychotics for treating agitation, aggression and distress in people living with dementia".

Role of the decision aid

Choosing whether or not to have an antipsychotic is a highly preference-sensitive decision. It involves trading-off possible clinical benefits against possible adverse effects and other consequences and features of treatment. The NICE decision aid can help healthcare professionals explain these trade-offs. The person facing the decision and their family members or carers (as appropriate) can review the written information before deciding. As well as describing the common and serious adverse effects of antipsychotics, the decision aid includes icon arrays (diagrams) to illustrate the expected absolute effects on the risk of stroke and death.

What are the options?

People living with dementia can sometimes become aggressive or very agitated. They might also hear voices or see things that are not really there (called hallucinations) or believe that something is real or true when it is not (called delusions). This can be very distressing for them and their carers, and the person may become violent. Several things should be tried first to help calm the person (for example music, exercise or aromatherapy). Antipsychotic medicines (often just called 'antipsychotics') can help control hallucinations and delusions and will also sedate the person (make them feel drowsy).

What does NICE recommend?

NICE recommends that a person should only try an antipsychotic if they are at risk of harming themselves or others, or if they are severely distressed. The antipsychotic should be tried alongside other activities to try to help their distress. It should be used at the lowest dose that helps the person, and for the shortest possible time. The person should be assessed at least every 6 weeks and the antipsychotic should be stopped if it is not helping or is no longer needed. The person does not have to have an antipsychotic. There are pros and cons, which this decision aid will help your healthcare professional to explain.

How likely is the person to benefit?

Most people who take an antipsychotic will be less agitated (this will depend on the dose used). They will be much less likely to harm themselves or others. Many people with hallucinations or delusions will find these go or are much less troubling, but if they have difficulties communicating it might be hard to tell if the antipsychotic is helping with this. It is not possible to know in advance what will happen to any individual person.

What are the side effects of antipsychotics?

The most common side effects of antipsychotics are:

- feeling sleepy or less alert (although some people have difficulty falling or staying asleep)
- headache
- changes in appetite, and weight gain
- symptoms like those of Parkinson's disease. These may include slowness or difficulty in moving, a sensation of stiffness or tightness of the muscles (making the person's movements jerky), and sometimes even a sensation of movement 'freezing up' and then restarting. The person may develop a slow shuffling walk, a tremor, increased saliva or drooling, and a loss of expression on the face. Not everyone will get these but many people will. The higher the dose of antipsychotic and the longer the person takes it, the more likely they are to get these side effects. There are also other less common side effects, and your healthcare professional can explain further. The most serious side effects include an increased risk of stroke and an increased risk of death. The diagrams on pages 3 and 4 show how likely this is to happen. It is not possible to know in advance what will happen to any individual person.

Other things to think about

- How are antipsychotics taken?

Antipsychotics are usually taken as a tablet or a liquid medicine, once or twice a day.

- Off-label use of antipsychotics

Only risperidone (for up to 6 weeks use) and haloperidol have a licence to treat these sorts of problems in people living with dementia. Other antipsychotics may still help, and your healthcare professional is allowed to prescribe them, but using them or using risperidone for longer than 6 weeks would be an 'off-label 'use. There is more information about medicines licensing on NHS Choices. Your healthcare professional can explain further about this and what it means for your decision.

When using antipsychotics:

Use the lowest effective dose and use them for the shortest possible time.

… It agreed that treatment should be restricted to the lowest effective does and the shortest possible time, in order to reduce adverse events as far as possible.

5.1.4.2 Antipsychotic treatment duration

Stop treatment with antipsychotics:

- **if the person is not getting a clear ongoing benefit from taking them**
- **and after discussion with the person taking them and their family members or carers (as appropriate).**

The committee agreed that it was necessary to regularly review people taking antipsychotics to ensure the treatment is still necessary, and to encourage a discussion about discontinuation wherever this is possible.

5.1.4.3 Risks of antipsychotics

Be aware that for people with dementia with Lewy bodies or Parkinson's disease dementia, antipsychotics can worsen the motor features of the condition, and in some cases cause severe antipsychotic sensitivity reactions.

It was also agreed to be appropriate to add a specific recommendation in the guideline around the risk of worsening motor features and antipsychotic sensitivity reactions in people with Parkinson's disease dementia or dementia with Lewy bodies taking antipsychotics. This recommendation links to the NICE guideline on Parkinson's disease, which contains additional recommendations on this topic

5.1.4.4 Complementary non-pharmacological approach

…As initial and ongoing management, offer psychosocial and environmental interventions to reduce distress in people living with dementia.

Ensure that people living with dementia can continue to access psychosocial and environmental interventions for distress while they are taking antipsychotics and after they have stopped taking them. For people living with dementia who experience agitation or aggression, offer personalised activities to promote engagement, pleasure and interest.

The committee agreed that reactions which are classified as behavioural symptoms of dementia were often responses to other underlying problems in the context of difficulty in communicating needs effectively. For example, people with pain or delirium or who are responding to inappropriate care may be labelled as having behavioural problems when in fact there is a need to treat the underlying pain or delirium, and/or to improve the environment. The committee therefore agreed that, before any interventions for distress are considered, it is important that a thorough structured assessment of the person and their environment be conducted to try and identify and address the underlying causes of distress. If this assessment is unsuccessful in identifying approaches that can resolve the problem, then in view of the clearly established harms of antipsychotics, the committee agreed it was appropriate that nonpharmacological management (both environmental and psychosocial) be offered before any thought is given to the use of antipsychotics.

It also agreed that the use of an antipsychotic was not a reason to discontinue non-pharmacological treatment, and that people either taking or being discontinued from antipsychotics should have access to the same range of non-pharmacological options as people not being treated with antipsychotics.

5.1.5 IRE 2019

IRE 2019 guideline on dementia discusses several general considerations as well as different specific psychotropic medications for non-cognitive symptoms of people with dementia. Psychotropic medications included were antipsychotics; antidepressants; anticonvulsants; benzodiazepines and z-

drugs; and acetylcholinesterase inhibitors (donepezil, rivastigmine and galantamine) and memantine when used for non-cognitive symptoms. The recommendations discussed below only concern the general aspect of the medication and antipsychotic medications.

The evidence based recommendations provided by IRE 2019 guideline were adapted and adopted from existing international guidelines that are already discussed in the present document as well as on recent systematic empiric evidence including : systematic reviews, meta-analyses and randomised controlled trails.

Table 2.6: International guidelines adapted for this National Clinical Guideline

Year	Guideline developer	Title
2016	National Health and Medical Research Council (NHMRC)	Clinical Practice Guidelines and Principles of Care for People with Dementia.
2016	American Psychiatric Association (APA)	Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients with Dementia.
2018	National Institute for Health and Care Excellence (NICE)	Dementia Assessment, management and support for people living with dementia and their carers.

Together, non-cognitive symptoms and responsive behaviours are often termed Behavioural and Psychological Symptoms of Dementia, or BPSD. In this guideline, we will often use the term non-cognitive symptoms in preference to BPSD. Nearly all people with dementia will develop one or more non-cognitive symptoms as the dementia progresses.

5.1.5.1 Non-pharmacological interventions

Whilst non-pharmacological interventions are not within the scope of this guideline, they clearly are "the other side of the coin" to pharmacological interventions, such that the provision of timely and appropriate non-pharmacological interventions may obviate the need for medications, or work in tandem with medications, or allow medications to be reduced once an acute episode of distress has settled.

At all times, and throughout the dementia trajectory, an individualised and person-centred approach should be promoted and practiced by all doctors, nurses, pharmacists, and health and social care professionals. (Good practice point)

Prior to considering any psychotropic medication in a person with dementia, a comprehensive assessment should be performed, by an appropriately trained healthcare professional. (Strong recommendation, low quality of evidence)

The authors noted great variation in how the same type of intervention was defined and applied, the follow-up duration, the type of outcome measured, and the typical modest sample size. Overall, they concluded that **music therapy** and **behavioural management techniques** were effective for reducing behavioural disturbances.

Non-pharmacological interventions should be used initially to treat non-cognitive symptoms in a person with dementia, unless there is severe distress, or an identifiable risk of harm to the person and/or others. (Strong recommendation, high quality of evidence)

5.1.5.2 Antipsychotics as pharmacological intervention

There was general consensus across guidelines that antipsychotic medications should only be used in certain situations.

Antipsychotic medication should be used with caution and only in cases where there is aggression, agitation or psychosis that either causes an identifiable risk of harm to the person with dementia and/or others or causes severe distress to the person. (Strong recommendation, high quality of evidence).

There is little evidence that antipsychotics are effective in the treatment of certain non-cognitive symptoms such as walking about, hoarding, fidgeting, inappropriate voiding, verbal aggression, screaming, sexual disinhibition and repetitive actions. Therefore, any use in the management of these symptoms needs to be particularly justified. (Good practice point)

The GDG felt that in all cases when doctors deem it necessary to prescribe an antipsychotic medication, the Summary of Products Characteristics (SmPC) and specific medication licence should be consulted, noting that most use will be off-label.

Symptoms that are likely/not likely to respond:

Several guidelines stated specific symptom indications for antipsychotics, and these were very consistent in naming **psychosis** and **agitation** as indications for antipsychotics. **Aggression** was also named as an indication in most of these.

Tampi et al. (2016) in a systematic review of 16 meta-analyses that evaluated the use of antipsychotics in individuals with dementia found that antipsychotics demonstrated modest efficacy in treating psychosis, aggression and agitation in individuals with dementia. They noted that their use in individuals with dementia is often limited by their adverse effect profile.In contrast, antipsychotic medications have been shown to have little effect on several non-cognitive symptoms and behaviours, including walking about, hoarding, repetitive actions, vocal disruptions, inappropriate behaviour, tugging, fidgeting, and inappropriate voiding. Reflecting this, the MHBC guideline (2012) states that the following behaviours are not usually amenable to antipsychotic treatment: walking about, vocally disruptive behaviour, inappropriate voiding, hiding and hoarding, inappropriate dressing/undressing, eating inedible objects, repetitive activity, tugging at seatbelts, pushing wheelchair bound residents.

Severity of symptoms that indicate antipsychotics may be needed:

Several guidelines stated that symptoms needed to be **significant or severe**, and/or cause **significant (severe)** distress to warrant an antipsychotic, with minor variations in the exact wording used. Tampi et al. (2016) similarly noted that the use of antipsychotics should be reserved for severe symptoms that have failed to respond adequately to non-pharmacological management strategies. Two guidelines also stated that an indication for the use of antipsychotics was the **risk of harm**, either to the person with dementia or to others.

5.1.5.3 Risks and adverse effects of antipsychotics

Cerebrovascular risk and mortality

People with Alzheimer's disease, vascular dementia or mixed dementias with *mild to moderate* non-cognitive symptoms should NOT be prescribed antipsychotic medication due to the increased risk of cerebrovascular adverse events and death. (Strong recommendation, high quality of evidence)

One guideline advised general "caution" with antipsychotics (APA, 2016). Some guidelines specified the increased risk of cerebrovascular adverse events and death. The MHBC guideline (2012) advises a discussion of the following risks: oversedation, postural hypotension, risk of falls, metabolic syndrome, extrapyramidal symptoms, tardive dyskinesia, stroke, and increased mortality. In addition, the BPS guidance (2015) states that *"Caution should be exercised in the use of antipsychotic medication in the context of the evidence of a high risk for cerebrovascular events and mortality".*

Based on pooled analysis of data from four published and unpublished studies of risperidone, which indicated a three-fold risk of cerebrovascular events (3.5% versus 1.2% with placebo), the UK Committee on Safety of Medicines stated in 2004 that risperidone or olanzapine should not be used for the treatment of BPSD, and that prescribers should carefully consider the risks of cerebrovascular events.

In 2008, the US Federal Drugs Authority (FDA) issued an alert that both conventional and atypical antipsychotics were associated with an increased risk of mortality in older people treated for dementia related psychosis. This was in addition to a previous alert by the FDA in 2007 on the association of haloperidol with QT prolongation (an ECG abnormality) and sudden death.

Cognitive side effects

The GDG felt that there was **insufficient evidence currently to make a recommendation** about the risk of cognitive side effects with antipsychotics, and that the more definite risk of harm due to stroke and death in a person with dementia was of sufficient concern without additional consideration of whether antipsychotics hastened cognitive decline.

Extrapyramidal effects-

People with dementia with Lewy bodies and Parkinson's disease dementia with *mild to moderate* non-cognitive symptoms should NOT be prescribed antipsychotic medication due to the increased risk of severe adverse reactions. (Strong recommendation, high quality of evidence)

People with Alzheimer's disease, vascular dementia, mixed dementias, dementia with Lewy bodies, or Parkinson's disease dementia, with *severe* non-cognitive symptoms, causing severe distress, or an identifiable risk of harm to the person and/or others, may be offered antipsychotic medication, where appropriate. (Conditional recommendation moderate quality of evidence)

Doctors, nurses, pharmacists and health and social care professionals are strongly advised to contact a specialist team with experience in treating people with Lewy body dementias for direct advice on a person with Parkinson's disease dementia or dementia with Lewy bodies who has distressing psychosis. (Good practice point)

The GDG agreed that there are significant risks with antipsychotics in dementia with Lewy bodies and Parkinson's disease dementia, above and beyond the usual risks of stroke and increased mortality in people with other dementias, and felt that a specific recommendation was required.

Although the GDG agreed that clozapine can be useful for the treatment of Parkinson's disease dementia as it doesn't have the propensity to worsen Parkinson's disease motor function, they felt that due to its own significant risks, it should only be prescribed by a team who specialise in clozapine prescribing and monitoring, and who have the facility to monitor bloods regularly, and know what to do if a blood dyscrasia develops. Equally, although the GDG agreed that low dose quetiapine does not worsen motor control to the same degree as other antipsychotics, members questioned the efficacy of low dose quetiapine for moderate to severe psychosis.

The GDG felt that given the available evidence, a recommendation for the use of clozapine and/or quetiapine could not be made at this time.

Risk/benefit discussion with family

The risk and benefits of pharmacological intervention using psychotropic medication should be discussed with the person and/or their relevant Decision Supporter, in all cases where possible. (Good practice point)

A full discussion with the person and/or their relevant Decision Supporter about the benefits and risks, including the increased risk of stroke, transient ischemic attack and mortality, should occur before antipsychotic medication is commenced. (Conditional recommendation, low quality of evidence)

Doctors and nurses who prescribe antipsychotics should have written information available for the person with dementia and their family about possible side effects (e.g. falls, confusion, drowsiness), as well as easy to understand information about the risk of serious adverse events (stroke, death). (Good practice point)

The GDG fully supported the principle that doctors, nurses, pharmacists and health and social care professionals should be expected to facilitate participation in decision-making by the person with dementia wherever possible, and/or their relevant Decision Supporter, where appropriate, given the significant risks associated with antipsychotic medications for non-cognitive symptoms. The GDG use the term *Decision Supporte*r rather than "family" in line with the terminology used in the ADMA (2015), as it is not assumed that the Decision Supporter (e.g. the Decision-Making Representative, Attorney, etc.) will always be a family member.

Although the GDG felt this discussion was a highly important component of appropriate prescribing, the recommendation was made conditional to reflect the acknowledged challenges and complexities of following this recommendation in clinical practice in every situation, and the evolving legal position of surrogate decision making in Ireland currently.

5.1.5.4 Choice of antipsychotic medication and administration route

Atypical versus typical antipsychotic medication

Atypical (second generation) antipsychotic medications are associated with fewer extrapyramidal effects and risks than typical (first generation) antipsychotics, and therefore second generation medication should be used if antipsychotic therapy is necessary for the management of non-cognitive symptoms. (Strong recommendation, moderate quality of evidence)

In terms of atypical (second generation) versus typical (first generation) antipsychotics, several guidelines recommended that atypical antipsychotics are preferred, given the reduced incidence of adverse effects associated with their use.

Specific antipsychotic medication

The MHBC guideline (2012) and NHMRC guideline (2016) both preferentially recommend risperidone for treating psychosis, and risperidone or olanzapine for treating agitation/aggression. Similarly, risperidone is recommended as the first choice in antipsychotic treatment by the Royal Australian and New Zealand College of Psychiatrists (2016) given that it is "the only oral medication approved in Australia and New Zealand for use in behavioural disturbances associated with Alzheimer's type dementia". This group specifically states that other medications (e.g. quetiapine, aripiprazole and olanzapine) if used for BPSD are off-label and hence should be considered only when risperidone is not tolerated or is inappropriate. The NICE guideline (2018) similarly notes that the only antipsychotic with a UK marketing authorization for use in dementia is risperidone; this marketing authorisation only covers short-term treatment (<6 weeks) of persistent aggression in people with moderate to severe Alzheimer's disease unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others.

The GDG agreed that where an antipsychotic is required, atypical (second generation) antipsychotic medications should be used as they have less risk of extrapyramidal effects (although the stroke/mortality risk compared to typical antipsychotics is not clear). There was much discussion about whether to only recommend risperidone, as the only licensed antipsychotic for BPSD (licensed for short term use for refractory and persistent aggression with risk of harm).

Members of the GDG noted that the evidence for olanzapine was not dissimilar to risperidone, and that quetiapine was far more commonly used in Ireland due to its lower risks of adverse effects (although less effective). The GDG finally agreed that the individual clinician would have to weigh up the risk and benefit in the individual circumstances, and that it was not appropriate to make a blanket recommendation. The GDG do however highlight to doctors and nurse prescribers that if they prescribe an antipsychotic other than risperidone for non-cognitive symptoms, and if they prescribe risperidone for an indication other than persistent aggression, they are doing so off-label.

Psychotropic route of administration

If psychotropic medication is necessary for the management of non-cognitive symptoms, oral medication should be used initially. In the exceptional case where parenteral treatment is necessary, the intramuscular route is preferred to intravenous administration, and single agents are preferred to combination therapy. (Good Practice Point)

The GDG agreed that when a psychotropic medication is being given, the oral route should always be considered prior to the parenteral route. The GDG felt that parenteral use would and should be an exceptional occurrence, necessitated by either an emergency situation with immediate risk to the

person or others, where immediate effects were required, or where a person was unable to swallow and psychotropic administration was deemed essential.

The GDG felt that on the rare occasions when a psychotropic medication was required for non-cognitive symptoms and could not be taken by mouth, the intramuscular route was the preferred route, rather than intravenous, and they agreed with the NHMRC statement that a single agent should be tried first, rather than combination therapy.

If rapid tranquilisation is needed, the attending doctors and nurses should be adequately trained and have access to adequate monitoring and resuscitation facilities, and should consult their local institutional policy. (Good Practice Point)

The GDG chose not to recommend any one agent, as the best medication in a particular situation would depend on the indication and the person's other medical issues.

5.1.5.5 Antipsychotic dosage

If a risk and benefit assessment favours the use of antipsychotic medication, treatment should be initiated at the lowest possible dose and titrated slowly, as tolerated, to the minimum effective dose. (Strong recommendation, moderate quality of evidence)

If an antipsychotic is being prescribed, it should be done as safely as possible. It is important that non-pharmacological interventions (unless ineffective) are not discontinued just because a psychotropic medication is temporarily required. In addition, following a period of treatment with psychotropic medication, a person may have a better response to a previously ineffective non-pharmacological intervention.

The GDG noted that as many people with dementia are older and have co-morbidities, and may have polypharmacy, prescribers should be mindful of the risk of drug accumulation due to renal or hepatic dysfunction and drug-drug interactions when deciding safe doses and titration/review frequency. It is not possible to give specific direction, but titration decisions should be informed by a comprehensive assessment that includes symptoms and their severity, general health and co-morbidities.

5.1.5.6 Duration of antipsychotic treatment

If there is a positive response to treatment with antipsychotic medication, decision making about possible tapering of the medication should occur within 3 months, accompanied by a discussion with the person with dementia and/or their relevant Decision Supporter. (Strong recommendation, low quality of evidence)

If a person with dementia is taking an adequate therapeutic dose of antipsychotic medication without clear clinical benefit, the medication should be tapered and stopped; where possible after discussion with the person and/or their relevant Decision Supporter. (Strong recommendation, moderate quality of evidence)

5.1.6 Canada 2018

(No specific recommendation on BPSD management)

Non pharmacologic approaches should be considered before pharmacologic approaches for management of BPSD when the situation is not urgent or when symptoms are not severe. These

approaches could include social contact interventions, sensory or relaxation interventions (eg, music therapy, aromatherapy), structured activities, or behavioural therapy.

5.2 Withdrawal/discontinuation of antipsychotics for BPSD

5.2.1 Summary

No specific recommendations or comments were provided regarding withdrawal of antipsychotics in AUS 2016 and NICE 2018. The Canada 2018 guideline was specifically developed to provide guidance for deprescribing antipsychotics for BPSD.

For both APA 2016 and Canada 2018 the benefits of antipsychotic deprescribing appear to outweigh harms. For both of them, as well as in IRE 2019 an attempt to taper antipsychotics is indicated in BPSD. However a small fraction of experts in APA 2016 favoured maintaining the dose of medication without a specific target date for a tapering attempt.

Recommendations from APA 2016 and IRE 2019:

- If there is no clinically significant response: taper and withdrawn after 4 weeks trial (APA 2016) or where possible (IRE 2019) after discussion with the patient and/or the carers.
- If adequate response of BPSD: taper and withdraw within 4 months, unless the patient experiences a recurrence of symptoms with prior attempts at tapering of antipsychotic medication (APA 2016). IRE 2019 recommends to taper within 3 months, the GDG however feels that two failed attempts at discontinuation are sufficient to indicate that the person required ongoing treatment. In this case they propose to review the person 6-monthly.

Canada 2018 rather recommends that adults with BPSD are treated for at least 3 months independently of clinical response before tapering. Canada 2018 recommends the following:

- Reduce to 75%, 50%, and 25% of the original dose on a biweekly basis.
- Alternatively, reduce the previous dose by approximately 50% every week down to 25% of the initial dose, then stop.
- Tapering might be individualized depending on the starting dose, available dosage form, and how tapering is tolerated.

For patients with severe or more chronic BPSD symptoms, APA 2016 mentions that the duration of treatment before tapering may be longer and Canada 2018 recommends slower tapering with close monitoring and a clear intervention plan. APA 2016 notes that there is insufficient evidence to determine whether individuals with more severe symptoms will have a greater risk of recurrence with discontinuation. There are also no data on whether symptom response is equivalent if antipsychotic medication is resumed after recurrence of symptoms.

APA 2016, IRE 2019 and Canada 2018 agree it is essential to discuss possible tapering of antipsychotic medication with the patient, family, and health care staff in order to elicit patient preferences and to review goals, benefits and side effects of antipsychotic treatment and discontinuation.

APA 2016, and Canada 2018 both recommend close monitoring of symptoms during the tapering process, using objective measures.

- APA 2016 recommends that assessment of symptoms should occur at least monthly during tapering and for at least 4 months after medication discontinuation.
- Canada 2018 suggests close monitoring every 1 to 2 weeks, with closer monitoring for patients receiving higher dosages of antipsychotics and those with higher global symptom severity.

IRE 2019 also recommends regular assessment of symptoms for re-emergence during tapering, and after the discontinuation of the antipsychotic without mentioning details on assessment periodicity and duration.

Canada 2018 further advices for whose BPSD recurs with discontinuation:

- Address pain, as it is a common underlying cause of agitation in dementia.
- Search for triggers and exacerbating factors including other diseases (e.g. common viral illnesses, other infections), environmental causes (e.g. new routine, relocation), physical problems (e.g. constipation), other medications, and depression, which treatment might reduce the need to restart antipsychotics.
- Possibly restart an antipsychotic (e.g. risperidone, olanzapine, aripiprazole) at the lowest dose with retrial of discontinuation after 3 months.

5.2.2 APA 2016

5.2.2.1 Starting withdrawal

APA recommends that in patients with dementia with agitation or psychosis, if there is no clinically significant response after a 4-week trial of an adequate dose of an antipsychotic drug, the medication should be tapered and withdrawn. (1B-Recommendation with moderate strength of evidence.**)**

If there is no clinically significant response within 4 weeks of reaching a typical therapeutic dose of medication, the medication should be tapered and stopped to avoid potential harms of medication treatment without any offsetting benefit. If severe, dangerous, or significantly distressing symptoms persist, a trial of a different antipsychotic medication may be considered after reevaluation for contributing factors to the patient's symptoms, additional review of the risks and benefits of treatment, and discussion with the patient and surrogate decision maker, with input from family and other involved individuals.

If a partial response to antipsychotic treatment occurs, further dose titration may be indicated depending on whether side effects are present and on the relative balance of benefits and harms for the patient.

APA recommends that in patients with dementia who show adequate response of behavioral/psychological symptoms to treatment with an antipsychotic drug, an attempt to taper and withdraw the drug should be made within 4 months of initiation, unless the patient experienced a recurrence of symptoms with prior attempts at tapering of antipsychotic medication. (1C-Recommendation with low strength of evidence.**)**

There are no published studies on the optimal duration of antipsychotic treatment in individuals with dementia, and experts are divided in their opinion on optimal treatment duration.

In terms of optimal treatment duration, the data suggest that the greatest risk of mortality occurs in the initial 120 days of antipsychotic use. The mechanisms by which heightened mortality could occur are unclear. In observational studies, unmeasured predisposing factors may lead both to a greater likelihood of antipsychotic treatment and to heightened mortality. However, although the greatest period of risk appears to occur with treatment initiation, the risk of adverse effects also persists with longer term treatment.

A number of studies have assessed the effects of discontinuing an antipsychotic medication in subjects with dementia, and the findings suggest a small effect of antipsychotic treatment. In individuals receiving placebo, there was a higher likelihood of symptom recurrence as compared with those continuing to receive an antipsychotic (moderate confidence), with some post hoc analyses showing that individuals who had higher baseline levels of symptoms or who were taking higher baseline doses of antipsychotic were more likely to have recurrent symptoms with discontinuation.

Discontinuation studies suggest that antipsychotic medications can be tapered and stopped in many patients without return of symptoms. Expert consensus also suggests that an attempt at tapering an antipsychotic medication is indicated, with variation in the suggested timing of a taper attempt; however, only a small fraction of experts (see “Expert Opinion Survey Data: Results” in the guideline) favored maintaining the dose of medication without a specific target date for a tapering attempt.

There is insufficient evidence to determine whether individuals with more severe dementia, psychosis, or agitation will have a greater risk of symptom recurrence with discontinuation. There are also no data on whether symptom response is equivalent if antipsychotic medication is resumed after recurrence of symptoms.

The strength of research evidence supporting statement 12 is rated as low because the precise timing of a tapering attempt was not studied in a randomized fashion and the recommendation to attempt a taper within 4 months was based on the timing of discontinuation in the available clinical trials and information from expert consensus. Some guideline writing group members also felt that a longer period of treatment may be justified in some patients before tapering is attempted because of the initial time needed to reach a clinically effective dose and the longer duration of psychosis in many patients as compared with the typical duration of agitated behaviors.

The duration of treatment before an attempt at tapering may depend on the chronicity of the symptom prior to treatment initiation and on the severity and degree of dangerousness of the target symptoms. If the initial reasons for antipsychotic medication treatment are unclear after information is obtained from treating health professionals, medical records, family members, or other sources of collateral information, an earlier attempt at tapering may be warranted. When symptoms have been long-standing or associated with significant physical risks, more caution will be needed in efforts at medication tapering. Similarly, if symptoms have recurred with previous tapering attempts, it may be appropriate to continue treatment without an attempt at tapering.

In addition, this recommendation is not intended to apply to individuals with a preexisting psychotic disorder such as schizophrenia for whom ongoing antipsychotic treatment may be necessary.

As with decisions about initiating antipsychotic treatment, it is essential to obtain input from patients, family, and other caregivers on an ongoing basis and review their preferences, values, and concerns about continued treatment or tapering in a person-centered fashion.

APA recommends that in a patient who has shown a positive response to treatment, decision making about possible tapering of antipsychotic medication should be accompanied by a discussion with the patient (if clinically feasible) as well as with the patient's surrogate decision maker (if relevant) with input from family or others involved with the patient. The aim of such a discussion is to elicit their preferences and concerns and to review the initial goals, observed benefits and side effects of antipsychotic treatment, and potential risks of continued exposure to antipsychotics, as well as past experience with antipsychotic medication trials and tapering attempts. (1C-Recommendation with low strength of evidence.**)**

It was also noted that for some patients, a medication taper could negatively affect quality of life or be dangerous for the patient or others. Some retrospective data also suggested that individuals with more severe symptoms may be at a greater risk of relapse with antipsychotic tapering, but the available research did not examine whether an a priori determination of such individuals would predict a high likelihood of symptom recurrence. Consequently, in the final guideline statement, the recommended attempt at tapering antipsychotics is accompanied by two additional recommendations. Statement 11 stresses the importance of patient, surrogate decision maker, and family input before a tapering attempt, as well as review of the clinical factors related to a tapering attempt, and statement 13 addresses the need for careful monitoring during tapering so that any recurrent symptoms can be addressed quickly *(see section 5.6 Follow up and monitoring during antipsychotic treatment)*

In the same way that clinical and patient-specific circumstances will require clinical judgment in the decision to initiate treatment with an antipsychotic, the clinician will need to weigh multiple factors in a decision to attempt a taper of medication. Discussion with the patient, surrogate decision maker, family, or others involved with the patient is also important. The aim of such a discussion is to elicit their preferences and concerns as well as to review the initial goals, observed benefits, and side effects of antipsychotic treatment; potential risks of continued exposure to antipsychotics; and past experience with antipsychotic medication trials and tapering attempts.

5.2.2.2 Withdrawal monitoring

APA recommends that in patients with dementia whose antipsychotic medication is being tapered, assessment of symptoms should occur at least monthly during the taper and for at least 4 months after medication discontinuation to identify signs of recurrence and trigger a reassessment of the benefits and risks of antipsychotic treatment. (1C-Recommendation with low strength of evidence.**)**

Although some individuals will have recurrence of symptoms with antipsychotic discontinuation (moderate confidence), such risks can likely be mitigated by careful monitoring during treatment cessation with adjustments made in the medication tapering plan based on clinical response. However, there are no data on the most appropriate frequency for monitoring or the extent to which monitoring can reduce the severity or risk of symptom recurrence, which is unpredictable.

When a medication taper is attempted, close monitoring will be needed to note signs of recurrent symptoms, with monthly symptom assessments recommended during the taper and for at least 4 months after medication discontinuation. The nature of such assessment may vary and can include face-to-face assessments, telephone contact, or other approaches to following symptoms and

behaviors. Again, it can be helpful to use quantitative measures or other structured approaches. If breakthrough symptoms are noted with tapering, this suggests that the benefit of the medication may outweigh the potential risks of continued treatment, that other contributing factors may need to be addressed, or that other nonpharmacological or pharmacological interventions may be indicated.

5.2.3 AUS 2016

In the context of BPSD, no specific recommendations or comments were provided regarding withdrawal of antipsychotics in this guideline.

5.2.4 NICE 2018

In the context of BPSD, no specific recommendations or comments were provided regarding withdrawal of antipsychotics in this guideline.

5.2.5 IRE 2019

5.2.5.1 Starting withdrawal

The following section applies to a person with non-cognitive symptoms where there has been **a recent commencement** of antipsychotic medication for one or more non-cognitive symptoms of dementia. It does not apply to people with a pre-existing, co-morbid mental health illness that may require life-long antipsychotics. If it can be ascertained that the indication for a long-term antipsychotic prescription was non-cognitive symptoms in the context of dementia and not a primary mental health illness, the recommendations can be followed.

If there is a positive response to treatment with antipsychotic medication, decision making about possible tapering of the medication should occur within 3 months, accompanied by a discussion with the person with dementia and/or their relevant Decision Supporter. (Strong recommendation, low quality of evidence)

If a person with dementia is taking an adequate therapeutic dose of antipsychotic medication without clear clinical benefit, the medication should be tapered and stopped; where possible after discussion with the person and/or their relevant Decision Supporter. (Strong recommendation, moderate quality of evidence)

5.2.5.2 Withdrawal monitoring

If antipsychotic treatment is being tapered, assessment of symptoms for re-emergence should occur regularly during tapering, and for a period after discontinuation of antipsychotic medication. (strong recommendation, moderate quality of evidence)

The GDG felt that review during tapering was an important part of deprescribing, given the risk of relapse. The GDG felt that it should be a rare occurrence to not consider attempting to discontinue antipsychotic medication when the indicator symptoms had settled, but that equally a person who suffers repeated (distressing) relapses should not have persistent attempts to discontinue antipsychotic medication. It was felt that pragmatically, two failed attempts at discontinuation were sufficient to indicate that the person required ongoing treatment with that same agent (or on occasions switching on recommencement to a different agent, if the clinical scenario indicated that a change in medication would be better). However, the person on long-term medication would still

require regular review for emerging side effects or change in the risk-benefit balance of continuing the medications.

In rare cases where a person with dementia has had two or more failed attempts of antipsychotic withdrawal and requires ongoing maintenance therapy with an antipsychotic, the person should be reviewed at the point of re-prescribing and at least 6 monthly thereafter. (Good practice point)

5.2.6 Canada 2018

For adults with BPSD treated for at least 3 mo (symptoms stabilized or no response to adequate trial), we recommend the following:

Taper and stop antipsychotics slowly in collaboration with the patient and caregivers: eg, 25%–50% dose reduction every 1–2 wk (strong recommendation, moderate-quality evidence)

The strong recommendation is based on the lack of evidence of substantial harms of deprescribing APs for BPSD, the evidence for benefits of avoiding unnecessary exposure to APs, the societal costs of inappropriate AP use, and the feasibility of this intervention in primary care and LTC. These recommendations place a high value on the minimal clinical risk of deprescribing, reducing the inappropriate use of APs and their side effects, and the associated resource use.

Overall, benefits of AP deprescribing appear to outweigh harms. Available evidence suggests that "many older people with Alzheimer's dementia and NPS can be withdrawn from chronic antipsychotic medication without detrimental effects on their behaviour".

A 2014 meta-analysis demonstrated statistically significant improvements in symptoms of BPSD as measured using 5 different scales for patients taking atypical antipsychotics compared with placebo. However, antipsychotic treatment initiated for BPSD is often continued chronically, despite a lack of documented ongoing indications for many patients. Because behavioural features of dementia change over time as the disease progresses, it is important to reassess the continued need for treatment.

Antipsychotics have been associated with numerous side effects, the most severe of which are increased overall risk of death and increased risk of cerebrovascular adverse events. Atypical antipsychotics can cause weight gain and precipitate or worsen diabetes. While the absolute risk of some of these events is small, older people are often at higher risk of these outcomes. When antipsychotics are inappropriately prescribed or used for extended periods, they might contribute to polypharmacy, with its attendant risks of nonadherence, prescribing cascades, adverse reactions, medication errors, drug interactions, emergency department visits, and hospitalizations.

A systematic review of antipsychotic deprescribing (dose reduction or discontinuation) in patients taking them to control BPSD failed to demonstrate negative outcomes resulting from deprescribing.

For patients stabilized for a minimum of 3 months on antipsychotic treatment for BPSD, gradual withdrawal of antipsychotics does not lead to worsening symptoms compared with those who continue taking antipsychotics. No consistent changes in cognition, mortality, or quality of life were observed, although 1 study found a significant decrease in mortality among those who discontinued antipsychotic treatment; a second small study found worsening of sleep efficiency in those who had had antipsychotics withdrawn

The baseline symptom level might have an influence on the success of deprescribing APs. Patients with more severe baseline scores were more likely to experience relapses (defined as a 30% increase

in the NPI score) in 2 studies. Withdrawal in patients with severe behavioural baseline scores might not be successful or should not be attempted.

As documented in figure 1 this guideline has developed an antipsychotic discontinuation algorithm as well.

Figure 1

Antipsychotic (AP) Deprescribing Algorithm

October 2016

Why is patient taking an antipsychotic?

- Psychosis, aggression, agitation (behavioural and psychological symptoms of dementia - BPSD) treated ≥ 3 months (symptoms controlled, or no response to therapy).
- Primary insomnia treated for any duration or secondary insomnia where underlying comorbidities are managed
- Schizophrenia
- Schizo-affective disorder
- Bipolar disorder
- Acute delirium
- Tourette's syndrome
- Tic disorders
- Autism
- Less than 3 months duration of psychosis in dementia
- Mental retardation
- Developmental delay
- Obsessive-compulsive disorder
- Alcoholism
- Cocaine abuse
- Parkinson's disease psychosis
- Adjunct for treatment of Major Depressive Disorder

Recommend Deprescribing

Strong Recommendation (from Systematic Review and GRADE approach)

Taper and stop AP (slowly in collaboration with patient and/or caregiver; e.g. 25%-50% dose reduction every 1–2 weeks)

Stop AP
Good practice recommendation

Continue AP
or consult psychiatrist if considering deprescribing

Monitor every 1-2 weeks for duration of tapering

Expected benefits:
- May improve alertness, gait, reduce falls, or extrapyramidal symptoms

Adverse drug withdrawal events (closer monitoring for those with more severe baseline symptoms):
- Psychosis, aggression, agitation, delusions, hallucinations

If BPSD relapses:

Consider:
- Non-drug approaches (e.g. music therapy, behavioural management strategies)

Restart AP drug:
- Restart AP at lowest dose possible if resurgence of BPSD with re-trial of deprescribing in 3 months
- At least 2 attempts to stop should be made

Alternate drugs:
- Consider change to risperidone, olanzapine, or aripiprazole

If insomnia relapses:

Consider
- Minimize use of substances that worsen insomnia (e.g. caffeine, alcohol)
- Non-drug behavioural approaches (see reverse)

Alternate drugs
- Other medications have been used to manage insomnia. Assessment of their safety and effectiveness is beyond the scope of this deprescribing algorithm. See AP deprescribing guideline for details.

Commonly Prescribed Antipsychotics

Antipsychotic	Form	Strength
Chlorpromazine	T IM, IV	25, 50, 100 mg l25 mg/mL
Haloperidol (Haldol®)	T L IR, IM, IV LA IM	0.5, 1, 2, 5, 10, 20 mg 2 mg/mL 5 mg/mL 50, 100 mg/mL
Loxapine (Xylac®, Loxapac®)	T L IM	2.5, 5, 10, 25, 50 mg 25 mg/L 25, 50 mg/mL
Aripiprazole (Abilify®)	T IM	2, 5, 10, 15, 20, 30 mg 300, 400 mg
Clozapine (Clozaril®)	T	25, 100 mg
Olanzapine (Zyprexa®)	T D IM	2.5, 5, 7.5, 10, 15, 20 mg 5, 10, 15, 20 mg 10mg per vial
Paliperidone (Invega®)	ER T PR IM	3, 6, 9 mg 50mg/0.5mL, 75mg/0.75mL, 100mg/1mL, 150mg/1.5mL
Quetiapine (Seroquel®)	IR T ER T	25, 100, 200, 300 mg 50, 150, 200, 300, 400 mg
Risperidone (Risperdal®)	T S D PR IM	0.25, 0.5, 1, 2, 3, 4 mg 1 mg/mL 0.5, 1, 2, 3, 4 mg 12.5, 25, 37.5, 50 mg

IM = intramuscular, IV = intravenous, L = liquid, S = suppository, SL = sublingual, T = tablet, D = disintegrating tablet, ER = extended release, IR = immediate release, LA = long-acting, PR = prolonged release

Antipsychotic side effects

- **APs associated with increased risk of:**
  - Metabolic disturbances, weight gain, dry mouth, dizziness
  - Somnolence, drowsiness, injury or falls, hip fractures, EPS, abnormal gait, urinary tract infections, cardiovascular adverse events, death
- **Risk factors**: higher dose, older age, Parkinsons', Lewy Body Dementia

Engaging patients and caregivers

Patients and caregivers should understand:
- The rationale for deprescribing (risk of side effects of continued AP use)
- Withdrawal symptoms, including BPSD symptom relapse, may occur
- They are part of the tapering plan, and can control tapering rate and duration

Tapering doses

- No evidence that one tapering approach is better than another
- Consider:
  - Reduce to 75%, 50%, 25% of original dose on a weekly or bi-weekly basis and then stop; or
- Consider slower tapering and frequent monitoring in those with severe baseline BPSD
- Tapering may not be needed if low dose for insomnia only

Sleep management

Primary care:
1. Go to bed only when sleepy
2. Do not use your bed or bedroom for anything but sleep (or intimacy)
3. If you do not fall asleep within about 20-30 min at the beginning of the night or after an awakening, exit the bedroom
4. If you do not fall asleep within 20-30 min on returning to bed, repeat #3
5. Use your alarm to awaken at the same time every morning
6. Do not nap
7. Avoid caffeine after noon
8. Avoid exercise, nicotine, alcohol, and big meals within 2 hrs of bedtime

Institutional care:
1. Pull up curtains during the day to obtain bright light exposure
2. Keep alarm noises to a minimum
3. Increase daytime activity and discourage daytime sleeping
4. Reduce number of naps (no more than 30 mins and no naps after 2pm)
5. Offer warm decaf drink, warm milk at night
6. Restrict food, caffeine, smoking before bedtime
7. Have the resident toilet before going to bed
8. Encourage regular bedtime and rising times
9. Avoid waking at night to provide direct care
10. Offer backrub, gentle massage

BPSD management

- Consider interventions such as: relaxation, social contact, sensory (music or aroma-therapy), structured activities and behavioural therapy
- Address physical and other disease factors: e.g. pain, infection, constipation, depression
- Consider environment: e.g. light, noise
- Review medications that might be worsening symptoms

Bjerre LM, Farrell B, Hogel M, Graham L, Lemay G, McCarthy L, et al. Deprescribing antipsychotics for behavioural and psychological symptoms of dementia and insomnia. Evidence-based clinical practice guideline. *Can Fam Physician* 2018;64:17-27 (Eng), e1-12 (Fr).

deprescribing.org Bruyère RESEARCH INSTITUTE open

Figure1: Antipsychotic deprescribing algorithm as copied from Canada 2018.

Is there an indication and are there risk factors that warrant continued use?

An important first step is to clarify when the antipsychotic was started and for what reason. This might require a chart review and discussion with the patient, caregivers, other prescribers (often other specialists), or pharmacist.

How should tapering be approached?

Suggested tapering strategies.

For those prescribed antipsychotics for the treatment of BPSD, we recommend considering the following:

- Reduce to 75%, 50%, and 25% of the original dose on a biweekly basis before stopping.
- Alternatively, reduce the previous dose by approximately 50% every week down to 25% of the initial dose, then stop

In addition we recommend the following:

- For patients with severe baseline BPSD symptoms or long-standing use of antipsychotics, we recommend slower tapering, close monitoring for withdrawal symptoms, and establishing a clear intervention plan emphasizing the use of nonpharmacologic approaches first, in the event of increased severity or recurrence of neuropsychiatric symptoms
- Furthermore, tapering might need to be individualized depending on the starting dose, available dosage forms, and how tapering is tolerated

What monitoring needs to be done and how often?

It is important to clarify with the patient, family, and health care staff what specific symptoms are being treated, what the desired response to treatment is, and the need to monitor the actual response following antipsychotic initiation and, likewise, discontinuation. This might require a retrospective chart review with the aim of documenting changes in the frequency or severity of target symptoms. It might be of value to use an objective measure such as the Neuropsychiatric Inventory (NPI) subscales or the behavioural subscales of the Resident Assessment Instrument–Minimum Data Set tool to quantify the frequency and severity of the symptoms at baseline and follow these parameters through time. Response can be defined as a decrease of 50% in the 3 target symptoms (psychosis, agitation, aggression). Physicians and caregivers should also monitor for expected benefits of deprescribing (such as reduced falls and improved cognition, alertness, function, extrapyramidal symptoms, and gait). Close monitoring (eg, every 1 to 2 weeks) is essential during the tapering process, and the use of objective measures can be helpful in identifying any behavioural recurrence or withdrawal symptoms, as well as the success of deprescribing.

Predictors of successful discontinuation of therapy include lower baseline severity of neuropsychiatric symptoms (NPI score <15) and lower dosage of antipsychotic to achieve symptom control. Those receiving a higher dosage and those with higher NPI scores or higher global severity (as NPI or other tools are not commonly used) might require closer monitoring. Monitoring tools such as the Cohen-Mansfield Agitation Inventory, which is brief and easy to apply, might be more amenable to use for patients in LTC settings, where health care professionals are present. In the outpatient setting, family and caregiver involvement is key to monitoring behavioural recurrence, with close medical follow-up.

How should symptoms be managed?

In patients whose BPSD recurs with discontinuation, addressing pain might be of value, as it is a common underlying cause of agitation in dementia; a recent randomized controlled trial in 352 patients reported a 17% improvement in agitation after stepped treatment with analgesics, similar to the benefit seen with antipsychotics. Further search for triggers and exacerbating factors including other diseases (eg, common viral illnesses, other infections), environmental causes (eg, new routine, relocation), physical problems (eg, constipation), other medications, and depression might also be of value. Such treatment is not a direct alternative to antipsychotics, but plays an important part in managing and preventing agitation and might reduce the need to restart antipsychotics.

Realistically, some patients will not be successful with discontinuation; restarting an antipsychotic (eg, risperidone, olanzapine, aripiprazole) at the lowest dose possible can be done with retrial of discontinuation after 3 month

5.3 Antipsychotics and delirium

5.3.1 Summary

Antipsychotics in the approach of delirium

NICE 2018 recommends on antipsychotic use for people living with dementia who experienced hallucinations or delusions that are causing them severe distress. If it is not possible to tell whether a person has delirium, dementia, or delirium superimposed on dementia, treat for delirium first.
Similarly APA 2016, notes that haloperidol may be appropriate in emergent situations or in the context of delirium.

NICE 2010 and NHG 2014 recommend to not routinely use antipsychotics for everyone with delirium. They recommend giving short term haloperidol only if a person with delirium is severely distressed and at risk to themselves or others and if non-verbal de-escalation techniques are ineffective.

- Use haloperidol for 1 week maximum.
- Start at the lowest clinically dose.
- Titrate cautiously according to symptoms.
- NHG 2014 recommends 0.5 to 1.5 mg twice a day orally.
- In crisis situations, haloperidol up to 10 mg/24 hours, evaluated every hour. If necessary, opt for i.m. administration (2.5 mg) (NHG 2014).

SIGN 2019 decides to not support formal recommendation on the use of antipsychotics for the treatment of patients in ICU with delirium because of insufficient evidence. Nevertheless expert opinion supports a role for antipsychotic medication for unmanageable agitation/distress, where the safety of the patient and others is compromised:

- Haloperidol 0.5-1mg orally (max 2mg/24 hours).
- Haloperidol 0.5mg i.m. (max 2mg/24 hours).
- Or atypical antipsychotics at low dose, for example, risperidone 0.25 mg daily, maximum 1mg in 24 hours.
- Review treatment on a daily basis.

Stop treatment:

- NHG 2014 recommends to discontinue treatment as soon as the patient had a good night's sleep twice in a row or after maximum 1 week, reducing by half the dosage every 2 days. Stop 2 days after a dose of 1 mg/day is reached.
- SIGN 2019 advices to stop treatment as soon as the clinical situation allows, typically within 1–2 days.

For people in whom delirium does not resolve:

- NICE 2010 recommends: Re-evaluate for underlying causes; follow up and assess for possible dementia.
- NHG 2014 : despite (the maximum dose) haloperidol, consider adding a benzodiazepine briefly and based on the symptoms, preferably lorazepam 0.5 to 2 mg/2 hours, orally or parenterally, or i.m. midazolam if acute parenteral administration is necessary.

For delirium in the palliative phase NHG 2014 recommends:

- Haloperidol, maximum dose of 20 mg / 24 hours, no limit on duration.
- If a patient remains very restless despite administering haloperidol, consider adding benzodiazepine briefly.
- In the event of insufficient effect, or if haloperidol is contraindicated, consult a GP/palliative care consultant.

Safety and adverse effects of antipsychotics during delirium:

SIGN 2019, NICE 2010 and NHG 2014 all note to use antipsychotic drugs with caution or not at all for delirium in patients with conditions such as Parkinson's disease, or dementia with Lewy bodies, as well as for patients with an antecedent of prolonged QTc time. Haloperidol is contra-indicated in combination with QTc prolonging drugs (SIGN 2019, NICE 2010 and NHG 2014)

No serious side effects were reported in the studies of haloperidol and overall adverse effects were poorly or rarely reported (SIGN 2019).

Haloperidol was associated with a higher incidence of extrapyramidal side effects and dystonias than SGAs, although this may be due to the high dose of haloperidol used in the trials (SIGN 2019).

NICE 2010 and NHG 2014 both report on the significant effect of antipsychotic drugs on the incidence of stroke in patients who have a median exposure time of 3 to 4 months. However they acknowledge that patients who receive antipsychotics for delirium, will have the drugs for much shorter periods. The risk of stroke is unknown.

Preferential antipsychotic medication

From APA 2016, NICE 2010, SIGN 2019, and NHG 2014 it appears that haloperidol is the first choice antipsychotic medication for delirium.

From expert opinion experience, SIGN 2019 also mentions the use of risperidone.

NHG 2014 further discusses the possible use of different antipsychotics. However, prescription of agents other than haloperidol (or possibly risperidone) for treating delirium is not advised. If required, risperidone appears to be a safer medicine for long-term symptom control.

There is no significant difference in effect on delirium scores and extrapyramidal side effects between haloperidol and olanzapine or risperidone at low doses of haloperidol (<3 mg/day). However, with higher doses of haloperidol (> 4.5 mg / day) extrapyramidal side effects occurred more often than with olanzapine (NHG 2014).
NHG 2014 also mentions that the Expertise Center for Pharmacotherapy in the Elderly (Ephor) prefers haloperidol or risperidone based on a literature study of therapeutic value (effectiveness, safety, experience and ease of use) of various antipsychotics in delirium in vulnerable elderly people. Ephor concludes that other antipsychotics, such as clozapine, olanzapine and quetiapine, have highly negative considerations with respect to the reference drug haloperidol; these agents are therefore not recommended for use in vulnerable elderly patients.

Regarding treatment of delirium in patients with Lewy body dementia or Parkinson’s disease, haloperidol and risperidone are contraindicated due to high risk of extrapyramidal effects,

therefore NHG 2014 considers using clozapine (low risk of extrapyramidal side effects)in patients with an appropriate leukocyte control given the risk of agranulocytosis.

5.3.2 APA 2016

While no formal recommendations have been made by APA 2016 for the treatment of delirium they stated on the use of haloperidol. In the context of BPSD, APA 2016 mentioned a possible use of haloperidol only for management of emergent situation such as delirium.

APA recommends that in the absence of delirium, if nonemergency antipsychotic medication treatment is indicated, haloperidol should not be used as a first-line agent. (1B- Recommendation with moderate strength of evidence.**)**

Thus, because of the greater risk of harms with haloperidol treatment reported in clinical trials and cohort studies, this medication is not recommended as a first-line agent for nonemergent use in individuals with dementia. On the basis of the available data on harms, it may be preferable to avoid use of other FGAs as well.

In emergent situations or in the context of delirium, use of haloperidol may still be appropriate, given its availability in an intravenous and short-acting intramuscular formulation and its relatively rapid onset of action relative to other parenteral antipsychotic medications. However, if longer-term treatment is indicated, a different agent should be chosen as a first-line medication.

5.3.3 NICE 2018

Only offer antipsychotics for people living with dementia who are either: at risk of harming themselves or others or experiencing agitation, hallucinations or delusions that are causing them severe distress.

For complete discussion on this recommendation see 5.1 Antipsychotics and BPSD.

If it is not possible to tell whether a person has delirium, dementia, or delirium superimposed on dementia, treat for delirium first. For guidance on treating delirium, see treating delirium in the NICE guideline on delirium (*see NICE 2010*)**.**

Be aware of the increased risk of delirium in people living with dementia who are admitted to hospital. See the NICE guideline on delirium for interventions to prevent and treat delirium *(see NICE 2010)***.**

The acute management of delirium superimposed on dementia is likely to be similar to the management of delirium in people without dementia. However, there may be differences in the

interventions needed to aid long-term recovery, particularly because people with different severities of dementia will have different baseline cognitive status.

5.3.4 SIGN 2019

Studies of the efficacy of antipsychotics are heterogenous and inconclusive. Most are small and rated as low or very low quality. **Because the studies identified are underpowered, further, larger trials are needed before recommendations can be made on the use of antipsychotics for the treatment of patients in ICU with delirium.**

If commenced, antipsychotics prescribed for delirium should be reviewed on a daily basis and stopped as soon as the clinical situation allows, typically within 1–2 days. In situations where it is deemed safer to continue antipsychotic therapy for delirium beyond discharge or transfer from hospital, a clear plan for early medication review and follow up in the community should be agreed.

One meta-analysis concluded that antipsychotics should not be used in non-ICU settings for the treatment of patients with delirium, while another concluded that antipsychotics were superior to placebo or usual care in reducing delirium severity scale scores. A Cochrane review concluded that antipsychotics did not reduce delirium severity, resolve symptoms or alter mortality in the acute care setting. The Cochrane review also identified a large RCT of patients receiving palliative cancer care, which found that patients treated with either risperidone or haloperidol had worse delirium symptom scores than those receiving placebo.

Pooled subgroup analysis of two small trials of patients in ICU with delirium found use of antipsychotics to be marginally superior to placebo in response rate at the studies' endpoint (risk ratio 0.25, 95% CI 0.06 to 1.02). Second generation antipsychotics were superior to haloperidol in reducing delirium severity scores in patients in ICU (standardised mean difference (SMD) -0.52, 95% CI -0.85 to -0.19). There was no difference in discontinuation rates or adverse events. A systematic review identified five studies, one of which reported that quetiapine reduced the duration of delirium (1 day v 4.5 days) compared to placebo in 36 patients. None of the studies reported a reduction in length of stay, or mortality.

Comparisons of haloperidol and other antipsychotics did not find any antipsychotic to be more effective than another. Two RCTs comparing the efficacy of haloperidol and quetiapine reported conflicting results.

No serious side effects were reported in the studies of haloperidol and overall adverse effects were poorly or rarely reported. Haloperidol was associated with a higher incidence of extrapyramidal side effects and dystonias than second generation antipsychotics, although this may be due to the high dose of haloperidol used in the trials.

The Cochrane review concluded that extrapyramidal symptoms were not more frequent with antipsychotics compared to non-antipsychotics and there was no difference between typical and atypical antipsychotics.

Haloperidol is contraindicated in combination with any drug that is associated with QTc prolongation. If it is used with other QT prolonging drugs, treatment is rendered unlicensed.

Urgent pharmacological intervention :

While the evidence for pharmacological treatment is insufficient to support a recommendation, expert opinion supports a role for medication in specific situations such as in patients in intractable distress, and where the safety of the patient and others is compromised.

See *figure 2* Scottish Delirium Association delirium management pathway:

From this scheme:

Medications for unmanageable agitation/distress:

- Haloperidol 0.5-1mg orally (max 2mg/24 hours)
- Haloperidol 0.5mg IM (max 2mg/24 hours)
- Haloperidol is contra-indicated in combination with QTc prolonging drugs, which makes it unlicensed and local "off label" policy should be followed.
- Or atypical antipsychotic at low dose, for example, risperidone 0.25 mgs daily, maximum 1mg in 24 hours

Do not use if signs of Parkinsonism or Lewy Body Dementia

If antipsychotics are contra-indicated (as above):

- Lorazepam 0.5-1mg orally (max 2mg/24 hrs)
- Midazolam 2.5mg IM (max 7.5mg/24 hours).

Younger patients may need higher drug doses

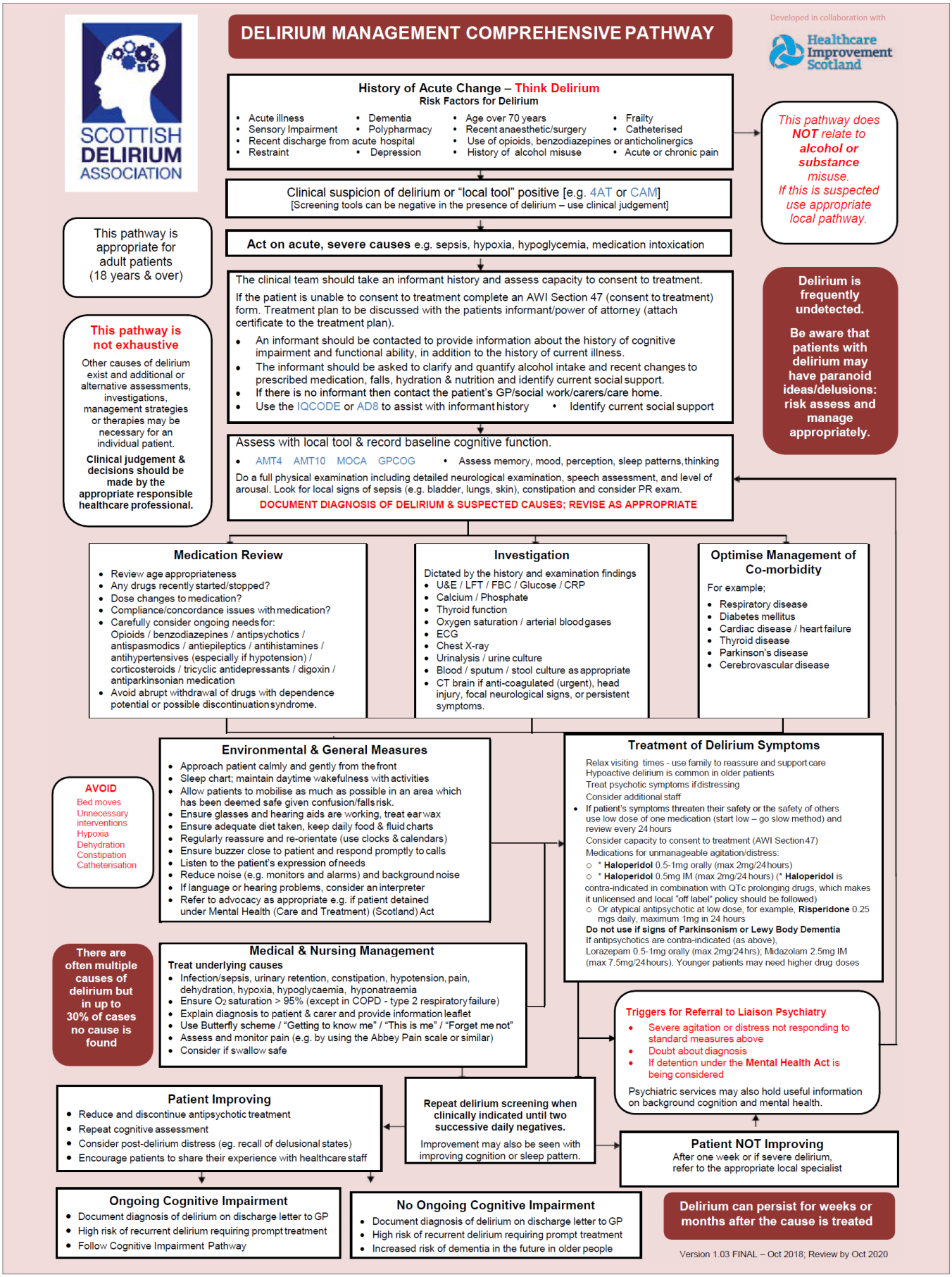


Figure 2: Scottish Delirium Association delirium management pathway

5.3.5 NICE 2010

"Think delirium"

The GDG considered the evidence noting that dementia, length of stay, death and new admission to long-term care were all significant consequences of delirium. The GDG felt that awareness of this information was very important, but acknowledged that a recommendation could not be made stating „be aware of the consequences of delirium". They recognised the difficulty of implementing and auditing a recommendation based on „awareness". So as not to lose this important message, the GDG agreed that "Think delirium" should appear as a prominent statement at the start of the list of recommendations.

The following paragraph was agreed by the GDG:

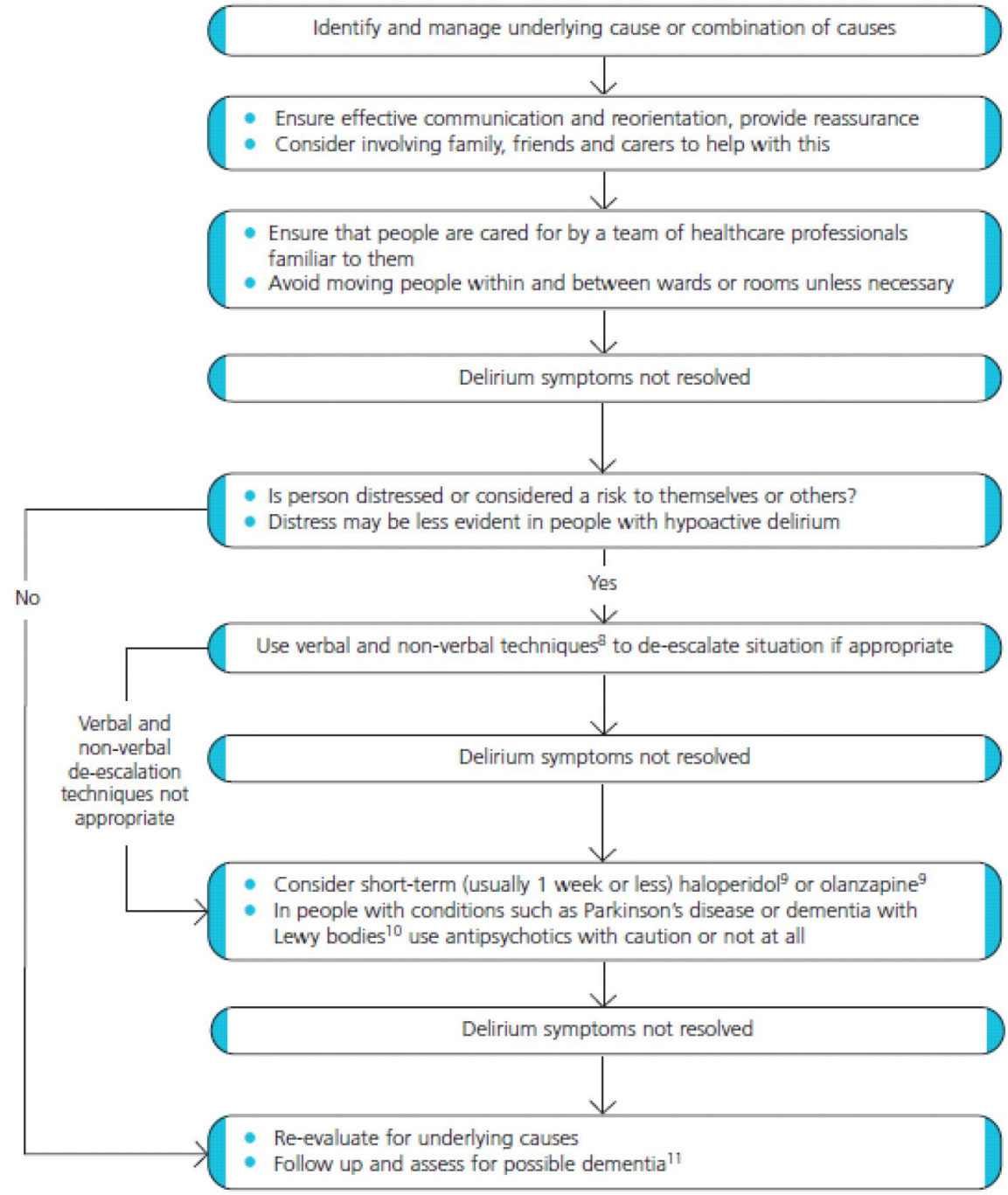
"THINK DELIRIUM"

Be aware that people in hospital or long-term care may be at risk of delirium. This can have serious consequences (such as increased risk of dementia and/or death) and, for people in hospital, may increase their length of stay in hospital and their risk of new admission to long-term care.

Pharmacological treatment

Nice 2010 propose the following scheme for delirium treatment (Figure 3).

Treating delirium



[8] See 'Violence' (NICE clinical guideline 25).
[9] Haloperidol and olanzapine do not have UK marketing authorisation for this indication.
[10] For more information on the use of antipsychotics for these conditions, see 'Parkinson's disease' (NICE clinical guideline 35) and 'Dementia' (NICE clinical guideline 42).
[11] For more information on dementia see 'Dementia' (NICE clinical guideline 42).

Figure 3: scheme proposed by NICE 2010 for delirium management.

Delirium is characterised by a range of symptoms that can cause distress, behaviour disturbance and place people at risk. Medications are used in clinical practice to manage these symptoms though the evidence base remains limited. Pharmacological agents that alter the course of delirium or control particular symptoms will need to demonstrate safety as well as effectiveness but would be a valuable development in treatment. The pathophysiology of delirium is complex and people with delirium may have serious physical illness that complicates the use of drug treatment. Should drugs be given routinely or for selected symptoms? If selected symptoms then for which symptoms? Does the clinical context alter decisions about drug treatments? Would all people receive them or those at risk? These are questions for which answers are needed.

If a person with delirium is distressed or considered at risk to themselves or others and verbal and non-verbal de-escalation techniques are ineffective or inappropriate, consider giving short-term (usually for 1 week or less) haloperidol. Start at the lowest clinically appropriate dose and titrate cautiously according to symptoms.

Updated 03-2019: Olanzapine has been removed from recommendation because the clinical need can now be met by a licensed product. The footnote to this recommendation stated that haloperidol and olanzapine do not have UK marketing authorisation for delirium treatment. However, haloperidol does now have marketing authorisation. Therefore, the footnote has been removed because it no longer applies to haloperidol.

Use antipsychotic drugs with caution or not at all for people with conditions such as Parkinson's disease or dementia with Lewy bodies.

For people in whom delirium does not resolve:

- **Re-evaluate for underlying causes.**
- **Follow up and assess for possible dementia.**

There was little evidence for the use of pharmacological agents for the treatment of delirium. The GDG observed that there was evidence from one moderate quality RCT, but did not wish to make a recommendation on the basis of a single study which had a risk of bias.

In the light of the adverse events associated with these drugs for longer term use, and their uncertainty about the evidence, the GDG did not want to recommend the routine use of these drugs for everyone with delirium. The GDG therefore decided to make a cautious recommendation that healthcare professionals consider giving pharmacological treatment as short term treatment. Short-term treatment was defined as 1 week or less, based on the evidence from the Hu (2006) study and usual practice. The GDG considered that this treatment should only be given to patients who had distressing symptoms and whose behaviour meant their safety or the safety of those around them was compromised. This was in line with the summary of product characteristics (SPC) indications for these drugs for the treatment of symptoms: „rapid control of agitation and disturbed behaviours in patients with schizophrenia or manic episode‟ for olanzapine and „As an adjunct to short term management of moderate to severe psychomotor agitation, excitement, violent or dangerously impulsive behaviour‟ for haloperidol‟ (SPCs).

The GDG were aware that antipsychotic drugs such as haloperidol and olanzapine should be used with caution or not at all for people with conditions such as Parkinson's disease and/or Lewy-body dementia. They therefore made a recommendation to this effect and cross-referred to the NICE guidelines on „Parkinson's disease" (NICE clinical guideline 35) and „Dementia" (NICE clinical guideline 42).

The GDG also wanted to give guidance for all people who had progressed through the care management and treatment pathway but whose delirium symptoms had not fully resolved. This could be due to underlying causes remaining to be addressed or could indicate that the person has dementia.

Adverse events

There is moderate quality evidence in a large:

- retrospective cohort study that antipsychotics have a significant effect on the incidence of stroke in patients who have a median exposure time of 3 to 4 months. This is indirect evidence for patients who receive antipsychotics for delirium, who will have the drugs for much shorter periods.
- mixed prospective-retrospective cohort study in patients with dementia to suggest there is no significant difference in the effects of typical relative to atypical antipsychotics compared with each other.
- retrospective cohort study to suggest that there is no significant difference between risperidone and olanzapine as risk factors for stroke in patients who received drugs for at least 30 days.

The GDG recognized the paucity of the reported adverse effects data is a major limitation. Most of the investigators appear to have focused on extrapyramidal effects, and omitted to consider or discuss the possibility of other adverse events. Another important limitation is that patients with delirium are unable to accurately describe of any untoward symptoms, and thus adverse events may have been missed by the clinicians.

Cost-effectiveness analyses of delirium prevention and pharmacological treatment

The occurrence of delirium has been shown in a systematic review to result in adverse consequences. The adverse consequences could lead to a reduction in patients" health-related quality of life, HRQoL, and the expenditure of the resources of the NHS or PSS. It will therefore be useful to know the cost effectiveness of prevention and treatment interventions for delirium. The GDG advised that the adverse consequences to be used in the economic model should include falls, pressure ulcer, new dementia, new admission to institution, extended stay in the hospital and fatality. We estimated the cost-effectiveness of prevention and treatment interventions using an original economic evaluation model. The use of multicomponent targeted interventions was found to be cost-effective in the prevention of delirium in the population groups considered in the model (elderly patients at risk of delirium who were admitted to the general medicine service and patients undergoing surgical repair of hip fracture). The use of haloperidol and olanzapine in the treatment of delirium was also

cost-effective. On average, haloperidol was associated with a higher net monetary benefit but there is wide uncertainty around the incremental cost-effectiveness.

5.3.6 NHG 2014

Het beleid bij een delier steunt op een aantal pijlers:

- behandeling van de oorzakelijke factoren;
- creëren en waarborgen van een veilige omgeving, waarin de patiënt behandeld en verzorgd kan worden;
- zo nodig medicamenteuze behandeling van symptomen.

Samenvatting diagnostiek en beleid bij delier

(see figure 4)

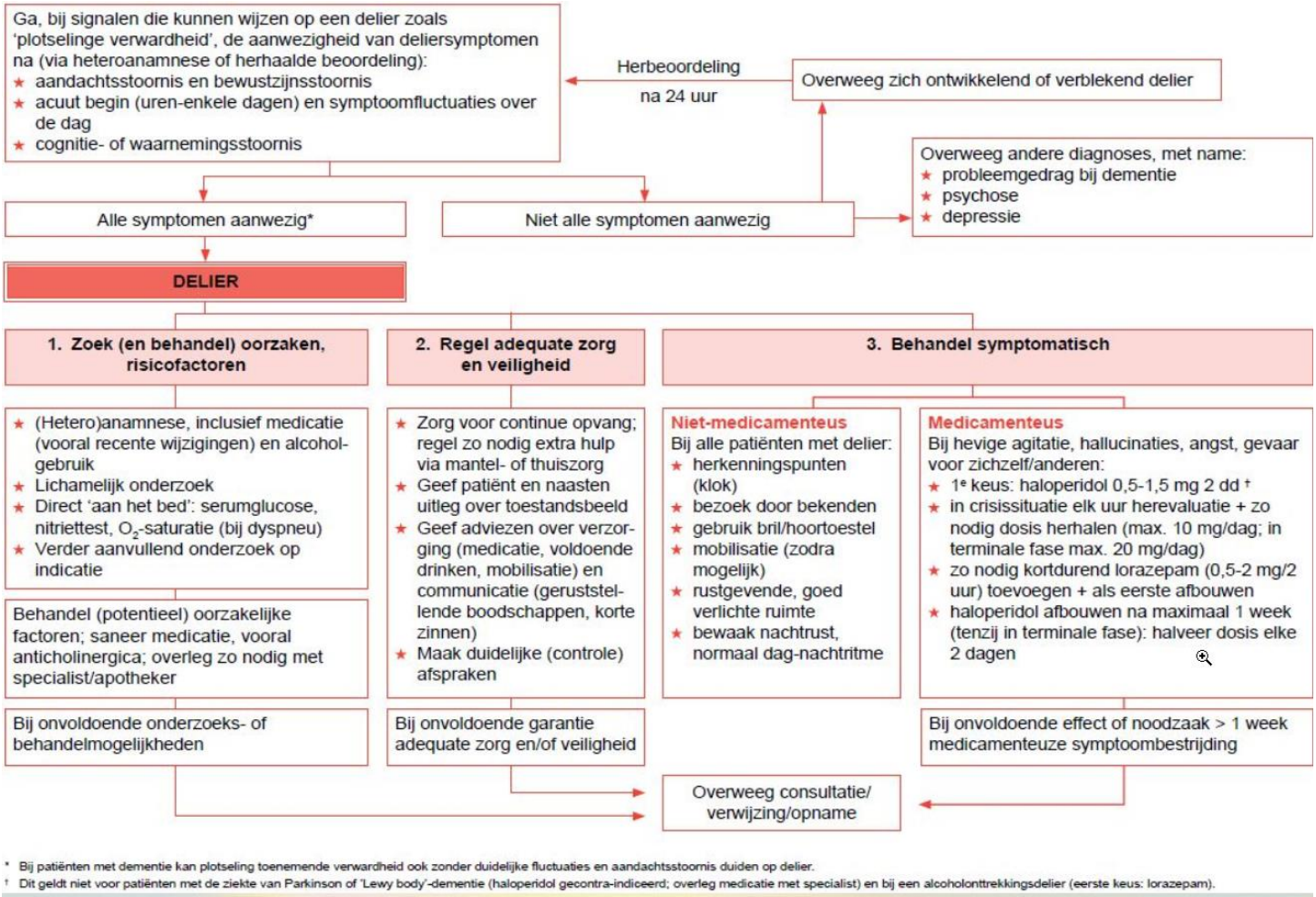


Figure 4: summary of delirium diagnostic and treatment as proposed by NHG 2014.

Effectiviteit en bijwerkingen typische en atypische antipsychotica

- **Start, vanwege potentiële bijwerkingen, niet routinematig met medicamenteuze behandeling van een delier en beperk, indien een medicament zoals haloperidol wordt voorgeschreven, deze behandeling tot de laagst effectieve dosis in tijd en duur (zo mogelijk maximaal een week). Overweeg medicamenteuze behandeling van de symptomen van een delier indien sprake is van een van de volgende indicaties:**
    - **angst en/of hallucinaties, achterdocht, (paranoïde) wanen;**
    - **hevige motorische onrust, mede om te voorkomen dat de patiënt zichzelf of anderen letsel toebrengt;**
    - **nachtelijke onrust en/of verstoord dag-nachtritme;**
    - **om essentieel onderzoek of behandeling mogelijk te maken.**

Indien symptomatische behandeling van een delier bij ouderen noodzakelijk wordt geacht, gaat de voorkeur uit naar haloperidol 0,5 tot 1,5 mg 2 dd oraal, gedurende maximaal 1 week.

Deze voorkeur geldt niet voor patiënten met de ziekte van Parkinson of 'Lewy body'-dementie en evenmin bij een delier als gevolg van alcohol- of benzodiazepineonttrekking (zie onder *Andere punten die van belang zijn*).

- **Start laag en bouw zo nodig geleidelijk op. De ervaring leert dat het effect van haloperidol individueel sterk kan verschillen; leeftijd, gewicht, geslacht en ernst van de symptomen zijn niet duidelijk richtinggevend voor het bepalen van de optimale (start)dosering.**
- **Naast tabletten van 1 en 5 mg is voor orale toediening ook druppelvloeistof beschikbaar (2 mg/ml; 1 druppel = 0,1 mg), waarmee het zo nodig buccaal kan worden toegediend. Ook subcutane, intramusculaire of intraveneuze toediening is mogelijk (ampul injectievloeistof à 1 ml bevat 5 mg haloperidol/ml), maar terughoudendheid is hierbij geboden: intramusculaire toediening is pijnlijk en alleen te overwegen bij ernstige motorische onrust; intraveneuze toediening kan (in hogere doseringen) leiden tot verlenging van de QTc-tijd.**
- **Overweeg in crisissituaties kortdurend een hogere dosis (tot maximaal 10 mg/24 uur): evalueer (telefonisch) na de startdosering elk uur of de motorische onrust en/of angst al voldoende onder controle zijn; herhaal zo nodig de startdosering of kies voor intramusculaire toediening (2,5 mg).**

De wetenschappelijke onderbouwing voor de medicamenteuze behandeling van het delier is beperkt. Bovendien wordt de klinische relevantie beperkt omdat onderzoeken veelal geen patiënten met dementie includeren, terwijl dit in de klinische praktijk de grootste groep patiënten met een delier is en antipsychotica in deze kwetsbare groep meer bijwerkingen hebben.

Vanwege de beperkt aangetoonde effectiviteit en de potentiële bijwerkingen (zie onder) adviseert de NICE-richtlijn Delirium om niet routinematig te starten met medicamenteuze behandeling van delier en indien een medicament (zoals haloperidol) wordt voorgeschreven deze behandeling te beperken tot de laagst effectieve dosis in tijd en duur (zo mogelijk maximaal een week). Het advies luidt pas te starten met medicatie bij ernstige symptomen, zoals agitatie en psychotische verschijnselen of als de veiligheid van de patiënt in het geding is [NICE 2010]. De werkgroep sluit aan bij dit advies.

Typische (= klassieke) antipsychotica

Haloperidol is een snel en sterk werkend typisch antipsychoticum dat een antipsychotisch effect heeft bij een lage dosering, omdat het een grote affiniteit voor dopaminereceptoren heeft. Het heeft een lage anticholinerge activiteit en minimale hypotensieve effecten; de bijwerkingen zijn voornamelijk extrapiramidaal.

In 2009 verscheen een Cochrane-review over de effectiviteit en incidentie van bijwerkingen van haloperidol in vergelijking met atypische antipsychotica (risperidon en olanzapine) en/of placebo. De eindconclusie van de Cochrane-review is dat er bij lage dosering haloperidol (< 3 mg/dag) geen significant verschil is in effect op delierscores en (extrapiramidale) bijwerkingen tussen haloperidol en de atypische antipsychotica olanzapine en risperidon. Bij een hogere dosering haloperidol (> 4,5 mg/dag) traden extrapiramidale bijwerkingen echter wel vaker op dan bij olanzapine.

Atypische antipsychotica

Een review uit 2009 over het effect van atypische antipsychotica bij delier laat zien dat verreweg het meeste onderzoek methodologisch zwak is.

In een gerandomiseerd onderzoek onder 32 patiënten van 36 tot 82 jaar (mediane leeftijd 70 jaar) met een delier die waren verwezen naar een Zuid-Koreaans universiteitsziekenhuis werd de effectiviteit van olanzapine en risperidon vergeleken, waarbij de beoordelaars van de delierscore geblindeerd waren. Dit onderzoek liet geen significant verschil zien tussen beide behandelgroepen wat betreft verbetering van de delierscore en het percentage patiënten met een gunstig effect. Wél was de respons op risperidon significant slechter in de groep vanaf 70 jaar, vergeleken met de groep jonger dan 70 jaar. Een dergelijk leeftijdseffect werd niet gevonden in de groep die met olanzapine werd behandeld. Een nadeel van olanzapine bij delier is echter dat het ook anticholinerg en sederend werkt, vooral bij hogere doseringen.

Een dubbelblind, gerandomiseerd, placebogecontroleerd onderzoek naar de effectiviteit van quetiapine onder 42 in het ziekenhuis opgenomen patiënten (gemiddelde leeftijd 84 jaar) liet zien dat delierscores in de quetiapinegroep significant sneller verbeterden dan in de controlegroep.

Op basis van literatuuronderzoek van het Expertisecentrum Pharmacotherapie bij Ouderen (Ephor) naar de therapeutische waarde (effectiviteit, veiligheid, ervaring en gebruiksgemak) van diverse antipsychotica bij een delier bij kwetsbare ouderen geeft Ephor de voorkeur aan haloperidol of risperidon. Ephor concludeert dat andere antipsychotica, zoals clozapine, olanzapine en quetiapine, sterk negatieve overwegingen hebben ten opzichte van het referentiegeneesmiddel haloperidol; deze middelen worden daarom niet geadviseerd voor toepassing bij kwetsbare oudere patiënten.

Risico op CVA

Retrospectief cohortonderzoek laat zien dat antipsychotica bij langdurig gebruik (3 tot 4 maanden) het risico op een CVA significant verhogen; bij atypische antipsychotica is dit effect sterker (relatief risico in vergelijking met geen behandeling 2,32; 95%-BI 1,73 tot 3,11) dan bij het typische antipsychoticum haloperidol (relatief risico in vergelijking met geen behandeling 1,28; 95%-BI 1,18 tot 1,40). Bij een behandelduur van ten minste 30 dagen werd geen verschil in risico op CVA

gevonden tussen risperidon en olanzapine. Het risico op een CVA bij de veel beperktere behandelduur van delier met antipsychotica (maximaal 1 week) is niet bekend.

Verlengde QTc-tijd bij intraveneuze toediening haloperidol

Intraveneus haloperidol kan de gecorrigeerde QT-tijd (QTc-tijd) verlengen met het risico op *torsades de pointes*, een ernstige ventriculaire aritmie. Dit risico is vooral relevant bij patiënten met een reeds verlengde QTc-tijd en/of gebruik van andere medicatie die de QTc-tijd verlengt (onder andere antiaritmica, sommige antibiotica, tamoxifen, furosemide).

Aanbeveling:

- Gezien de potentiële bijwerkingen is de werkgroep van mening dat, zeker bij toch al kwetsbare patiënten, zorgvuldig moet worden afgewogen of het gebruik van antipsychotica bij een delier strikt noodzakelijk is.
- Als dat het geval is, geniet vooralsnog een lage dosis haloperidol de voorkeur (mits niet gecontra-indiceerd zoals bij patiënten met de ziekte van Parkinson), omdat hiermee wijdverbreid de meeste ervaring is opgedaan.
- Vanwege het risico op ernstige bijwerkingen is voorzichtigheid geboden bij intraveneuze toediening van haloperidol in de thuissituatie.

Benzodiazepine als comedicatie

- **Overweeg, als de patiënt ondanks (de maximale dosering) haloperidol erg onrustig blijft, kortdurend en op geleide van de symptomen een benzodiazepine toe te voegen, bij voorkeur lorazepam 0,5 tot 2 mg/2 uur oraal of parenteraal (of indien acute parenterale toediening noodzakelijk is: midazolam intramusculair, zie ook de Farmacotherapeutische Richtlijn Geneesmiddelen en zuurstof in spoedeisende situaties). Als de patiënt tot rust is gekomen wordt de benzodiazepine ook weer als eerste afgebouwd.**

Als een oudere of terminaal zieke patiënt ondanks toedienen van haloperidol erg onrustig blijft, kan het toevoegen van een benzodiazepine zinvol zijn. Benzodiazepinen moeten echter nooit zonder haloperidol worden voorgeschreven, omdat deze middelen het bewustzijn verder verlagen. Dit is onwenselijk omdat het de patiënt de kans ontneemt om greep te krijgen op zijn situatie en een toename van angst en onrust tot gevolg kan hebben. Indien een patiënt tot rust is gekomen, is het raadzaam eerst het benzodiazepine en daarna de haloperidol af te bouwen.

De voorkeur bij ouderen gaat uit naar lorazepam of midazolam, omdat deze middelen een korte halfwaardetijd hebben en geen actieve metabolieten. Hoewel beide middelen parenteraal kunnen worden toegediend, zijn in de NHG-Checklist Spoedgeneesmiddelen in de visitetas midazolam-ampullen wel opgenomen, maar lorazepam alleen in tabletvorm. In situaties waarin een indicatie bestaat voor acute toediening van een benzodiazepine, maar orale toediening van lorazepam niet mogelijk is, wordt derhalve aanbevolen om midazolam intramusculair te geven (zie ook de Farmacotherapeutische Richtlijn Geneesmiddelen en zuurstof in spoedeisende situaties).

Maximale duur symptoombehandeling met antipsychotica

- **Bouw haloperidol na maximaal 1 week af; bij langer gebruik neemt het risico op ernstige bijwerkingen (parkinsonisme, tardieve dyskinesie, CVA) toe. Hanteer als vuistregel om met de afbouw te starten zodra de patiënt 2 maal achtereen een goede nachtrust had. Bouw af door elke 2 dagen de dosering te halveren; stop 2 dagen nadat een dosis van 1 mg/dag is bereikt.**

In aansluiting op een vragenlijstonderzoek onder 52 Amerikaanse deskundigen (ouderenpsychiaters, geriaters en huisartsen) over het optimale gebruik van antipsychotica bij ouderen werd consensus bereikt om bij delirante patiënten met een goede respons op het voorgeschreven antipsychoticum het middel na 1 week af te bouwen. Ook de NICE-richtlijn Delirium adviseert om het gebruik van antipsychotica te beperken tot maximaal 1 week. De standaard sluit zich aan bij deze adviezen.

Antipsychotica bij 'Lewy body'-dementie en de ziekte van Parkinson

- **Overleg over medicamenteuze behandeling van delier bij patiënten met *'Lewy body'-dementie* en *de ziekte van Parkinson* met een (behandelend) specialist; beide aandoeningen zijn een contra-indicatie voor haloperidol, wegens een hoog risico op extrapiramidale bijwerkingen of toename van motorische parkinsonverschijnselen (zie ook de NHG-Standaard Dementie en de NHG-Standaard Ziekte van Parkinson).**

Bij de behandeling van een delier bij een patiënt met 'Lewy body'-dementie zijn typische antipsychotica (zoals haloperidol) en ook het atypische antipsychoticum risperidon gecontra-indiceerd, vanwege een sterke dopaminerge bindingscapaciteit en een hoog risico op extrapiramidale bijwerkingen of toename van motorische parkinsonverschijnselen.

Alleen bij het atypische antipsychoticum clozapine is het risico op extrapiramidale bijwerkingen gering. Bij het gebruik van clozapine is leukocytencontrole geïndiceerd vanwege het risico op agranulocytose: wekelijks in de eerste achttien weken van het gebruik, bij langer gebruik maandelijks en tevens bij koorts.

Bij contra-indicaties voor clozapine komt quetiapine nog in aanmerking, hoewel hier minder bewijs voor is. Het lijkt een veilig alternatief.

Ook olanzapine is hiervoor onderzocht, maar is eveneens minder onderbouwd en heeft bovendien een negatief effect op de motoriek. Omdat de meeste huisartsen met het voorschrijven van deze middelen geen ervaring hebben, is bij patiënten met 'Lewy body'-dementie en een delier overleg met de behandelend specialist gewenst.

Evenals bij patiënten met 'Lewy body'-dementie zijn typische antipsychotica (zoals haloperidol) en ook het atypische antipsychoticum risperidon bij patiënten met de ziekte van Parkinson gecontra-indiceerd, vanwege een sterke dopaminerge bindingscapaciteit en hoog risico op extrapiramidale bijwerkingen of toename van motorische parkinsonverschijnselen.

De NHG-Standaard Ziekte van Parkinson adviseert in aansluiting bij de Multidisciplinaire Richtlijn Parkinson bij een psychose/delier bij patiënten met de ziekte van Parkinson met de behandelend neuroloog of geriater te overleggen over eventuele aanpassing van de parkinsonmedicatie.

Indien aanpassing niet mogelijk is of geen effect heeft, is behandeling met clozapine een mogelijkheid, omdat hierbij het risico op extrapiramidale bijwerkingen gering is. Vanwege het risico

bij clozapine op granulocytopenie of agranulocytose, is gedurende deze behandeling intensieve leukocytencontrole noodzakelijk.

Geadviseerd wordt dit middel uitsluitend in overleg met de behandelend specialist voor te schrijven, zie ook de NHG-Standaard Ziekte van Parkinson.

Specifieke aandachtspunten bij een delier in de palliatieve fase

- **Geef ter bestrijding van angst, hallucinaties of motorische onrust haloperidol (zie boven), met een maximale dosering van 20 mg/24 uur en zonder beperking in de duur.**
- **Bouw, bij opklaren van het delier, haloperidol af zoals beschreven onder delier bij ouderen.**
- **Overweeg, als een patiënt ondanks toedienen van haloperidol erg onrustig blijft, kortdurend een benzodiazepine toe te voegen (zie boven). Bij patiënten die niet kunnen slikken: lorazepam sublinguaal 1 tot 2 mg, zo nodig elke 6 uur (kan ook i.m., s.c. of i.v. worden toegediend). Als de patiënt tot rust is gekomen wordt dit ook weer als eerste afgebouwd.**
- **Consulteer bij onvoldoende effect of indien haloperidol gecontra-indiceerd is (zie eerder) een kaderhuisarts/consulent palliatieve zorg; overweeg, in nauwe samenspraak met naasten, palliatieve sedatie als ondanks maximale behandeling symptomen van delier persisteren.**

In een Cochrane-review uit 2012 werd het beschikbare bewijs over de effectiviteit van medicatie voor de symptomatische behandeling van een delier in de palliatieve fase geëvalueerd, waarbij gezocht werd naar prospectief onderzoek al dan niet gerandomiseerd en/of geblindeerd. Er werd slechts 1 (dubbelblind, niet-placebogecontroleerd) onderzoek gevonden, uitgevoerd in 1996 onder 30 in het ziekenhuis opgenomen terminaal zieke aidspatiënten met een delier (gemiddelde leeftijd 39,2 jaar, spreiding 23 tot 56 jaar), waarin de effectiviteit en bijwerkingen van haloperidol, chloorpromazine en lorazepam werden vergeleken. De score op de Delirium Rating Scale verbeterde bij zowel haloperidol als chloorpromazine alleen gedurende de eerste 24 uur na het starten van de medicatie. De cognitieve status verbeterde in de chloorpromazinegroep gedurende de eerste 24 uur, maar verslechterde weer vanaf de 2^{e} behandeldag. Bij patiënten in de lorazepam groep verslechterde de cognitie en vanwege excessieve sedatie werd deze behandelarm voortijdig gestaakt. In geen van de behandelgroepen deden zich ernstige extrapiramidale bijwerkingen voor.

De auteurs van de Cochrane-review concluderen dat er onvoldoende bewijs is om conclusies te trekken over de rol van medicamenteuze behandeling van een delier bij terminaal zieke volwassenen en adviseert vooralsnog de huidige richtlijnen, met haloperidol als middel van eerste keus, te volgen.

Conclusie: er is vrijwel geen bewijs voor de effectiviteit van medicamenteuze behandeling van een delier in de palliatieve fase en de middelenkeuze.

Aanbevelingen: ook bij de behandeling van een delier in de palliatieve fase is haloperidol middel van eerste keus.

Andere punten die van belang zijn:

- **Indien na toediening van haloperidol de agitatie en onrust toenemen is mogelijk sprake van een paradoxale reactie; dit is reden voor verwijzing.**
- **Indien de maximale dosering haloperidol (eventueel gecombineerd met een benzodiazepine) onvoldoende effect sorteert of als symptoombestrijding langer dan 1 week**

noodzakelijk is, is dit een indicatie om een specialist te consulteren of de patiënt te verwijzen. Voor langdurige symptoombestrijding lijkt risperidon een veiliger middel.

- **Het voorschrijven van andere middelen dan haloperidol (of eventueel risperidon) bij delier wordt in deze standaard niet geadviseerd; de effectiviteit van andere antipsychotica en cholinesteraseremmers is niet goed onderbouwd en de ervaring met deze middelen in de eerste lijn is beperkt.**
- **Geef ouderen met een delier ten gevolge van *alcohol- of benzodiazepineonttrekking*, waarbij zich hevige angst of onrust voordoet lorazepam (0,5 tot 2 mg/2 uur oraal of parenteraal, op geleide van de symptomen). Voeg, indien de symptomen persisteren, haloperidol toe. Bij een alcohol (onttrekkings) delier moet tevens op korte termijn worden gestart met vitamine-B_1-suppletie (zie ook de NHG-Standaard Problematisch Alcoholgebruik).**

<u>Symptoombestrijding bij een hypoactief delier</u>

De Rooij et al. verrichtten een systematische review (op basis van 10 onderzoeken, met in totaal 1065 patiënten met een delier) naar de klinische relevantie van subtypering van delier, onder meer gelet op de therapeutische consequenties. Zij concludeerden dat een psychomotorisch hypoactief delier (bij kankerpatiënten) even intensief en stressvol kan zijn als andere, onrustige vormen, maar dat de verschijnselen van een hypoactief delier mogelijk minder responsief zijn voor antipsychotica. Psychostimulantia zijn wel geopperd voor de behandeling van een hypoactief delier, maar de effectiviteit is niet bewezen.

5.4 Antipsychotics and insomnia

5.4.1 Summary

Antipsychotics for insomnia.

Canada 2018 : the evidence in support of the effectiveness of atypical antipsychotics for insomnia is poor and of low quality. No recommendations were formulated in this guideline.

EUR 2017 does not recommend antipsychotics for insomnia treatment because of insufficient evidence of their efficacy and considering their side effects.

WOREL 2018 states there is no place for antipsychotics, such as quetiapine, in the indication of insomnia due to their potentially serious adverse effects.

USA 2016: no information have been found concerning antipsychotics despite the authors stated they will investigate their off-label use in insomnia.

Therapeutic approach of insomnia: other therapeutic classes and first-choice drugs.

Antihistamines, antipsychotics, melatonin and phytotherapy are not recommended for insomnia (EUR 2017, WOREL 2018). Barbiturates as a sleeping pill is considered obsolete in primary care (WOREL 2018).

If required, EUR 2017 and WOREL 2018 recommend a pharmacological intervention for insomnia only for the short term treatment (≤4 weeks) and if cognitive behavioral therapy is not effective or not available.

- EUR 2017 and WOREL 2018 propose benzodiazepines and benzodiazepine receptor agonists as effective drugs for insomnia. Drugs with shorter half-lives are preferred because they have less side-effects concerning sedation in the morning.
- EUR 2017 proposes that some sedating antidepressants may be used for short-term treatment of insomnia as well, but contra-indications have to be carefully considered. However, WOREL 2018 recommends to avoid antidepressants (including trazodone) for this indication because of side effects and lack of evidence.

No medication is indicated for the first-line management of insomnia in the elderly (WOREL 2018).

Safety of antipsychotics in the context of insomnia.

EUR 2017 and WOREL 2018 consider the risk of potentially severe adverse effects in their recommendation not to prescribe antipsychotics for insomnia.

Canada 2018 considers that antipsychotics are generally taken at a lower dose for insomnia than for other indications. Therefore, the adverse effect profile might not be the same for insomnia. However they found little information concerning harms of atypical antipsychotics for insomnia.

5.4.2 Canada 2018

While this guideline was primarily aimed at given recommendations for deprescribing of antipsychotics for BPSD and insomnia authors gave the following statements:

As there were no studies examining the deprescribing of antipsychotics used for the treatment of insomnia, we decided to focus on finding evidence for the effectiveness of such treatment.

Are antipsychotics effective for treating insomnia?

The evidence in support of the effectiveness of atypical antipsychotics for insomnia is poor and of low quality.

Only 1 study involving 13 participants was identified in the literature.23 Given that it showed modest but not statistically significant improvements in all 3 sleep outcomes, additional studies could strengthen the evidence for or against using antipsychotics for this purpose.

There is very low certainty surrounding a lack of evidence that atypical APs are effective for managing insomnia

What is the adverse effect profile of antipsychotics prescribed for the treatment of insomnia?

There is minimal information surrounding harms of atypical APs for insomnia; however, their use for other indications suggests potential for harm (eg, EPS, somnolence, metabolic disturbances, anticholinergic adverse effects)

Antipsychotics are generally taken at a lower dose for the treatment of insomnia than for other indications; however, the harms literature generally reports on antipsychotics used at higher doses. The adverse effect profile might not be the same in the case of insomnia.

5.4.3 EUR 2017

In the presence of co-morbidities, clinical judgement should decide whether insomnia or the co-morbid condition is treated first, or whether both are treated at the same time. CBT-I

CBT-I is recommended as first-line treatment for chronic insomnia in adults of any age (strong recommendation, high-quality evidence).

A pharmacological intervention can be offered if CBT-I is not effective or not available.

BZ and BZRA

BZ and BZRA are effective in the short-term treatment of insomnia (≤4 weeks; high-quality evidence).

The newer BZRA are equally effective as BZ (moderate-quality evidence).

BZ/BZRA with shorter half-lives may have less side-effects concerning sedation in the morning (moderate-quality evidence).

Long-term treatment of insomnia with BZ or BZRA is not generally recommended because of a lack of evidence and possible side-effects/risks (strong recommendation, low-quality evidence). In patients using medication on a daily basis, reduction to intermittent dosing is strongly recommended (strong recommendation, low-quality evidence).

Sedating antidepressants

Sedating antidepressants are effective in the short-term treatment of insomnia; contraindications have to be carefully considered (moderate-quality evidence). Long-term treatment of insomnia with sedating antidepressants is not generally recommended because of a lack of evidence and possible side-effects/risks (strong recommendation, low-quality evidence).

Antihistaminics

Because of insufficient evidence, antihistaminics are not recommended for insomnia treatment (strong recommendation, low-quality evidence).

Antipsychotics

Because of insufficient evidence and in light of their side-effects, antipsychotics are not recommended for insomnia treatment (strong recommendation, very low-quality evidence).

Melatonin

Melatonin is not generally recommended for the treatment of insomnia because of low efficacy (weak recommendation, low-quality evidence).

Phytotherapy

Valerian and other phytotherapeutics are not recommended for the treatment of insomnia because of poor evidence (weak recommendation, low-quality evidence).

Light therapy and exercise

Light therapy and exercise regimes may be useful as adjunct therapies (weak recommendation, low-quality evidence).

Complementary and alternative medicine

Acupuncture, aromatherapy, foot reflexology, homeopathy, meditative movement, moxibustion and yoga are not recommended for the treatment of insomnia because of poor evidence (weak recommendation, very low-quality evidence).

Available substances include BZ and BZRAs, antidepressants, antipsychotics, antihistamines, phytotherapeutic substances and melatonin (*see figure 5*).

Table 8 Major drug classes used to treat insomnia in Europe

BZ	Diazepam, flunitrazepam, flurazepam, lormetazepam, nitrazepam, oxazepam, temazepam, triazolam
BZRA	Zaleplone, zolpidem, zopiclone
Antidepressants	Agomelatine, amitriptyline, doxepin, mianserin, mirtazapine, trazodone, trimipramine
Antipsychotics	Chlorprothixene, levomepromazine, melperone, olanzapine, pipamperone, prothipendyl, quetiapine
Antihistamines	Diphenhydramine, doxylamine, hydroxyzine, promethazine
Phytotherapeutics	Hops, melissa, passiflora, valerian
Melatonin receptor agonists	Melatonin, ramelteon, slow-release melatonin

BZ, benzodiazepines; BZRA, benzodiazepine receptor agonists.

Figure 5: Table of drug classes used to treat insomnia and reported in EUR 2017.

There are no meta-analyses on the efficacy of antipsychotics in insomnia, but four related systematic reviews exist. Monti and Monti and Cohrs concluded that sedating antipsychotics increase total sleep time and the amount of slow-wave sleep in patients with schizophrenia. However, Anderson and Vande Griend, and Thompson et al. conclude that the evidence on quetiapine is insufficient to recommend its use in the treatment of insomnia, in the absence of psychiatric disorders, particularly in light of its potential side-effects.

The pharmacological literature summarized dealt with the short-term treatment of insomnia (≤4 weeks). The rationale for this is that the hypnotics available are exclusively indicated, and approved, only for short-term treatment in most European countries. Arguably, however, the long-term treatment of insomnia using hypnotics is clinically relevant because insomnia typically returns following withdrawal.

The aforementioned evidence suggests that BZ and BZRAs may be used in the short term if the first-line treatment (CBT-I) is ineffective or unavailable (high-quality evidence). Some sedating antidepressants too may be used for short-term treatment (moderate-quality evidence). Further, antihistamines and antipsychotics are not recommended for the treatment of insomnia (strong recommendation – low- to very-low-quality evidence), and melatonin and phytotherapy are not recommended for insomnia (weak recommendation – low-quality evidence).

<u>Long-term treatment of insomnia with hypnotics</u>

The pharmacological literature summarized above dealt with the short-term treatment of insomnia (≤4 weeks). The rationale for this is that the hypnotics available are exclusively indicated, and approved, only for short-term treatment in most European countries.

Arguably, however, the long term treatment of insomnia using hypnotics is clinically relevant because insomnia typically returns following withdrawal.

These long-term studies show that the efficacy of hypnotics may remain stable over longer periods of administration. However, in some studies the effects decreased over time.

Based upon the evidence, **BZ and BZRAs are not recommended in the longer-term treatment of insomnia (**strong recommendation – low-quality evidence**)**.

5.4.4 WOREL 2018

Faut-il envisager un envisager un traitement médicamenteux ?

Chez les patients qui présentent une forme aiguë d'insomnie sévère associée à une souffrance importante, envisagez un traitement de courte durée avec un somnifère (GRADE 2C- Faible recommandation, niveau de preuve faible à très faible **).**

Prescrivez la dose efficace la plus faible possible, et ce pour une durée la plus brève possible. La durée exacte d'administration dépend de l'origine sous-jacente de la forme aiguë d'insomnie sévère, mais ne doit pas excéder une semaine. Il peut parfois se révéler nécessaire d'administrer plus longtemps une benzodiazépine ou un médicament de type « z-drug », mais cette décision exige une réévaluation du patient et de son insomnie, parfois assortie du besoin de réduire progressivement a posteriori les somnifères.

Ne prescrivez pas de somnifères à des patients souffrant d'insomnie aiguë ou chronique qui se trouvent dans une situation critique et qui entrent en ligne de compte pour une prise en charge multimodale selon les principes de la thérapie comportementale cognitive (GRADE 1B- Forte recommandation, niveau de preuve modéré**).**

Discutez également d'emblée d'une stratégie d'arrêt dès l'entame de l'administration des somnifères (GRADE 1C- Forte recommandation, niveau de preuve faible à très faible**).**

Il existe donc des données probantes de faible qualité portant sur l'effet que peut avoir cette intervention pour éviter un usage chronique de somnifères. Les avantages de cette intervention pèsent plus lourds que les inconvénients.

Parallèlement, proposez aussi au patient des informations sur la prise en charge non médicamenteuse de son insomnie et/ou de la problématique sous-jacente (voir également la question clinique 2) (GPP-Good Practice Point**).**

L'évocation (succincte) (de la possibilité) d'une prise en charge non médicamenteuse à la première consultation est considérée comme un « good clinical practice » et constitue une manière de préparer le patient à une continuation non médicamenteuse après une brève prise en charge médicamenteuse.

Quel traitement médicamenteux ?

Envisagez comme somnifère une benzodiazépine à durée d'action intermédiaire ou un z-drug, à une dose la plus faible possible et pour une durée la plus courte possible (maximum une semaine) (GRADE 2C-Faible recommandation, niveau de preuve faible à très faible**).**

Partant de la littérature existante, rien n'indique de privilégier clairement les benzodiazépines classiques ou les z-drugs plus récents. Il s'avère préférable d'opter pour une benzodiazépine à demi-vie intermédiaire, de type lormétazépam, vu le risque moindre d'effet « gueule de bois ». Les produits qui présentent un long temps de demi-vie, comme le diazépam ou le nitrazépam, sont à éviter pour l'indication d'insomnie. Dans le groupe des benzodiazépines ou des z-drugs, aucun produit de premier choix n'est mis en avant.

La trazodone est un antidépresseur fortement sédatif prescrit hors indication en cas d'insomnie (utilisation « off-label »). Certains médecins et patients estiment qu'à faible dose, p. ex. 25 à 50 mg, le produit constituerait un somnifère « plus sûr » que les benzodiazépines ou z-drugs classiques. Pourtant, la trazodone connaît bon nombre d'effets indésirables avérés sur la mémoire à court terme, le processus d'apprentissage, le tonus musculaire et l'équilibre ; elle occasionne aussi plus fréquemment des cauchemars. C'est pourquoi la trazodone n'est pas recommandée comme produit de premier choix.

Dans le traitement de l'insomnie en première ligne, le manque de données probantes ne laisse malheureusement pas de place à d'autres antidépresseurs à action sédative (type amitriptyline, faible dose, p.ex. 10 mg le soir, ou miansérine).

L'usage de barbituriques et de leurs dérivés comme somnifère est considérée comme obsolète dans la prise en charge en première ligne.

Melatonine : seulement etudiée chez pers âgée.

Il n'y a pas non plus de place pour les anciens antihistaminiques sédatifs, comme la prométhazine, ni pour les antipsychotiques, de type quétiapine, dans l'indication d'insomnie du fait de leurs effets indésirables potentiellement graves.

L'efficacité de la quétiapine en cas d'insomnie sans comorbidité : cette analyse conclut que son efficacité n'est pas démontrée pour cette indication.

La synthèse méthodique évoque également un risque accru de mort cardiaque subite en cas d'utilisation d'antipsychotiques atypiques, également à faible dose (RR= 1,59, IC à 95 % 1,03 à 2,46). Précisément pour la quétiapine, on rapporte un risque accru lorsque tous les dosages sont regroupés dans l'analyse (RR= 1,88, IC à 95 % 1,30 à 2,71). Les analyses de sensibilité en fonction de la dose ne montrent un risque accru qu'en cas d'utilisation d'une dose moyenne à élevée. Les effets indésirables d'une faible dose ne sont pas connus avec une précision suffisante. Partant de ces données, (profil de risque défavorable) le groupe d'auteurs a décidé de déconseiller l'usage d'antipsychotiques pour le traitement de l'insomnie.

Nous déconseillons en outre le recours à la phytothérapie, p. ex. la valériane, la passiflore, etc., en raison du manque de clarté autour de son efficacité et de l'incertitude par rapport aux effets indésirables possibles et aux effets à long terme.

Points d'attention concernant les personnes âgées
Prise en charge médicamenteuse

Une médication n'est pas indiquée dans la prise en charge en première ligne de l'insomnie chez les personnes âgées (GRADE 1C- Forte recommandation, niveau de preuve faible à très faible).

Benzodiazépines et z-drugs: Lorsque des somnifères sont tout de même prescrits à des personnes âgées, la dose doit être divisée par deux.

Pourtant, en Belgique, l'usage (chronique) des somnifères demeure très élevé chez les personnes âgées (institutionnalisées). Ce n'est qu'à travers une offre accessible et pluridisciplinaire d'interventions non médicamenteuses structurées (et au sein d'un centre de services de soins et de logement de préférence avec l'appui des décideurs et en se concentrant sur un changement culturel largement soutenu par rapport à l'approche des problèmes de santé mentale) que peut avoir lieu un revirement de situation au niveau de l'usage de somnifères.

Mélatonine : La place de la mélatonie dans la prise en charge de l'insomnie chez les personnes âgées, et surtout chez les personnes de plus de 55 ans, n'a pas suffisamment été étudiée.

5.4.5 USA 2016

Authors from this guideline stated that they will review and evaluate psychological and pharmacological treatments of chronic insomnia. Among these is included off label use of drugs such as antidepressants and antipsychotics. In spite of this, no information was found concerning antipsychotics in this guideline.

5.5 Withdrawal/discontinuation of antipsychotic drugs for insomnia

5.5.1 Summary

EUR 2017 and WOREL 2018 : No recommendations were formulated in these guidelines.

USA 2016: no information was found concerning the discontinuation of antipsychotics.

Canada 2018 recommends stopping antipsychotics for adults with primary insomnia treated for any duration, or with secondary insomnia in which underlying comorbidities are managed; tapering is not needed. This recommendation is based on the lack of evidence for the efficacy of antipsychotics and places high value in minimal clinical risk of deprescribing and in reducing the inappropriate use of antipsychotics and their side effects.

Suggested tapering strategy:

- If the patient has been taking an antipsychotic for a short period of time (e.g. < 6wk) stop antipsychotic use immediately.
- If the patient has been taking the antipsychotic for a longer period of time, consider tapering the dose first before stopping.
- If there are concerns on the part of either the patient or the prescriber about possible side effects of immediate discontinuation, tapering can also be considered.
- All patients should be counseled about non-pharmacologic approaches to sleep.

5.5.2 Canada 2018

For adults with primary insomnia treated for any duration or secondary insomnia in which underlying comorbidities are managed, we recommend the following:

- **Stop antipsychotics; tapering is not needed (good practice recommendation).**

The QoE for effectiveness of atypical APs for insomnia is very low. One RCT (N=13) demonstrated no statistical difference in total sleep time, onset of sleep latency, or sleep satisfaction for quetiapine vs placebo over 2 wk for primary insomnia. The trial was very low quality owing to imprecision and risk of bias.

There is minimal information surrounding harms of atypical APs for insomnia; however, their use for other indications suggests potential for harm (eg, EPS, somnolence, metabolic disturbances, anticholinergic adverse effects) .

The magnitude of benefits of deprescribing in terms of cognition, psychomotor status, reductions in adverse effects of AP, or mortality are unclear. Declercq et al report that “Individual studies did not report significant differences between groups on any other outcome except one trial that found a significant difference in a measure of verbal fluency, favouring discontinuation. Most trials lacked power to detect clinically important differences between groups”.

Based on the lack of evidence for the efficacy of antipsychotics for treating insomnia, and the potential for harm and high cost, we rated the recommendation to eliminate antipsychotic use for the treatment of insomnia as strong. These recommendations place a high value on the minimal clinical risk of deprescribing, reducing the inappropriate use of APs and their side effects, and the associated resource use given the high cost, both monetary and nonmonetary, associated with long-term AP use. They place some value on the potential for harms from attempted deprescribing and on potentially increased caregiver resource use as a result of deprescribing APs.

Suggested tapering strategies

For those prescribed antipsychotics for the treatment of insomnia, we recommend the following:

- If the patient has been taking an antipsychotic for a short period of time (eg, < 6wk) stop antipsychotic use immediately.
- If the patient has been taking the antipsychotic for a longer period of time, consider tapering the dose first before stopping.
- If there are concerns on the part of either the patient or the prescriber about possible side effects of immediate discontinuation, tapering can also be considered.
- All patients should be counseled about nonpharmacologic approaches to sleep (so-called sleep hygiene).

Clinicians at the LTC ….were comfortable with abrupt cessation when low-dose antipsychotics had been prescribed for insomnia.

In all cases, regardless of the severity of BPSD or the use for insomnia, patient and caregiver involvement in the decision to deprescribe antipsychotics is essential. Good communication should include the rationale (eg, risk of side effects) and consideration of values and preferences, and should ensure understanding and agreement with the proposed changes (“buy-in”), as well as involvement in making the deprescribing and monitoring plans.

Furthermore, an antipsychotic deprescribing algorithm has been developed in this guideline for BPSD and insomnia and is provided as figure 1 in section 5.2 Withdrawal/discontinuation of antipsychotics for PBSD.

5.5.3 EUR 2017

No specific recommendations or comments were provided regarding deprescribing of antipsychotic for insomnia.

5.5.4 WOREL 2018

No specific recommendations or comments were provided regarding deprescribing of antipsychotic for insomnia.

5.5.5 USA 2016

Authors from this guideline stated that they will review and evaluate psychological and pharmacological treatments of chronic insomnia. Among these is included off label use of drugs such as antidepressants and antipsychotics. In spite of this, no information have been found concerning antipsychotics in this guideline.

5.6 Follow up and monitoring during antipsychotic treatment

For the recommendations or the comments regarding particular monitoring or follow up during the tapering phase of the antipsychotic treatment we refer to the section "5.2 withdrawal/discontinuation of antipsychotics for PBSD" or section "5.5 Withdrawal/discontinuation of antipsychotic drugs for insomnia".

5.6.1 Summary

Antipsychotic follow up in the treatment of BPSD

APA 2016, AUS 2016, NICE 2018 and IRE 2019 stress the importance or recommend a regular review of the antipsychotic titration and/or continuing treatment.

- AUS 2016 recommends that treatment is reviewed every 4 to 12 weeks.
- NICE 2018 recommends a review of the antipsychotic treatment every 6 weeks.
- APA 2016 only made formal recommendations for reviewing the treatment when patients experience a clinical adverse effect. APA 2016 states that if there is no sufficient clinical response, treatment should be stopped within 4 weeks. If a partial response to antipsychotic treatment occurs, further dose titration may be indicated.
- IRE 2019 mentions for psychotropic substances that treatment should be regularly reviewed without formulating specific time for initial review or specific review periodicity. IRE 2019 nevertheless states to review the person with dementia who has had two or more failed attempts of antipsychotic withdrawal and requires ongoing maintenance therapy with an antipsychotic at least 6-monthly.

Measurement of BPSD should be undertaken using tools with strong psychometric properties (AUS 2016). Use of quantitative measures can be helpful in tracking longitudinal responses (APA 2016).

Review should include recording of changes in cognition and target symptoms, as well as monitoring for adverse effects including metabolic syndrome (APA 2016, AUS 2016).

APA 2016 further recommends that patients with dementia have a documented comprehensive treatment plan that includes appropriate person-centered non-pharmacological and pharmacological interventions, monitoring of physiological parameters (e.g., weight, blood pressure), point-of-care testing (e.g., glucose fingersticks), laboratory testing, and other individuals information on needs, desires, preferences, and values to provide comprehensive person-centered care.

Antipsychotic follow up in the treatment of delirium

NICE 2010 : No recommendations were formulated in this guideline.

SIGN 2019: antipsychotics prescribed for delirium should be reviewed on a daily basis and stopped as soon as the clinical situation allows, typically within 1–2 days.

NHG 2014: In crisis situations, haloperidol up to 10 mg/24 hours, evaluate every hour whether the motor unrest and/or anxiety are sufficiently under control. If delirium does not resolve, adjust the pharmacological treatment or further evaluate for other underlying causes.

Antipsychotic follow up in the treatment of insomnia

EUR 2017, WOREL 2018, USA 2016, Canada 2018: No recommendations were formulated in these guidelines.

Antipsychotic monitoring:

APA 2016: Specific recommendations about the timing of laboratory monitoring have not been developed for individuals with dementia who are being treated with antipsychotic medication. Based on individuals with schizophrenia, the following is suggested:

- Abnormal Involuntary Movement Scale (AIMS): at least every 6 months in geriatric patients (American Psychiatric Association 2004).
- Monitoring blood pressure, weight, body mass index (BMI), waist circumference, fasting glucose, fasting lipid profile, and personal/family history: at baseline for individuals receiving antipsychotic medication.
- Personal/family history and waist circumference annually.
- Blood pressure and fasting plasma glucose at 12 weeks and annually.
- Lipid profile at 12 weeks and every 5 years.
- Weight with calculation of BMI monthly for 3 months, then quarterly.
- Haemoglobin A1C monitoring may be substituted for a fasting glucose level.

No other information was found from other guidelines regarding monitoring of antipsychotics for adults.

Specific information regarding physiological and clinical parameters to be monitored, as well as the time schedule for monitoring in children is provided in CAMASA 2011. See monitoring summary tables and practical tool for metabolic monitoring (figures 6, 7 and 8).

- Beyond the first year of monitoring, CAMESA 20111 suggests to repeat laboratory tests yearly in stable patients with normal physical examination, and previous normal laboratory tests. Physical examination maneuvers are completed during all follow-up visits, as a part of the routine care.
- Given the evidence for metabolic side effects in children treated with SGAs, and the long term sequelae of these problems, CAMESA 2011 states that monitoring of all children prescribed SGAs is appropriate.

The role of different healthcare professions in the follow-up of antipsychotic treatment

AUS 2016 formally recommends on the training of health professional in the correct use of medication for behavioural control. Health professionals should be able to assess the risks associated with antipsychotics, particularly in people who may be dehydrated or physically ill.

They should understand the cardiorespiratory effects of antipsychotics, be learned about the need to titrate dosage to effects, the need of monitoring vital signs, the importance of positioning people who have received these medications in the recovery position, and be familiar with and trained in the use of resuscitation equipment.

NICE 2018 and APA 2016 also state for enhanced psychosocial interventions including staff training, individualized interpersonally based education, support for caregivers, and appropriate use of non-pharmacological methods that appear to reduce the use of antipsychotic therapies in persons with dementia-related agitation.

5.6.2 APA 2016

Treatment follow up

A key issue is the way in which behavioral and psychological symptoms are defined and measured, with the definition and measurement of agitation being particularly problematic. Rating scales for behavioral and psychological symptoms define and measure agitation and aggressive behaviors in different ways and often mix measures of symptom frequency with measures of severity. New, shorter scales are also needed for routine clinical use.

As dose titration proceeds and at all points in the course of treatment with an antipsychotic, the clinician will want to assess the patient and obtain information from caregivers about response to treatment, possible medication side effects, and adherence. As described above, use of quantitative measures can be helpful in tracking longitudinal response. Poor adherence may be due to factors such as cost, difficulties with swallowing, resistance to taking medication, or intolerable side effects.

APA recommends that if a patient with dementia experiences a clinically significant side effect of antipsychotic treatment, the potential risks and benefits of antipsychotic medication should be reviewed by the clinician to determine if tapering and discontinuing of the medication is indicated. (1C-Recommendation with low strength of evidence**)**

If side effects are observed or reported, the nature, frequency, and severity of these side effects will determine whether the risks and benefits of treatment favor ongoing treatment, an attempt at tapering, or immediate discontinuation of the medication. Monitoring for tolerability is also important so that sedation, extrapyramidal effects, gait disturbance, cognitive impairing effects, and other side effects can be minimized.

If a partial response to antipsychotic treatment occurs, further dose titration may be indicated depending on whether side effects are present and on the relative balance of benefits and harms for the patient. When patients are being treated for psychotic symptoms, relief of distress or associated agitation may occur even though hallucinations or delusions persist. In such circumstances, further dose adjustments may not be necessary and would add to the potential for side effects.

If there is no clinically significant response within 4 weeks of reaching a typical therapeutic dose of medication, the medication should be tapered and stopped to avoid potential harms of medication treatment without any offsetting benefit. If severe, dangerous, or significantly distressing symptoms persist, a trial of a different antipsychotic medication may be considered after reevaluation for

contributing factors to the patient's symptoms, additional review of the risks and benefits of treatment, and discussion with the patient and surrogate decision maker, with input from family and other involved individuals.

Development of treatment plan

APA recommends that patients with dementia have a documented comprehensive treatment plan that includes appropriate person-centered non-pharmacological and pharmacological interventions, as indicated. (1C- Recommendation with low strength of evidence**)**

Given the risks associated with antipsychotic medications, if nonemergent use of antipsychotic medication is being considered to address agitation or psychosis, it is important to review all aspects of the assessment and the treatment plan. The aims of such a review are to determine the frequency and severity of symptoms in a systematic fashion, identify consequences of agitation or psychosis (e.g., distress to the patient, danger to self or others), discover previously unrecognized contributors to agitation or psychosis, reassess the clinical response to nonpharmacological or pharmacological treatments, and decide whether different interventions might be indicated.

Such a plan does not need to adhere to a defined development process (e.g., face-to-face multidisciplinary team meeting) or format (e.g., time-specified goals and objectives), but it should give an overview of the identified clinical and psychosocial issues along with a specific plan for further evaluation, ongoing monitoring, and nonpharmacological and pharmacological interventions, as indicated. Depending on the urgency of the initial clinical presentation, the availability of caregivers, and the time for assessment, the initial plan may need to be augmented over several visits and as more details of the history and treatment response are obtained. If a symptom is rare, reassurance and redirection, with education of family and other caregivers, are likely to be sufficient, with other time-limited interventions used if needed.

In addition to nonpharmacological interventions, the treatment plan may include pharmacological interventions to address physical conditions or symptoms such as pain or constipation. Although outside the scope of this practice guideline, cholinesterase inhibitors or memantine for dementia, and medications for other psychiatric disorders such as depression or anxiety disorders, may also be part of the treatment plan. Monitoring of physiological parameters (e.g., weight, blood pressure), point-of-care testing (e.g., glucose fingersticks), or laboratory testing may be included when indicated. Other elements of the treatment plan will be unique to the individual and his or her past experiences, needs, desires, preferences, and values to provide comprehensive person-centered care that is aimed at alleviating distress, promoting comfort, and enhancing quality of life.

Any prescribed medications should also be reviewed for their benefits and for evidence of adverse effects.

Psychosocial interventions that include individualized interpersonally based education and support for caregivers also appear to reduce the use of antipsychotic therapies in persons with dementia-related agitation. Education should increase knowledge, skills, and attitudes related to unmet needs, environmental regulation, and respect for individual preferences.

Laboratory monitoring

Specific recommendations about the timing of laboratory monitoring have not been developed for individuals with dementia who are being treated with antipsychotic medication; however, in individuals with schizophrenia, it has been suggested that an Abnormal Involuntary Movement Scale (AIMS) be done at least every 6 months in geriatric patients (American Psychiatric Association 2004). Monitoring blood pressure, weight, body mass index (BMI), waist circumference, fasting glucose, fasting lipid profile, and personal/family history have been suggested at baseline for individuals receiving antipsychotic medication, with additional personal/family history and waist circumference annually, blood pressure and fasting plasma glucose at 12 weeks and annually, lipid profile at 12 weeks and every 5 years, and weight with calculation of BMI monthly for 3 months, then quarterly. Hemoglobin A1C monitoring may be substituted for a fasting glucose level.

5.6.3 AUS 2016

Antipsychotic treatment follow up

AUS 2016 formulated the following general recommendation precising conditions that should also be met as additional formal recommendations:

People with dementia and severe behavioural and psychological symptoms of dementia (i.e., psychosis and/or agitation/aggression) causing significant distress to themselves or others, may be offered treatment with an antipsychotic medication.

The following conditions should also be met:

…

• Monitoring for adverse effects including the metabolic syndrome should occur.

• Treatment should be reviewed every four to 12 weeks, considering the need for antipsychotics and possible cessation of medication.

•If there is no efficacy observed within a relatively short timeframe (usually one to two weeks), treatment should be discontinued.

• Review should include regular assessment and recording of changes in cognition and target symptoms.

(EBR-Moderate, evidence-based recommendation-moderate strength of evidence**)**

The objective measurement of behavioural and psychological symptoms of dementia should be

undertaken using tools with strong psychometric properties and used to monitor the type and patterns of behaviours. (EBR-Low, evidence-based recommendation-low strength of evidence)

Health professionals who use medication in the management of violence, aggression and extreme agitation in people with dementia should:

• be trained in the correct use of medications for behavioural control

• be able to assess the risks associated with pharmacological control of violence, aggression and extreme agitation, particularly in people who may be dehydrated or physically ill

• understand the cardiorespiratory effects of the acute administration of any medications used and the need to titrate dosage to effect

• recognise the importance of positioning people who have received these medications in the recovery position and of monitoring vital signs

• be familiar with and trained in the use of resuscitation equipment

• undertake annual retraining in resuscitation techniques

• understand the importance of maintaining a clear airway

• be knowledgeable about the laws for informed consent in their jurisdiction.

(PP-Practice point.**)**

Where people with dementia have moderate to severe behavioural and psychological symptoms that puts themselves or others at risk, referral to a specialist service for the management of behavioural and psychological symptoms should occur. (PP-Practice point.**)**

5.6.4 NICE 2018

<u>Antipsychotic treatment follow up</u>

When using antipsychotics:

Reassess the person at least every 6 weeks, to check whether they still need medication.

The committee agreed that it was necessary to regularly review people taking antipsychotics to ensure the treatment is still necessary, and to encourage a discussion about discontinuation wherever this is possible.

<u>Care providers and staff training</u>

Beside recommendations regarding the approaches for treating non cognitive symptoms of dementia, NICE 2018 also made general recommendations on staff training that could have consequences for antipsychotics use and treatment follow up :

Care providers should provide additional face-to-face training and mentoring to staff who deliver care and support to people living with dementia. This should include:

• understanding the organisation's model of dementia care and how it provides care

…

• advice on interventions that reduce the need for antipsychotics and allow doses to be safely reduced

…

Quality of evidence: The committee agreed the evidence underpinning the recommendations on person-centred care and multisensory stimulation was of moderate to high quality. However, it noted that the evidence base was entirely composed of studies conducted in care homes, and not in other clinical or community settings.

The committee noted that the evidence on using enhanced psychosocial care to reduce antipsychotic prescribing rates came from a single study. Therefore, whilst it was confident to recommend that this

should form part of the training given to staff to manage anxiety, it did not feel that it was appropriate to recommend any specific form these interventions should take based on this single study.

Trials which focused primarily on managing agitation and/or aggression whilst reducing the use of ether antipsychotics medicines or physical restraint were also identified. The aim of these trials was somewhat different, in that rather than trying to improve symptoms, they focused on reducing the use of potentially harmful medicines or procedures, without an increase in symptoms over a defined time period. The committee noted there was clear evidence from these studies that an approximately 50% reduction could be achieved in the use of either antipsychotics or physical restraint without any significant increase in behavioural or other symptoms, and the committee therefore agreed it was appropriate to include this in the recommendation for training interventions.

The committee also noted that the evidence showed that staff training in appropriate use of non-pharmacological methods showed the use of antipsychotics could be significantly reduced without any subsequent increase in neuropsychiatric symptoms, and therefore it was agreed this would form an appropriate part of the training staff should receive in managing non-cognitive symptoms (this is included as part of a recommendation in section 16 on staff training). Moderate-quality evidence from 1 RCT containing 338 people found a lower proportion of people taking antipsychotics in homes that offered an enhanced psychosocial care intervention compared with usual care, but very low- to low-quality evidence from the same study could not differentiate rates of falls or levels of aggression and wellbeing.

5.6.5 IRE 2019

Treatment follow up

Psychotropic medication that is commenced for non-cognitive symptoms in a person with dementia should be reviewed regularly to assess efficacy, adverse effects and continued need. (Good practice point)

The GDG were in agreement that if a decision to commence psychotropic medication is made, the person with dementia should be reviewed regularly, and the effect of the medication on symptom improvement or worsening should be monitored and recorded. The psychotropic medication should be stopped if not improving symptoms after a reasonable trial (using clinician's judgement as to final

dose tried and the duration of trial at this dose, based on initial symptoms, degree of distress, and side effects). The GDG also felt that, in general, there should be a trial of tapering or withdrawing psychotropic medication once symptom stability is reached (although this may not be possible with some depressive episodes where relapse likelihood is high), in conjunction with re-trialling non-pharmacological interventions to maintain symptom remission. A good practice point was formulated to reflect this consensus.

The GDG felt that it was important that the guideline recommendations were feasible in clinical practice. Within a residential care setting or an acute hospital, it would be feasible for staff to review a person regularly (even if the person was not seen by the prescriber in person, but instead by an appropriately qualified other staff member). Many felt that it would however be unreasonable to expect a General Practitioner (GP) or a prescriber in a clinic (out-patient setting) to review a person within 1-2 weeks, and this frequency of review might be onerous for the person with dementia. Other options such as a telephone call to their family/carer were discussed, noting that this would not always be equivalent to an in-person review. Some GDG members felt that the length of time before a review should be individualized as it may depend on the person's functional status, the nature of the non-cognitive symptoms, and the duration, persistence, and severity of symptoms.

Thus, a decision was made by the GDG **not to recommend a specific time for initial review** for early efficacy or side effects, or to specify the duration of a trial of treatment before the treating MDT would conclude that treatment had failed. However, the GDG also felt it was very important that people with a positive response to antipsychotics were not continued on antipsychotics indefinitely. Based on the timelines recommended in international guidelines the GDG chose to specify that a review for possible trial of discontinuation needed to occur within 3 months.

In rare cases where a person with dementia has had two or more failed attempts of antipsychotic withdrawal and requires ongoing maintenance therapy with an antipsychotic, the person should be reviewed at the point of re-prescribing and at least 6 monthly thereafter. (Good practice point)

5.6.6 SIGN 2019

Antipsychotic treatment follow up for delirium

If commenced, antipsychotics prescribed for delirium should be reviewed on a daily basis and stopped as soon as the clinical situation allows, typically within 1–2 days. In situations where it is deemed safer to continue antipsychotic therapy for delirium beyond discharge or transfer from hospital, a clear plan for early medication review and follow up in the community should be agreed.

5.6.7 NICE 2010

No specific recommendations or comments were provided regarding the monitoring of antipsychotic treatment.

5.6.8 NHG 2014

Antipsychotic treatment follow up for delirium

Indien symptomatische behandeling van een delier bij ouderen noodzakelijk wordt geacht, gaat de voorkeur uit naar haloperidol 0,5 tot 1,5 mg 2 dd oraal, gedurende maximaal 1 week.

- **Overweeg in crisissituaties kortdurend een hogere dosis (tot maximaal 10 mg/24 uur): evalueer (telefonisch) na de startdosering elk uur of de motorische onrust en/of angst al voldoende onder controle zijn.**

Pas de medicamenteuze behandeling aan of verricht nadere diagnostiek naar nog niet onderkende oorzaken indien het delier niet opklaart.

5.6.9 EUR 2017

No specific recommendations or comments were provided regarding the follow up or the monitoring of antipsychotic treatment.

5.6.10 WOREL 2018

No specific recommendations or comments were provided regarding the follow up or the monitoring of antipsychotic treatment.

5.6.11 USA 2016

No specific recommendations or comments were provided regarding the follow up or the monitoring of antipsychotic treatment.

5.6.12 Canada 2018

No specific recommendations or comments were provided regarding the follow up or the monitoring of antipsychotic treatment.

5.6.13 CAMESA 2011

The clinical questions addressed in this guideline are:

1. What is the evidence for metabolic and neurological side effects associated with SGA treatment of pediatric mental health disorders?

The risk of weight gain, increased BMI and abnormal lipids appears greatest with olanzapine, followed by clozapine and quetiapine. The risk of neurological side effects of treatment appears greatest with risperidone, olanzapine and aripiprazole. Neurological side effects appear very uncommon in children treated with quetiapine and clozapine, and there is not enough pediatric data on ziprasidone to make conclusions.

Second generation antipsychotics can cause other side effects which were not discussed in this guideline, including sedation, drooling, a decrease in absolute neutrophil count (with clozapine), cataracts (with quetiapine) and prolongation of the QTc interval. Clinicians prescribing these medications should familiarize themselves with the most common adverse events associated with

the SGA they are prescribing, and consult appropriate resources on when to perform absolute neutrophil counts, electrocardiograms, and slit lamp eye examinations.

With respect to the noted metabolic side effects of SGA treatment, the long term health consequences of obesity and dyslipidemia in children are concerning. Higher BMI during childhood is associated with an increased risk of coronary heart disease in adulthood.

The social and emotional consequences of obesity in a child who may already be seen as different due to their mental health disorder is also worth considering. A prospective study has demonstrated that women with the metabolic syndrome in childhood have higher levels of depressive symptoms in adulthood than women free of the childhood metabolic syndrome.

2. When and how should clinicians monitor for metabolic and neurological side effects when an SGA has been initiated in a child/adolescent?

Separate recommendations were made for monitoring procedures at baseline (before medication is started), at three months, six months and one year.

Monitoring summary tables for physical examination maneuvers and laboratory tests with recommendation grades according to each individual SGA have been created (Table 2 and 3).

(see figures 6 and 7)

Table 2. Monitoring summary table: physical examination maneuvers					
	Antipsychotic	Baseline	3 months	6 months	1 year
Height (cm):	Risperidone	STRONG 1A	STRONG 1A	STRONG 1A	STRONG 1C
	Olanzapine	STRONG 1A	STRONG 1A	STRONG 1C	STRONG 1C
	Quetiapine	STRONG 1A	STRONG 1A	STRONG 1C	WEAK 3
	Aripiprazole	STRONG 1A	STRONG 1A	STRONG 1C	STRONG 1C
	Clozapine	STRONG 1A	STRONG 1A	STRONG 1C	WEAK 3
	Ziprasidone	STRONG 1C	WEAK 3	STRONG 1C	WEAK 3
Weight (kg):	Risperidone	STRONG 1A	STRONG 1A	STRONG 1A	STRONG 1C
	Olanzapine	STRONG 1A	STRONG 1A	STRONG 1C	STRONG 1C
	Quetiapine	STRONG 1A	STRONG 1A	STRONG 1C	WEAK 3
	Aripiprazole	STRONG 1A	STRONG 1A	STRONG 1C	STRONG 1C
	Clozapine	STRONG 1A	STRONG 1A	STRONG 1C	WEAK 3
	Ziprasidone	STRONG 1C	WEAK 3	STRONG 1C	WEAK 3
BMI (kg/WEAK 3):	Risperidone	STRONG 1A	STRONG 1A	STRONG 1A	STRONG 1C
	Olanzapine	STRONG 1A	STRONG 1A	STRONG 1C	STRONG 1C
	Quetiapine	STRONG 1A	STRONG 1A	STRONG 1C	WEAK 3
	Aripiprazole	STRONG 1A	STRONG 1A	STRONG 1C	STRONG 1C
	Clozapine	STRONG 1A	STRONG 1A	STRONG 1C	WEAK 3
	Ziprasidone	STRONG 1C	WEAK 3	STRONG 1C	WEAK 3
Waist circumference: (at the level of the umbilicus)	Risperidone	STRONG 1C	STRONG 1C	WEAK 3	WEAK 2B
	Olanzapine	STRONG 1C	STRONG 1C	WEAK 3	WEAK 3
	Quetiapine	STRONG 1C	STRONG 1C	WEAK 3	WEAK 3
	Aripiprazole	STRONG 1C	STRONG 1C	WEAK 3	WEAK 3
	Clozapine	WEAK 3	WEAK 3	WEAK 3	WEAK 3
	Ziprasidone	WEAK 3	WEAK 3	WEAK 3	WEAK 3
Blood pressure:	Risperidone	STRONG 1A	STRONG 1A	WEAK 3	WEAK 3
	Olanzapine	STRONG 1A	STRONG 1A	WEAK 3	WEAK 3
	Quetiapine	STRONG 1A	STRONG 1A	WEAK 3	WEAK 3
	Aripiprazole	WEAK 3	WEAK 3	WEAK 3	WEAK 3
	Clozapine	WEAK 3	WEAK 3	WEAK 3	WEAK 3
	Ziprasidone	WEAK 3	WEAK 3	WEAK 3	WEAK 3
Neurological examination for extrapyramidal symptoms and signs:	Risperidone	STRONG 1A	STRONG 1A	STRONG 1A	STRONG 1C
	Olanzapine	STRONG 1A	STRONG 1A	STRONG 1C	WEAK 3
	Quetiapine	WEAK 2B	WEAK 3	WEAK 2B	WEAK 3
	Aripiprazole	STRONG 1A	STRONG 1A	WEAK 2B	STRONG 1C
	Clozapine	WEAK 2B	WEAK 2B	WEAK 3	WEAK 3
	Ziprasidone	STRONG 1C	STRONG 1C	STRONG 1C	WEAK 3

Figure 6: Recommendations for physical examination manoeuvres for antipsychotic monitoring reported in CAMESA 2011.

Table 3. Monitoring summary table: laboratory tests

	Antipsychotic	Baseline	3 months	6 months	12 months
Fasting plasma Glucose:	Risperidone	STRONG 1C	STRONG 1C	WEAK 2B	WEAK 2B
	Olanzapine	STRONG 1C	STRONG 1C	WEAK 3	WEAK 2B
	Quetiapine	STRONG 1C	STRONG 1C	STRONG 1C	WEAK 3
	Aripiprazole	STRONG 1C	Not recommended	WEAK 3[5]	STRONG 1C
	Clozapine	STRONG 1C	WEAK 3	STRONG 1C	WEAK 3
	Ziprasidone	WEAK 3	Not recommended	WEAK 3[6]	WEAK 3[4]
Insulin:	Risperidone	WEAK 3	WEAK 3	WEAK 3	WEAK 2B[3]
	Olanzapine	STRONG 1A	STRONG 1A	WEAK 3	WEAK 3
	Quetiapine	WEAK 3	WEAK 3	WEAK 3	WEAK 3
	Aripiprazole	Not recommended	Not recommended	Not recommended	Not recommended
	Clozapine	WEAK 3	WEAK 3	WEAK 3	WEAK 3
	Ziprasidone	WEAK 3	Not recommended	Not recommended	Not recommended
Total cholesterol:	Risperidone	WEAK 3	WEAK 3	WEAK 3[2]	WEAK 2B[3]
	Olanzapine	STRONG 1A	STRONG 1A	STRONG 1C	WEAK 3[4]
	Quetiapine	STRONG 1C	STRONG 1C	STRONG 1C	WEAK 3[4]
	Aripiprazole	STRONG 1C	Not recommended	WEAK 2B[5]	STRONG 1C
	Clozapine	STRONG 1A	STRONG 1A	STRONG 1C	WEAK 3[4]
	Ziprasidone	WEAK 3	Not recommended	WEAK 3[6]	WEAK 3[4]
Fasting LDL-C:	Risperidone	WEAK 3	WEAK 3	WEAK 3[2]	WEAK 2B[3]
	Olanzapine	STRONG 1A	STRONG 1A	WEAK 3	WEAK 3[4]
	Quetiapine	STRONG 1C	STRONG 1C	WEAK 3	WEAK 3[4]
	Aripiprazole	STRONG 1C	Not recommended	WEAK 2B[5]	STRONG 1C
	Clozapine	WEAK 3	WEAK 3	WEAK 3	WEAK 3[4]
	Ziprasidone	WEAK 3	Not recommended	WEAK 3[6]	WEAK 3[4]
Fasting HDL-C:	Risperidone	WEAK 3	WEAK 3	WEAK 3[2]	WEAK 2B[3]
	Olanzapine	STRONG 1A	STRONG 1A	WEAK 3	WEAK 3[4]
	Quetiapine	STRONG 1C	STRONG 1C	WEAK 3	WEAK 3[4]
	Aripiprazole	STRONG 1C	Not recommended	WEAK 2B[5]	STRONG 1C
	Clozapine	WEAK 3	WEAK 3	WEAK 3	WEAK 3[4]
	Ziprasidone	WEAK 3	Not recommended	WEAK 3[6]	WEAK 3[4]
Fasting triglycerides:	Risperidone	STRONG 1C	STRONG 1C	WEAK 3[2]	WEAK 2B[3]
	Olanzapine	STRONG 1A	STRONG 1A	WEAK 3	WEAK 2B[4]
	Quetiapine	STRONG 1A	STRONG 1A	WEAK 3	WEAK 3[4]
	Aripiprazole	WEAK 2B	Not recommended	WEAK 2B[5]	STRONG 1C
	Clozapine	STRONG 1A	STRONG 1A	STRONG 1C	WEAK 3[4]
	Ziprasidone	WEAK 3	Not recommended	WEAK 3[6]	WEAK 3[4]
AST:	Risperidone	WEAK 3	Not recommended	WEAK 2B[3]	WEAK 2B[3]
	Olanzapine	STRONG 1A	STRONG 1A	STRONG 1C	WEAK 3[3]
	Quetiapine	WEAK 3	WEAK 3[3]	WEAK 3[3]	WEAK 3[3]
	Aripiprazole	WEAK 3[3]	Not recommended	WEAK 3[3]	WEAK 3[3]
	Clozapine	WEAK 3	WEAK 3[3]	WEAK 3[3]	WEAK 3[3]
	Ziprasidone	WEAK 3	Not recommended	WEAK 3[6]	WEAK 3[4]

Table 3. Monitoring summary table: laboratory tests *continued*

	Antipsychotic	Baseline	3 months	6 months	12 months
ALT:	Risperidone	WEAK 3	Not recommended	WEAK 2B[3]	WEAK2B[3]
	Olanzapine	STRONG 1A	STRONG 1A	STRONG 1C	WEAK 3[3]
	Quetiapine	WEAK 3	WEAK 3[3]	WEAK 3[3]	WEAK 3[3]
	Aripiprazole	WEAK 3[3]	Not recommended	WEAK 3[3]	WEAK 3[3]
	Clozapine	WEAK 3	WEAK 3[3]	WEAK 3[3]	WEAK 3[3]
	Ziprasidone	WEAK 3	Not recommended	WEAK 3[6]	WEAK 3[4]
Prolactin:	Risperidone	STRONG 1A	STRONG 1A	WEAK2A[1]	WEAK 3[1]
	Olanzapine	STRONG 1A	STRONG 1A	WEAK 3[1]	WEAK 3[1]
	Quetiapine	WEAK 3	Not recommended	Not recommended	Not recommended
	Aripiprazole	WEAK 3	Not recommended	Not recommended	Not recommended
	Clozapine	WEAK 3	Not recommended	Not recommended	Not recommended
	Ziprasidone	WEAK 2B	Not recommended	WEAK 2B	WEAK 3[1]
Thyroid stimulating hormone (TSH):	Risperidone	Not recommended	Not recommended	Not recommended	Not recommended
	Olanzapine	Not recommended	Not recommended	Not recommended	Not recommended
	Quetiapine	STRONG 1C	Not recommended	STRONG 1C	Not recommended
	Aripiprazole	Not recommended	Not recommended	Not recommended	Not recommended
	Clozapine	Not recommended	Not recommended	Not recommended	Not recommended
	Ziprasidone	Not recommended	Not recommended	Not recommended	Not recommended

1 Decision to measure prolactin at these time points may be based on the presence of clinical symptoms of hyperprolactinemia, such as menstrual irregularity, gynecomastia, or galactorrhea. If no symptoms of hyperprolactinemia are present, recommend monitoring of prolactin occur on a yearly basis.

2 If three month screening laboratory tests are normal, the BMI percentile has remained under the 85th percentile, and the waist circumference has remained at less than the 90th percentile, repetition of lab work for cholesterol, LDL-C, HDL-C and triglycerides can be made on a yearly basis.

3 Testing recommended in overweight or obese children.

4 If six month screening laboratory tests are normal, BMI remains below the 85th percentile and waist circumference remains below the 90th percentile, repetition of lab work for cholesterol, LDL-C, HDL-C and triglycerides can be made on a yearly basis.

5 Given the very limited data on abnormalities on laboratory tests of metabolic parameters at this time point, if child is not overweight, may consider deferring laboratory testing until the one year time point.

6 Given the paucity of long term data on ziprasidone in children,clinicians should consider doing laboratory testing for metabolic side effects at 6 months, especially if BMI percentile scores rise above the 85th percentile, or waist circumference increases above the 90th percentile.

Note: Due to the absence of data, paliperidone was not included in the evidence tables

Figure 7: Recommendations for laboratory tests for antipsychotic monitoring reported in CAMESA 2011.

We have attempted to create an evidence-based monitoring protocol for physicians to follow when prescribing an SGA to a child for a mental health condition. As the risk of metabolic and neurological side effects varies between SGA medications, we have provided the levels of evidence associated with the specific side effects of each drug.

Recognizing that some clinicians may not have adequate resources to apply these drug specific recommendations, we have also created a simplified single screening and monitoring tool (Table 4) for ease of use in the clinical setting. *(see figure 8)*

Table 4. A practical tool for metabolic monitoring of children & youth treated with second-generation antipsychotics

Parameter		Pre-treatment Baseline	1 month	2 month	3 month	6 month	9 month	12 month
Assessment date								
Height (cm)[1]								
Height percentile								
Weight (kg)[1]								
Weight percentile								
BMI: (kg/m^2)[1]								
BMI percentile								
Waist circumference (At the level of the umbilicus)[2]								
Waist circumference percentile								
Blood pressure (mm/Hg)[3]								
Blood pressure percentile								
Neurological examination[4]		☐ completed	☐ completed	☐ completed	☐ completed	☐ completed	☐ completed	☐ completed
Laboratory evaluations:	Normal values							
Fasting plasma glucose	≤ 6.1 mmol/L[5]		NR	NR			NR	
Fasting insulin[6]	≤ 100 pmol/L[7]		NR	NR			NR	
Fasting total cholesterol	< 5.2 mmol/L		NR	NR			NR	
Fasting LDL-C	< 3.35 mmol/L		NR	NR			NR	
Fasting HDL-C	≥ 1.05 mmol/L		NR	NR			NR	
Fasting triglycerides	< 1.5 mmol/L		NR	NR			NR	
AST			NR	NR	NR		NR	
ALT			NR	NR	NR		NR	
TSH (Quetiapine ONLY)			NR	NR	NR		NR	
Prolactin[8]			NR	NR		NR	NR	
Other_____ (e.g. Amylase, A1C, OGTT etc.)[9]								
Physician Initials: →								

1 To determine height, weight and BMI percentiles, use age and sex specific growth charts at http://www.cdc.gov/growthcharts/.

2 To determine age and sex specific percentiles, go to http://www.idf.org/webdata/docs/Mets definition children.pdf (pages 18-19).

3 To determine age and sex specific percentiles, go to http://pediatrics.aappublications.org/cgi/content/full/114/2/S2/555.

4 Tools available for monitoring extrapyramidal symptoms include: Abnormal Involuntary Movement Scale (AIMS), Simpson Angus Scale, Extrapyramidal Symptom Rating Scale, Barnes Akathisia Rating Scale.

5 For FPG values of 5.6-6.0 mmol/L, consideration should be given to performing an oral glucose tolerance test (OGTT).

6 Note that this assessment is NOT recommended for aripiprazole or ziprasidone, but IS appropriate for all other SGAs.

7 For fasting insulin levels > 100pmol/L, consideration should be given to performing an OGTT. Normal reference range may vary between centres.

8 Assessment of prolactin levels should be completed according to protocol except when the patient is displaying clinical symptoms of hyperprolactinemia (i.e. menstrual irregularity, gynecomastia, or galactorrhea), in which case more frequent monitoring may be warranted. Please also note that risperidone has the greatest effect on prolactin.

9 It is recommended that amylase levels be monitored in case where the patient presents with clinical symptoms of pancreatitis (i.e. abdominal pain, nausea, vomiting).

NR = not recommended

Figure 8: simplified single screening and monitoring tool proposed by CAMESA 2011 for ease of use in the clinical setting.

Experience suggests that, in situations in which an SGA is recommended, the average number of SGAs trialed for a given patient is between two to three. As a result, it is important to complete full baseline measures on patients receiving any one of the SGAs.

Notable in Table 4 is the recommendation to complete a clinical assessment including physical exam maneuvers, such as height, weight, waist circumference, and blood pressure at four and eight weeks following initiation of the SGA.

In addition to determining effectiveness of the medications following their initiation, careful monitoring at these time points is necessary given the current evidence which suggests that significant changes may occur in weight and waist circumference within four weeks of initiating SGAs. Early intervention with conservative lifestyle measures if weight and/or waist circumference are increasing within the first three months of treatment with an SGA may mitigate these metabolic side effects.

Prolactin monitoring is recommended after three months of treatment with risperidone or olanzapine, and after 6 months with ziprasidone, and if normal, on a yearly basis thereafter in asymptomatic children. This is because prepubertal children may not develop clinical symptoms or signs of hyperprolactinemia (menstrual irregularity, gynecomastia, or galactorrhea), and the long-term consequences of chronic elevation of prolactin on future sexual, bone and breast development are unknown. While there is evidence to suggest that prolactin levels may normalize over time in children on chronic treatment, this is not always the case, and therefore we have adopted a conservative stance until further information is available. Prolactin undergoes diurnal fluctuations, and can be altered by medication and food intake. Prolactin levels should therefore be drawn fasting with the other scheduled blood work, some of which also requires a twelve hour fast (e.g. blood lipids).

As we found no evidence of abnormalities in electrolytes or renal function tests such as urea or creatinine with the use of SGAs, we have not made any screening recommendations for these tests as a part of routine monitoring of SGA safety.

We have not made evidenced-based recommendations for monitoring beyond one year due to the poverty of long term studies. At this time, we recommend that clinicians use their clinical judgment to make decisions about monitoring children beyond one year of treatment based on the results of their monitoring to date. Beyond the first year of monitoring, it is the clinical practice of members of our guideline group to repeat laboratory tests yearly in stable patients with a normal physical examination, and previous normal laboratory tests. Physical examination maneuvers are completed during all follow-up visits as a part of routine care.

Given the evidence for metabolic side effects in children treated with SGAs, and the long term sequelae of these problems, monitoring of all children prescribed SGAs is appropriate. There has been a notable lag however in the translation of the research evidence into changes in clinical practice. We recognize that there may be organizational barriers to applying the recommendations of this guideline. Clinicians have a number of demands on their time; the need to perform specific physical examination maneuvers and laboratory tests will add time to clinical visits.

We advise that given the good evidence for specific metabolic and neurological side effects associated with SGAs, clinicians who are unprepared to monitor children for side effects should choose not to prescribe these medications.

While there are cost implications with respect to the use of laboratory tests for monitoring safety, we believe that the cost of these preventive measures will be far less than the costs of managing the long-term effects of obesity and hyperlipidemia on cardiovascular disease.

5.7 Approach of patients in home situation versus in residential care center

5.7.1 Summary

Approaches of patients in home and in residential care center situations for BPSD management

No information on particular patient approaches were found in the APA 2016 guideline.The IRE 2019 guideline applies to all settings that provide care for adults with dementia.

AUS 2016 recommends to refer to a specialist service for the management of BPSD when people have moderate to severe symptoms that put themselves or others at risk. AUS 2016 suggests a management model based on symptom severity. This model advises management in nursing-homes if dementia is accompanied by sever BPSD symptoms such as severe depression, severe agitation, psychosis or screaming.

NICE 2018 warns about the increased risk of delirium in people living with dementia who are admitted to hospital.

NICE 2018 committee has investigated for specific interventions to improve hospital care for people living with dementia. No recommendations were formulated as none of the interventions tested showed consistent evidence of benefits for either patients or carers. The committee feels that a geriatric wards is usually more appropriate than general hospital wards. They agree that the correct approach is to take elements of best care found in specialist units and apply these to all geriatric units.

NICE 2018 insists on needs :

- to transfer information (care and support plans) between different care settings (home, inpatient, community and residential care);
- to review person's needs and wishes (including any care and support plans) after every transition.

Differences in approach for delirium management between patients living at home and patients in residential care

NHG 2014 suggests to refer to a (non-psychiatric) hospital in case of:

• insufficient research, treatment and care options or safety in the home situation;

• insufficient effect of the treatment set up or the need to continue medication management for longer than one week;

• patients with Parkinson's disease or Lewy body dementia.

NHG 2014 warns against an important pitfall along which patients are referred to psychiatric institutions, which are often insufficiently equipped for proper somatic diagnosis and treatment. A geriatric general hospital constitutes safe environment, with both good somatic care and attention to the treatment of the delirium.

Upon hospital admission, SIGN 2019 and NHG 2014 advice to code the patient's file to highlight episodes of delirium (increased risk of readmission).

Upon hospital discharge SIGN 21019 advices:

- that delirium is noted in the discharge letter for the primary care team.
- patients be reviewed by the primary care team.

Both SIGN 2019 and NHG 2014 stress the importance of properly liaise with the patient, family/carers and caregivers regarding discharge arrangements.
NHG 2014 clearly notes that after discharge the aim is to taper a prescribed antipsychotic as quickly as possible.

NHG 2014 also warns for caution when using intravenous administration of haloperidol at home.

Differences in approach for insomnia between patients living at home and patients in residential care

No information on particular patient approaches were found from EUR 2017, WOREL 2018 or USA 2016.

5.7.2 APA 2016:

No information on particular patient approaches were found.

5.7.3 AUS 2016

Where people with dementia have moderate to severe behavioural and psychological symptoms of dementia that puts themselves or others at risk, referral to a specialist service for the management of behavioural and psychological symptoms should occur. (PP-Practice point.**)**

A seven-tiered model of management of BPSD according to symptom severity has been proposed by Brodaty and colleagues (figure 9)

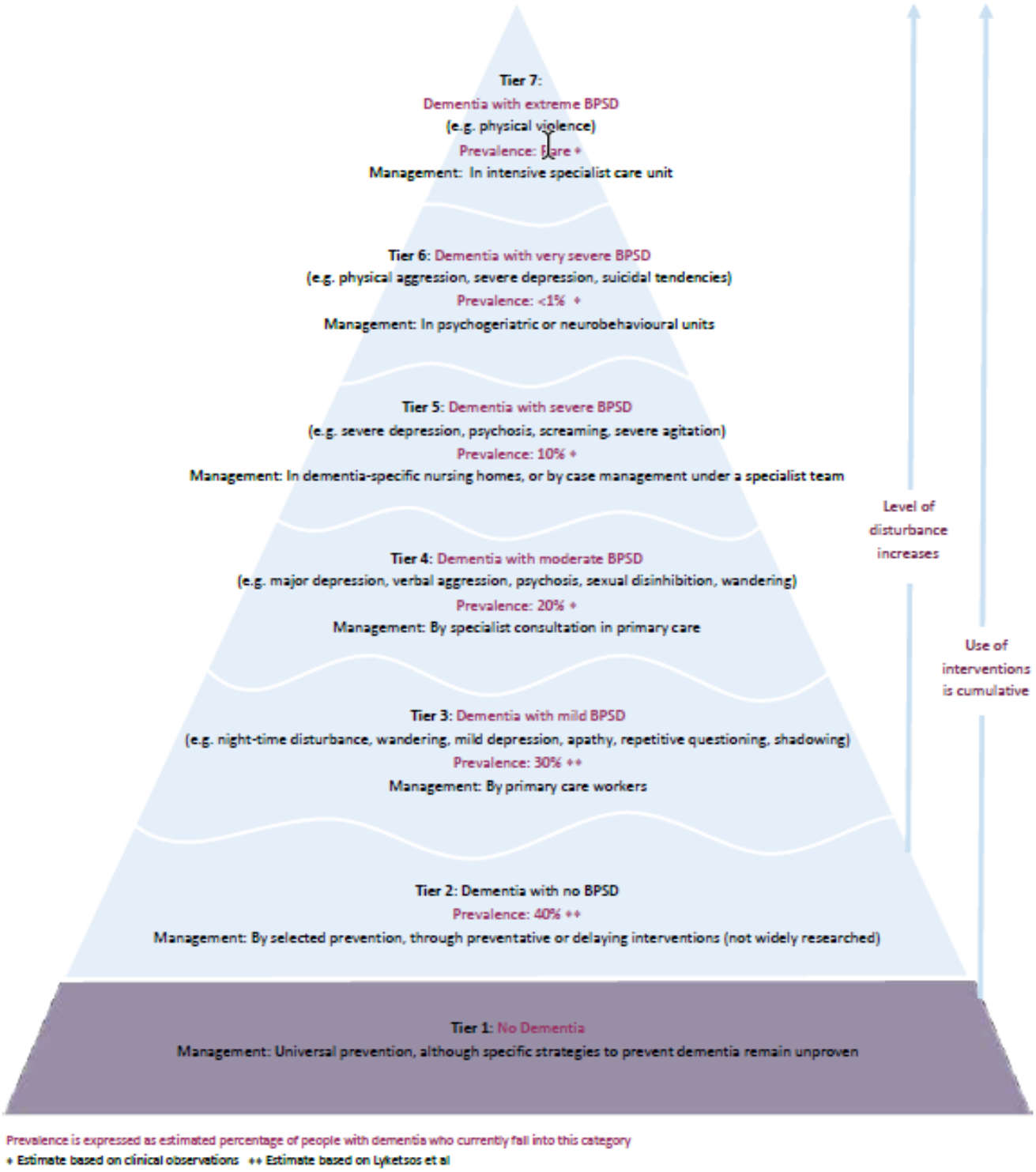


Figure 9: A seven-tiered model of management of BPSD according to symptom severity has been proposed by Brodaty and colleagues and reported in AUS 2016.

5.7.4 NICE 2018

The bibliography group points out that the following recommendations have been made with regard to people living with dementia in general and not only regarding the BPSD.

Inpatient care

People with dementia often experience longer durations of hospital admission, delays in leaving hospital and reduced levels of independent functioning. Acute hospital admission can be a time of distress, confusion and delirium for someone with dementia. These factors may contribute to a decline in global functioning and reduced ability to return home to independent living. Acute hospital admission has been identified as a key opportunity for people with previously undiagnosed dementia to access appropriate assessment & diagnosis of dementia to; improve their care and treatment while in hospital, facilitate appropriate early discharge and enable access to a full range of post-diagnostic support and interventions.

Be aware of the increased risk of delirium in people living with dementia who are admitted to hospital. See the NICE guideline on delirium for interventions to prevent and treat delirium.

The committee agreed that none of the interventions tested showed consistent evidence of benefits for either patients or carers, and therefore it was not appropriate to make any specific recommendations based on these trials.

The committee agreed that, despite the lack of evidence found for specific interventions to improve hospital care for people living with dementia, there were nonetheless specific issues people with dementia faced in hospital. In particular, they agreed it was often not appropriate for people living with dementia to be treated on general hospital wards, and felt that a geriatric ward was usually a more appropriate location. Whilst these wards are not dementia specific, a high enough proportion of people passing through them are likely to have dementia (simply based on the underlying prevalence in the population) and therefore the staff are likely to be better trained and more experienced with people living with dementia than those on a general hospital ward.

The committee also agreed that because the hospital population fluctuates, there are times when there will be a higher proportion of people living with dementia than at other times. Therefore, it would not be viable for the NHS to arrange units for older aged care into separate units specifically for people who are living with dementia and those who do not have dementia. The committee agreed the correct approach was rather to take elements of best care found in specialist units and apply these to all geriatric units, thereby raising the overall standard of care.

Care setting transitions

When developing care and support plans and advance care and support plans, request consent to transfer these to different care settings as needed.

Service providers should ensure that information (such as care and support plans and advance care and support plans) can be easily transferred between different care settings (for example home, inpatient, community and residential care).

Staff delivering care and support should maximise continuity and consistency of care. Ensure that relevant information is shared and recorded in the person's care and support plan.

For guidance on managing transition between care settings for people living with dementia, see:

- **the NICE guideline on transition between inpatient hospital settings and community or care home settings for adults with social care needs**
- **the NICE guideline on transition between inpatient mental health settings and community or care home settings**

- **section 1.2 of the NICE guideline on medicines optimisation.**

Follow the principles in these guidelines for transitions between other settings (for example from home to a care home or respite care).

Review the person's needs and wishes (including any care and support plans and advance care and support plans) after every transition.

Improper/poorly managed discharges from a service/environment (home, care home, hospital or respite care) can lead to increased stress and anxiety, both for people living with dementia and those caring for them. This uncertainty of transition can amplify negative feelings and cause unnecessary distress. Poor transition/planning between services can lead to increased likelihood of re hospitalisation, delayed discharges, failed discharges, inappropriate placements and carer breakdown.

There is much documentation surrounding poor communication and planning when transitioning from one setting to another. Completing multi-disciplinary discharge meetings and ensuring all relevant parties are included in such decisions is vital in maintaining good communication and positive outcomes. Working in a collaborative manner increases positive outcomes by ensuring that everyone is aware of the support required and where this can best be achieved.

When transitioning from one environment/setting to another the fundamental principles that apply are: planning, communication, collaboration and person centred support.

The committee noted that when people living with dementia are transferred from their home to residential care, their information is often not sent with them. As a result, when the person living with dementia is transferred to a residential care home, their care and support plan often has to be created again. In addition, when information is not sent with the person to the residential care home, established personal routines are sometimes not respected. Therefore, the committee agreed that service providers should ensure that information about people living with dementia (including care and support plans and advanced care and support plans) can be easily transferred between different care settings (including between home, community and residential care), including requesting consent for these to be transferred when they are produced.

5.7.5 IRE 2019

A person with dementia can transition across many services and sectors, and this guideline applies to their care in any and all settings (living in the community or in residential settings, including during episodes of admission to hospital)

5.7.6 SIGN 2019

The guideline applies to all settings: home, long-term care, hospital, and hospice. It is important to note that, to date, much of the existing evidence and the focus of other guidelines, is in acute care settings.

Patient records should be coded to highlight a previous episode of delirium so that hospital

staff are aware of the increased risk on readmission. (Good-practice point)

Ensure that delirium is noted in the discharge letter for the primary care team. (Good-practice point)

All patients who have had delirium should be reviewed by the primary care team. (Good-practice point)

Checklist for provision of information:

The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

At discharge following an acute episode of delirium:

- Liaise with the family/carers regarding discharge arrangements. Discuss with family/carers whether they need extra support. Some patients may still be recovering, not be entirely themselves or be less able than usual to carry out their daily activities.
- Inform carers of their right to have a new or updated adult carer support plan.
- Ensure that support is in place before the patient is discharged to their home.
- If there are concerns about cognitive impairment in the following months, advise the patient/carers to see their general practitioner.

5.7.7 NICE 2010

No information on particular patient approaches were found.

5.7.8 NHG 2014

Vanwege het risico op ernstige bijwerkingen is voorzichtigheid geboden bij intraveneuze toediening van haloperidol in de thuissituatie.

Consultatie en verwijzing

Overleg in de palliatieve fase met een consulent palliatieve zorg en overweeg verzorging in een hospice.

Indicaties voor consultatie en/of verwijzing bij (vermoeden van) een delier zijn:

- onvoldoende onderzoeks-, behandel- en verzorgingsmogelijkheden of veiligheid in de thuissituatie;
- onvoldoende effect van de ingestelde behandeling;
- noodzaak om medicamenteuze symptoombestrijding langer dan één week te continueren;
- patiënten met de ziekte van Parkinson of ‘Lewy body’-dementie.

Indien verwijzing of opname geïndiceerd is, verwijst de huisarts naar een (niet-psychiatrisch) ziekenhuis.

Het is van belang een delier te herkennen als een ernstig psychiatrisch syndroom ten gevolge van een lichamelijke aandoening. Een belangrijke valkuil is dat de gedragsstoornis die bij het delier hoort als een primair psychiatrische aandoening wordt beschouwd, waarna lichamelijk onderzoek achterwege

blijft en de patiënt wordt verwezen naar een psychiatrische instelling, die veelal onvoldoende is toegerust voor goede somatische diagnostiek en behandeling.

Een delirante patiënt heeft een aangepaste veilige omgeving nodig, met zowel goede somatische zorg als aandacht voor de behandeling van het delier. Een geriatrische afdeling algemeen ziekenhuis (GAAZ) voldoet aan deze criteria, waarbij onderlinge afspraken binnen het ziekenhuis uiteindelijk bepalend zijn waar een patiënt het beste opgenomen kan worden.

Overdracht en zorg na ontslag uit het ziekenhuis bij persisterende symptomen van delier

Als een patiënt een delier in het ziekenhuis heeft doorgemaakt is deze vaak niet volledig hersteld bij ontslag. Het streven is een voorgeschreven antipsychoticum zo snel mogelijk, op geleide van de symptomen af te bouwen (zie Medicamenteuze behandeling).

Als voorbereiding op het ontslag van een patiënt met nog aanwezige symptomen is transmuraal overleg tussen behandelend specialist en huisarts vereist om adequate zorg in een veilige omgeving te waarborgen (zie kader Aandachtspunten voor overdracht naar de huisarts bij ontslag van een patiënt met persisterende symptomen van delier vanuit een ziekenhuis/instelling naar (verzorgings)huis) evenals afstemming met patiënt, mantelzorger, professionals van de afdeling waar de patiënt heeft gelegen, en eventueel de thuiszorgorganisatie.

Aandachtspunten voor de overdracht naar de huisarts bij ontslag van een patiënt met persisterende symptomen van delier vanuit een ziekenhuis/instelling naar (verzorgings)huis:

- Gebruikelijke overdrachtgegevens; tevens waarden van het ADL-functioneren om het niveau van noodzakelijke steun te bepalen, de aanwezige symptomen van delier (met eventueel de DOS-score) en de mate van cognitief functioneren (bijvoorbeeld MMSE) bij ontslag.
- Informatie over de verstrekte informatie aan patiënt en mantelzorger over het delier.
- Afbouwschema van deliermedicatie (indien van toepassing).
- Contactgegevens van de behandelaar van het delier, met wie de huisarts contact zoekt als het delier niet verbleekt of de medicatieafbouw niet lukt.
- Gegevens van degenen die thuis ADL-ondersteuning gaan bieden (thuiszorg/mantelzorg).
- Afspraak wie informatie verstrekt over de prognose van het delier qua herstel en recidief.
- Advies over niet-medicamenteuze maatregelen.

Zorg voor een goede overdracht naar de huisartsenpost voor de continuïteit van zorg in avond-, nacht- en weekenddiensten.

- Adviseer om bij opnieuw optreden van vergelijkbare symptomen direct contact met de huisarts op te nemen.
- Verricht bij eventuele restverschijnselen in overleg met de patiënt gericht aanvullend onderzoek (zoals MMSE; zie de NHG-Standaard Dementie).
- Vermeld een doorgemaakt delier duidelijk in het dossier van de patiënt en bij een eventuele nieuwe ziekenhuisopname.

5.7.9 EUR 2017

No information on particular patient approaches were found.

5.7.10 WOREL 2018

No information on particular patient approaches were found.

5.7.11 USA 2016

No information on particular patient approaches were found.

5.7.12 Canada 2018

No information on particular patient approaches were found.

5.7.13 CAMESA 2011

No information on particular patient approaches were found.

6 Antipsychotics for BPSD: summary and conclusions from the literature review

6.1 Efficacy

6.1.1 SGA versus placebo for BPSD

6.1.1.1 Aripiprazole versus placebo

Aripiprazole versus placebo for BPSD			
Bibliography: AHRQ 2011(6), including Breder 2004(29)/Mintzer 2007(30), De Deyn 2005(31), Streim 2004(32)/Streim 2008(33)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Efficacy for overall BPSD	951 (3) 10 weeks	SMD 0.20 (95%CI: 0.04, 0.35) I^2= 22.1% **SS in favour of aripiprazole**	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (high dropout) Consistency: ok Directness: ok Imprecision: ok
Efficacy for psychosis	951 (3) 10 weeks	SMD 0.14 (95%CI: -0.02, 0.29) I^2= 18.8% NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (high dropout) Consistency: ok Directness: ok Imprecision: ok
Efficacy for agitation	743 (2) 10 weeks	SMD 0.31 (95%CI: 0.10, 0.52); **SS in favour of aripiprazole** SMD 0.30 (95%CI: 0.05, 0.55); **SS in favour of aripiprazole**	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (high dropout) Consistency: ok Directness: ok Imprecision: ok

The AHRQ 2011 review(6) compared aripiprazole with placebo for the treatment of BPSD. Three studies in a nursing home setting with each a study duration of 10 weeks were included (Breder 2004(29)/Mintzer 2007(30), De Deyn 2005(31), Streim 2004(32)/Streim 2008(33)).

Two studies had an unclear risk for "sequence generation".(29)/(30), (31) The dropout rate was high (>20% in each arm) in 2 studies.(29)/(30),(32)/(33)

There was a **statistical significant effect** of aripiprazole compared to placebo for the treatment of patients with **overall BPSD**.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

There was **no difference** between aripiprazole and placebo for the treatment of **psychosis** in patients with BPSD.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

Two studies were included for the comparison of aripiprazole versus placebo for the outcome agitation (Breder 2004(29)/Mintzer 2007(30), Streim 2004(32)/Streim 2008(33)).

There was a **statistical significant effect** of aripiprazole compared to placebo for the treatment of **agitation** in patients with BPSD.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

6.1.1.2 Asenapine versus placebo

The systematic review of Yunusa 2019(4) found no studies comparing asenapine with placebo in patients with BPSD.

GRADE: Insufficient evidence

6.1.1.3 Clozapine versus placebo

The systematic review of Yunusa 2019(4) found no studies comparing clozapine with placebo in patients with BPSD.

GRADE: Insufficient evidence

6.1.1.4 Olanzapine versus placebo

Olanzapine versus placebo for BPSD			
Bibliography: AHRQ 2011(6), including De Deyn 2004(34), Deberdt 2005(35), Kennedy 2005(36), Schneider 2006(37)/Sultzer 2008(38), Street 2000(39)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Efficacy for overall BPSD	1773 (4) 6-12 weeks	SMD 0.12 (95%CI: 0.00, 0.25) I^2= 0.0%	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (serious limitations) Consistency: ok

		SS in favour of olanzapine	Directness: ok Imprecision: ok
Efficacy for psychosis	2041 (5) 6-26 weeks	SMD 0.05 (95%CI: -0.07, 0.17) I^2= 14.7% NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (serious limitations) Consistency: ok Directness: ok Imprecision: ok
Efficacy for agitation	1773 (4) 6-12 weeks	SMD 0.19 (95%CI: 0.07, 0.31) I^2= 0.0% **SS in favour of olanzapine**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (serious limitations) Consistency: ok Directness: ok Imprecision: ok

The AHRQ 2011 review(6) compared olanzapine with placebo for the treatment of BPSD. A total of five studies with a study duration between 6 weeks and 26 weeks were included (De Deyn 2004(34), Deberdt 2005(35), Kennedy 2005(36), Schneider 2006(37)/Sultzer 2008(38), Street 2000(39)). One study was not included for the outcomes overall BPSD and agitation (Kennedy 2005(36)).

Schneider 2006(37)/Sultzer 2008(38) had a poor rating for quality with a Jadad score of 1/5 (single blind, no similar groups at baseline, outcome assessor not masked). The study by De Deyn 2004(34) had an intermediate risk of bias mainly due to unclear risk for sequence generation and the lack of an ITT analysis. Deberdt 2005(35) had an intermediate risk of bias mainly due to an unclear sequence generation (Jadad score 2/5). The dropout rate was high in most studies.

There was a **statistical significant effect** of olanzapine compared to placebo for the treatment of patients with **overall BPSD**.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

There was **no difference** between olanzapine and placebo for the treatment of **psychosis** in patients with BPSD.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

There was a **statistical significant effect** of olanzapine compared to placebo for the treatment of **agitation** in patients with BPSD.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

6.1.1.5 *Paliperidone versus placebo*

The systematic review of Yunusa 2019(4) found no studies comparing paliperidone with placebo in patients with BPSD.

GRADE: Insufficient evidence

6.1.1.6 *Quetiapine versus placebo*

Quetiapine versus placebo for BPSD			
Bibliography: AHRQ 2011(6), including Ballard 2005(40), Paleacu 2008(41), Schneider 2006(37)/Sultzer 2008(38), Tariot 2006(42), Zhong 2004(43)/Zhong 2007(44)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Efficacy for overall BPSD	1038 (3) 6-12 weeks	SMD 0.13 (95%CI: -0.03, 0.28) I^2= 0.0% NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (serious limitations) Consistency: ok Directness: ok Imprecision: ok
Efficacy for psychosis	1038 (3) 6-12 weeks	SMD 0.04 (95%CI: -0.11, 0.19) I^2= 0.0% NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (serious limitations) Consistency: ok Directness: ok Imprecision: ok
Efficacy for agitation	1771 (5) 6-26 weeks	SMD 0.05 (95%CI: -0.14, 0.25) I^2= 38.4% NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (serious limitations) Consistency: ok Directness: ok Imprecision: ok

The AHRQ 2011 compared quetiapine with placebo for the treatment of BPSD. Three studies with a study duration between 6 weeks and 12 weeks were included for the outcomes overall BPSD and psychosis (Schneider 2006(37)/Sultzer 2008(38), Tariot 2006(42), Zhong 2004(43)/Zhong 2007(44)). Two additional studies with a study duration of 6 weeks and 26 weeks were included for the outcome agitation (Ballard 2005(40), Paleacu 2008(41)).

Schneider 2006(37)/Sultzer 2008(38) had a poor rating for quality with a Jadad score of 1/5 (single blind, no similar groups at baseline, outcome assessor not masked). The study by Paleacu 2008(41) with a small sample size (n=40) had overall an intermediate risk of bias due to unclear risk for sequence generation. The dropout rate was high across the studies.

There was **no difference** between quetiapine and placebo for the treatment of patients with **overall BPSD**.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

There was **no difference** between quetiapine and placebo for the treatment of **psychosis** in patients with BPSD.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

There was **no difference** between quetiapine and placebo for the treatment of **agitation** in patients with BPSD.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

6.1.1.7 Risperidone versus placebo

Risperidone versus placebo for BPSD			
Bibliography: AHRQ 2011(6), including Brodaty 2003(45)/Brodaty 2005(46), Deberdt 2005(35), De Deyn 1999(47), Katz 1999(48), Mintzer 2006(49), Schneider 2006(37)/Sultzer 2008(38)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Efficacy for overall BPSD	2702 (6) 8-12 weeks	SMD 0.19 (95%CI: 0.00, 0.38) I^2= 74.6% **SS in favour of risperidone**	⨁⨁⨀⨀ **LOW** Study quality: -1 (serious limitations) Consistency: -1 (heterogeneity) Directness: ok Imprecision: ok
Efficacy for psychosis	2358 (5) 8-12 weeks	SMD 0.20 (95%CI: 0.05, 0.36) I^2= 55.0% **SS in favour of risperidone**	⨁⨁⨁⨀ **MODERATE** Study quality: -1 (serious limitations) Consistency: ok Directness: ok Imprecision: ok
Efficacy for agitation	2702 (6) 8-12 weeks	SMD 0.22 (95%CI: 0.09, 0.35) I^2= 43.7%, **SS in favour of risperidone**	⨁⨁⨁⨀ **MODERATE** Study quality: -1 (serious limitations) Consistency: ok Directness: ok Imprecision: ok

The AHRQ 2011 compared risperidone with placebo for the treatment of BPSD. A total of six studies with a study duration between 8 weeks and 12 weeks were included (Brodaty 2003(45)/Brodaty 2005(46), Deberdt 2005(35), De Deyn 1999(47), Katz 1999(48), Mintzer 2006(49), Schneider 2006(37)/Sultzer 2008(38)). One was not included for the outcome psychosis (De Deyn 1999(47)).

Schneider 2006(37)/Sultzer 2008(38) had a poor rating for quality with a Jadad score of 1/5 (single blind, no similar groups at baseline, outcome assessor not masked). The study by De Deyn 1999(47), Mintzer 2006(49) and Deberdt 2005(35) (Jadad score 2/5) had an intermediate risk of bias mainly due to unclear risk for sequence generation. The dropout rate was high in most studies.

There was a **statistical significant effect** of risperidone compared to placebo for the treatment of patients with **overall BPSD**.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was a **statistical significant effect** of risperidone compared to placebo for the treatment of **psychosis** in patients with BPSD.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

There was a **statistical significant effect** of risperidone compared to placebo for the treatment of **agitation** in patients with BPSD.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

6.1.1.8 Sertindole versus placebo

We found no studies comparing sertindole with placebo in patients with BPSD.

GRADE: Insufficient evidence

6.1.2 SGA versus haloperidol for BPSD

SGA versus haloperidol for BPSD			
Bibliography: AHRQ 2011,(6) including Moretti 2005(50), Verhey 2006(51), Savaskan 2006(52), Tariot 2006(42), De Deyn 1999(47).			
Outcomes	**N° of participants**	**Results**	**Quality of the evidence**

	(studies) Follow up		(GRADE)
Efficacy for overall BPSD	972 (5) 5 weeks-12months	SMD 0.16 (95%CI: -0.16, 0.47) I^2= 74.6% NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 (very serious limitations) Consistency: -1 (heterogeneity) Directness: ok Imprecision: ok
Efficacy for psychosis		No data	**Insufficient evidence**
Efficacy for agitation	716 (4) 5-12 weeks	SMD 0.03 (95%CI: -0.15, 0.21) I^2= 0.0% NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (very serious limitations) Consistency: ok Directness: ok Imprecision: ok

The AHRQ 2011 review(6) compared SGA as a group with haloperidol for the treatment of BPSD. There were too few trials to pool by specific SGA. A total of five studies with study durations between 5 and 12 weeks and one study with a study duration of 12 months were included (Moretti 2005(50), Verhey 2006(51), Savaskan 2006(52), Tariot 2006(42), De Deyn 1999(47)). One study was not included for the outcome agitation.(50)

Olanzapine(50),(51) and quetiapine(52),(42) were each studied in 2 RCTs and risperidone(47) in one study.

Two studies (Moretti 2005(50, Savaskan 2006{Savaskan, 2006 #39, Savaskan 2006{Savaskan, 2006 #39, Savaskan 2006{Savaskan, 2006 #39, Savaskan 2006{Savaskan, 2006 #39)) included in the meta-analysis did not meet our inclusion criteria due to an open label design. We decided to retain the results from the meta-analyses. One study had only a small sample size (n=30)(52), however both studies had a poor rating for quality with a Jadad score of ≤2/5.

The other three studies had a good rating for quality with a Jadad score of ≥3/5. The dropout rate was high in the two largest studies.(42),(47)

There was **no difference in efficacy** between SGA and haloperidol for **overall BPSD**.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

There was a **no difference in efficacy** between SGA and haloperidol for **agitation** in patients with BPSD.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

6.1.3 SGA versus SGA for BPSD

6.1.3.1 Risperidone versus olanzapine

Risperidone versus olanzapine for BPSD			
Bibliography: AHRQ 2011(6), including Deberdt 2005(35), Schneider 2006(37)/Sultzer 2008(38)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Efficacy for overall BPSD	915 (2) 10-12 weeks	-SMD 0.10 (95%CI: -0.10, 0.30); NS -SMD -0.27 (95%CI: -0.56, 0.02); NS	⨁⨁⊖⊖ **LOW** Study quality: -2 (very serious limitations) Consistency: ok Directness: ok Imprecision: ok
Efficacy for psychosis	915 (2) 10-12 weeks	-SMD -0.03 (95%CI: -0.23, 0.17); NS -SMD -0.27 (95%CI: -0.56, 0.02); NS	⨁⨁⊖⊖ **LOW** Study quality: -2 (very serious limitations) Consistency: ok Directness: ok Imprecision: ok
Efficacy for agitation	915 (2) 10-12 weeks	-SMD -0.04 (95%CI: -0.24, 0.16); NS -SMD 0.17 (95%CI: -0.12, 0.46); NS	⨁⨁⊖⊖ **LOW** Study quality: -2 (very serious limitations) Consistency: ok Directness: ok Imprecision: ok

The systematic review from AHRQ 2011(6) compared risperidone with olanzapine for efficacy in patients with BPSD. Two RCT's (Deberdt 2005(35), Schneider 2006(37)) with a study duration of 10-12 weeks were included. The data could not be pooled.

One study had an intermediate risk of bias mainly due to unclear risk for sequence generation and a high dropout rate.(35) The second study had a poor rating for quality with a Jadad score of 1/5 (single blind, no similar groups at baseline, outcome assessor not masked).(37).

There was **no difference in efficacy** between risperidone and olanzapine for **overall BPSD**.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was a **no difference in efficacy** between risperidone and olanzapine for the treatment of **psychosis** in patients with BPSD.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was a **no difference in efficacy** between risperidone and olanzapine for the treatment of **agitation** in patients with BPSD.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

6.1.3.2 Risperidone versus quetiapine

Risperidone versus quetiapine for BPSD			
Bibliography: AHRQ 2011(6), including Rainer 2007(53), Schneider 2006(37)/Sultzer 2008(38)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Efficacy for overall BPSD	493 (2) 8-12 weeks	-SMD -0.06 (95%CI: -0.55, 0.43); NS -SMD -0.24 (95%CI: -0.53, 0.06); NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (very serious limitations) Consistency: ok Directness: ok Imprecision: ok
Efficacy for psychosis	421 (1) 12 weeks	SMD -0.24 (95%CI: -0.54, 0.05); NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (very serious limitations) Consistency: NA Directness: ok Imprecision: ok
Efficacy for agitation	493 (2) 8-12 weeks	-SMD -0.17 (95%CI: -0.66, 0.32); NS -SMD 0.10 (95%CI: -0.20, 0.39); NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (very serious limitations) Consistency: ok Directness: ok Imprecision: ok

The systematic review from AHRQ 2011(6) compared risperidone with quetiapine for efficacy in patients with BPSD. Two RCT's (Rainer 2007(53), Schneider 2006(37)/Sultzer 2008(38)) with a study duration of 8-12 weeks were included. The data could not be pooled. One study could not be included for the outcome psychosis (Rainer 2007(53)).

The study by Schneider 2006(37)/Sultzer 2008(38) had a poor rating for quality with a Jadad score of 1/5 (single blind, no similar groups at baseline, outcome assessor not masked). Rainer 2007(53) had overall an intermediate risk of bias mainly due to unclear risk for blinding.

There was **no difference in efficacy** between risperidone and quetiapine for **overall BPSD**.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was a **no difference in efficacy** between risperidone and quetiapine for the treatment of **psychosis** in patients with BPSD.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was a **no difference in efficacy** between risperidone and quetiapine for the treatment of **agitation** in patients with BPSD.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

6.2 Safety: cerebrovascular accidents

6.2.1 SGA versus placebo for BPSD

6.2.1.1 Aripiprazole versus placebo

Aripiprazole versus placebo for BPSD - CVA			
Bibliography: Ma 2014(23), including De Deyn 2005(31), Mintzer 2007(30), Streim 2008(33)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
CVA	951 (3) 10 weeks	8/603 vs 2/348 OR 1.58 (95%CI: 0.38, 6.55) I^2= 0% **NS**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (serious limitations) Consistency: ok Directness: ok Imprecision: -1 (wide CI)

The systematic review from Ma 2014(23) compared aripiprazole with placebo for the risk of CVA in patients with BPSD. Three RCT's (De Deyn 2005(31), Mintzer 2007(30), Streim 2008(33)) with a study duration of 10 weeks were included.

Two of the three included studies had overall a medium risk of bias mainly due to an unclear risk for "sequence generation".(31),(30) The dropout rate was high (>20%) in the two largest studies.(30),(33))

There was **no difference** between aripiprazole and placebo for **the risk of CVA** in patients with BPSD.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

6.2.1.2 *Olanzapine versus placebo*

Olanzapine versus placebo for BPSD – CVA			
Bibliography: Ma 2014(23), including Deberdt 2005(35), Schneider 2006(37)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
CVA	540 (2) 10-12 weeks	7/304 vs 1/236 OR 3.93 (95%CI: 0.62, 25.10) I^2= 0% NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (serious limitations) Consistency: ok Directness: ok Imprecision: -1 (wide CI)

The systematic review from Ma 2014(23) compared olanzapine with placebo for the risk of CVA in patients with BPSD. Two RCT's (Deberdt 2005(35), Schneider 2006(37)) with a study duration of 10-12 weeks were included.

One study had an intermediate risk of bias mainly due to unclear risk for sequence generation and a high dropout rate.(35) The second study had a poor rating for quality with a Jadad score of 1/5 (single blind, no similar groups at baseline, outcome assessor not masked).(37).

There was **no difference** between olanzapine and placebo for **the risk of CVA** in patients with BPSD.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

6.2.1.3 *Quetiapine versus placebo*

Quetiapine versus placebo for BPSD - CVA			
Bibliography: Ma 2014(23), including Schneider 2006(37), Tariot 2006(42), Zhong 2007(44)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
CVA	759 (3) 10-12 weeks	4/426 vs 5/333 OR 0.65 (95%CI: 0.16, 2.58) I^2= 0% NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (serious limitations) Consistency: ok Directness: ok Imprecision: -1 (wide CI)

The systematic review from Ma 2014(23) compared quetiapine with placebo for the risk of CVA in patients with BPSD. Three RCT's (Schneider 2006(37), Tariot 2006(42), Zhong 2007(44)) with a study duration between 10 and 12 weeks were included.

The largest of the three studies had a poor rating for quality with a Jadad score of 1/5 (single blind, no similar groups at baseline, outcome assessor not masked).(37) The dropout rate was overall high.

There was **no difference** between quetiapine and placebo for **the risk of CVA** in patients with BPSD.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

6.2.1.4 Risperidone versus placebo

Risperidone versus placebo for BPSD - CVA			
Bibliography: Ma 2014(23), including Brodaty 2003(45), Deberdt 2005(35), Mintzer 2006(49), Schneider 2006(37)			
Outcomes	**N° of participants (studies)** **Follow up**	**Results**	**Quality of the evidence (GRADE)**
CVA	1327 (4) 8-12 weeks	24/683 vs 5/644 OR 4.53 (95%CI: 1.75, 11.72) p=0.002 I^2=0% **SS in favour of risperidone**	⨁⨁⊖⊖ **LOW** Study quality: -2 (serious limitation) Consistency: ok Directness: ok Imprecision: ok

The systematic review from Ma 2014(23) compared risperidone with placebo for the risk of CVA in patients with BPSD. Four RCT's (Brodaty 2003(45), Deberdt 2005(35), Mintzer 2006(49), Schneider 2006(37)) with a study duration between 10 and 12 weeks were included.

One study had an intermediate risk of bias mainly due to unclear risk for sequence generation and a high dropout rate.(35) Another study had a poor rating for quality with a Jadad score of 1/5 (single blind, no similar groups at baseline, outcome assessor not masked).(37). The dropout rate was overall high across the studies.

There were **significantly more CVAs** for risperidone compared to placebo in patients with BPSD.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

6.2.1.5 SGA as group versus placebo

SGA versus placebo for BPSD - CVA
Bibliography: Ma 2014(23),

Including Brodaty 2003(45), De Deyn 2005(31), Deberdt 2005(35), Mintzer 2007(30), Schneider 2006(37), Tariot 2006(42), Mintzer 2006(49), Zhong 2007(44), Streim 2008(33)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
CVA	3577 (9) 8-12 weeks	43/2016 vs 13/1561 OR 2.50 (95%CI: 1.36, 4.60) P=0.003 I^2= 0% **SS in favour of SGA**	⨁⨁⨀⨀ **LOW** Study quality: -2 (serious limitations) Consistency: ok Directness: ok Imprecision: ok

The systematic review from Ma 2014(23) compared SGA as group (aripiprazole, olanzapine, quetiapine, risperidone) with placebo for the risk of CVA in patients with BPSD. A total of nine RCT's were included. The study duration varied between 8-12 weeks.

Multiple studies suffered from risks of bias (see individual comparisons).

There was **significantly more CVAs** for SGA as a group compared to placebo in patients with BPSD.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

6.2.2 SGA versus haloperidol for BPSD

The AHRQ 2011 review(6) found no studies comparing SGA with haloperidol for the risk of CVA in patients with dementia.

GRADE: Insufficient evidence

6.2.3 SGA versus SGA for BPSD

6.2.3.1 Risperidone versus olanzapine

Risperidone versus olanzapine for BPSD - CVA			
Bibliography: AHRQ 2011(6), including Deberdt 2005(35), Schneider 2006(37)/Sultzer 2008(38)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**

CVA	224 (2) 10-12 weeks	2/104 vs 4/120 OR 1.75 (95%CI: 0.05, 10.48) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 (serious limitations) Consistency: ok Directness: ok Imprecision: -1 (wide CI)

The systematic review from AHRQ 2011(6) compared risperidone with olanzapine for the risk of CVA in patients with BPSD. Two RCT's (Deberdt 2005(35), Schneider 2006(37)) with a study duration of 10-12 weeks were included.

One study had an intermediate risk of bias mainly due to unclear risk for sequence generation and a high dropout rate.(35) The second study had a poor rating for quality with a Jadad score of 1/5 (single blind, no similar groups at baseline, outcome assessor not masked).(37).

There was **no difference** between risperidone and olanzapine for **the risk of CVA** in patients with BPSD.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

6.2.3.2 Risperidone versus quetiapine

Risperidone versus quetiapine for BPSD - CVA			
Bibliography: AHRQ 2011(6), including Rainer 2007(53), Schneider 2006(37)/Sultzer 2008(38)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
CVA	251 (2) 8-12 weeks	2/119 vs 2/132 OR 0.90 (95%CI: 0.06, 12.71) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 (serious limitations) Consistency: ok Directness: ok Imprecision: -1 (wide CI)

The systematic review from AHRQ 2011(6) compared risperidone with quetiapine for the risk of CVA in patients with BPSD. Two RCT's (Rainer 2007(53), Schneider 2006(37)) with a study duration of 10-12 weeks were included.

One study had an intermediate risk of bias due to unclear risk for blinding.(53) The second study had a poor rating for quality with a Jadad score of 1/5 (single blind, no similar groups at baseline, outcome assessor not masked).(37).

There was **no difference** between risperidone and quetiapine for **the risk of CVA** in patients with BPSD.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

6.3 Safety: mortality

6.3.1 SGA versus placebo for BPSD

6.3.1.1 Aripiprazole versus placebo

Aripiprazole versus placebo for BPSD - Mortality			
Bibliography: Yeh TC 2019(54), including De Deyn 2005(31), Mintzer 2007(30), Streim 2008(33)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	921 (3) 10 weeks	OR 1.649 (0.644, 4.225); p=0.297 NS	⨁⨁⊖⊖ **LOW** Study quality: -2 (high dropout, unclear sequence generation) Consistency: ok Directness: ok Imprecision: ok

The systematic review from Yeh 2019(54) included three RCT's comparing aripiprazole with placebo for **mortality** in patients with BPSD. The study duration was 10 weeks in each study.

Two studies had overall a medium risk of bias mainly due an unclear risk for sequence generation.(30),(31) The dropout rate was high (>20%) in two studies.(30),(33)

There was **no difference** between aripiprazole and placebo for **mortality** in patients with BPSD.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

6.3.1.2 Olanzapine versus placebo

Olanzapine versus placebo for BPSD - Mortality
Bibliography: Yeh TC 2019(54), including Satterlee 1995(55), Street 2000(39), De Deyn 2004(34)

Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
Mortality	1096 (3) 6-10 weeks	OR 1.919 (0.660, 5.582); p=0.232 NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (serious limitations) Consistency: ok Directness: ok Imprecision: ok

The systematic review from Yeh 2019(54) included three RCT's comparing olanzapine with placebo for **mortality** in patients with BPSD. The study duration varied between 6 and 10 weeks.

Two studies were judged as having overall a high risk of bias and one study as having an unclear risk of bias. The dropout rate was overall high.

There was **no difference** between olanzapine and placebo for **mortality** in patients with BPSD.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

6.3.1.3 Quetiapine versus placebo

Quetiapine versus placebo for BPSD - Mortality			
Bibliography: Yeh TC 2019(54), including Ballard 2005(40), Tariot 2006(42), Zhong 2007(44)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	710 (3) 10-26 weeks	OR 1.663 (0.674, 4.102); p=0.270 NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (serious limitations) Consistency: ok Directness: ok Imprecision: ok

The systematic review from Yeh 2019(54) included three RCT's comparing quetiapine with placebo for **mortality** in patients with BPSD. The study duration varied between 10 and 26 weeks.

The study by Ballard 2005(40) had an unclear risk for blinding. Tariot 2006(42) had an unclear risk for sequence generation and allocation concealment. The dropout rate was high (>20%) in all three studies.

There was **no difference** between quetiapine and placebo for **mortality** in patients with BPSD.
GRADE: MODERTATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

6.3.1.4 Risperidone versus placebo

Risperidone versus placebo for BPSD - Mortality			
Bibliography: Yeh TC 2019(54), including De Deyn 1999(47), Katz 1999, Brodaty 2003(45), Mintzer 2006(49), RIS-BEL-14 (unpublished), RIS-INT-83 (unpublished)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	1721 (6) 4-12 weeks	OR 1.354 (0.757, 2.422); p=0.307 NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (serious limitations) Consistency: ok Directness: ok Imprecision: ok

The systematic review from Yeh 2019(54) included six RCT's comparing risperidone with placebo for **mortality** in patients with BPSD. The study duration varied between 4 and 12 weeks.

De Deyn 1999 had an unclear risk in three domains, Katz 1999 in two domains, Mintzer 2006 in one domain. All of the included studies had at least an unclear risk of bias for sequence generation. The two small unpublished studies had an unclear risk for most domains. None of the studies had a high risk of bias in any of the domains. The dropout rate was overall high across the studies.

There was **no difference** between risperidone and placebo for **mortality** in patients with BPSD.
GRADE: MODERTATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

6.3.1.5 SGA as group versus placebo

SGA versus placebo for BPSD - Mortality			
Bibliography: Yeh TC 2019(54), including De Deyn 2005(31), Mintzer 2007(30), Streim 2008(33), Satterlee 1995(55), Street 2000(39), De Deyn 2004(34), Ballard 2005(40), Tariot 2006(42), Zhong 2007(44), De Deyn 1999(47), Katz 1999, Brodaty 2003(45), Mintzer 2006(49), RIS-BEL-14 (unpublished), RIS-INT-83 (unpublished)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	1721 (15) 4-26 weeks	OR 1.536 (1.028, 2.296); p=0.036 **SS in favour of SGA**	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (serious limitations) Consistency: ok Directness: ok Imprecision: ok

The systematic review from Yeh 2019(54) included 15 RCT's comparing SGA (aripiprazole, olanzapine, quetiapine, risperidone) with placebo for **mortality** in patients with BPSD. The study duration varied between 4 and 26 weeks.

There was **significantly more mortality** with SGA as a group (aripiprazole, olanzapine, quetiapine, risperidone) compared to placebo in patients with BPSD.

GRADE: MODERTATE quality of evidence

We have moderate confidence that the results of the studies reflect the true effect.

6.3.2 SGA versus haloperidol for BPSD

SGA versus haloperidol for BPSD - mortality			
Bibliography: AHRQ 2011(6) including Moretti 2005(50)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	346 (1) 12 months	6/173 vs 4/173 OR 0.66 (95%CI: 0.13, 2.84) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (open label, jadad score 0/5) Consistency: NA Directness: ok Imprecision: -1 (wide CI)

The AHRQ 2011(6) review included one study comparing mortality between SGA and FGA in patients with BPSD. Moretti 2005(50) compared olanzapine with FGA (60 patients receiving promazine chloridrate and 113 patients receiving haloperidol). The study had a follow-up of 12 months.

The study by Moretti 2005(50) did not meet our inclusion criterion for study type (open label). However, we decided to retain the results of this study for the outcome mortality. This study had a poor rating for quality with a jadad score of 0/5. No separate results were reported for haloperidol and promazine chloridrate.

No other RCT's were found comparing mortality between other SGA and haloperidol.

There was **no difference for mortality** between olanzapine and FGA in patients with BPSD.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

6.3.3 SGA versus SGA for BPSD

6.3.3.1 Risperidone versus olanzapine

Risperidone versus olanzapine for BPSD - Mortality			
Bibliography: AHRQ 2011(6) including Schneider 2006(37)/Sultzer 2008(38), Rainer 2007(53)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	185 (1) 12 weeks	1/85 vs 1/100 OR 0.85 (95%CI: 0.01, 67.39) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (serious limitations) Consistency: NA Directness: ok Imprecision: -1 (wide CI)

The AHRQ 2011 review(6) included one study comparing mortality between risperidone and olanzapine in patients with BPSD.(37) The study duration was 12 weeks.

The study by Schneider 2006(37)/Sultzer 2008(38) had a poor rating for quality with a Jadad score of 1/5 (single blind, no similar groups at baseline, outcome assessor not masked).

There was **no difference** between risperidone and olanzapine for **mortality** in patients with BPSD.

GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

6.3.3.2 Risperidone versus quetiapine

Risperidone versus quetiapine for BPSD - Mortality			
Bibliography: AHRQ 2011(6) including Schneider 2006(37)/Sultzer 2008(38), Rainer 2007(53)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	251 (2) 8-12 weeks	1/119 vs 3/132 OR 2.75 (95%CI: 0.22, 147.08) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (serious limitations) Consistency: NA Directness: ok Imprecision: -1 (wide CI)

The AHRQ 2011 review(6) included two studies comparing mortality between risperidone and quetiapine in patients with BPSD.(37),(53) The study duration was 8-12 weeks.

The study by Schneider 2006(37)/Sultzer 2008(38) had a poor rating for quality with a Jadad score of 1/5 (single blind, no similar groups at baseline, outcome assessor not masked). The study by Rainer 2007(53) had an intermediate risk of bias mainly due to unclear risk for blinding.

There was **no difference** between risperidone and quetiapine for **mortality** in patients with BPSD.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

6.4 Safety: extrapyramidal symptoms

6.4.1 SGA versus placebo for BPSD

6.4.1.1 Aripiprazole versus placebo

Aripiprazole versus placebo for BPSD – extrapyramidal symptoms			
Bibliography: Ma 2014(23), including De Deyn 2005(31), Mintzer 2007(30), Streim 2008(33)			
Outcomes	**N° of participants (studies)**	**Results**	**Quality of the evidence (GRADE)**

	Follow up		
Extrapyramidal symptoms	951 (3) 10 weeks	39/603 vs 16/348 OR 1.29 (95%CI: 0.70, 2.40) I^2=0% NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (very serious limitations) Consistency: ok Directness: ok Imprecision: ok

The systematic review from Ma 2014(23) compared aripiprazole with placebo for the risk of extrapyramidal symptoms in patients with BPSD. Three RCT's (De Deyn 2005(31), Mintzer 2007(30), Streim 2008(33)) with a study duration of 10 weeks were included.

Two of the three included studies had overall a medium risk of bias mainly due to an unclear risk for "sequence generation".(31),(30) The dropout rate was high (>20%) in the two largest studies.(30),(33))

There was no difference between aripiprazole and placebo for the risk of extrapyramidal symptoms in patients with BPSD.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

6.4.1.2 Olanzapine versus placebo

Olanzapine versus placebo for BPSD – extrapyramidal symptoms			
Bibliography: Ma 2014(23), including Deberdt 2005(35), Schneider 2006(37)/Sultzer 2008(38)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Extrapyramidal symptoms	540 (2) 10-12 weeks	85/304 vs 29/236 OR 1.83 (95%CI: 1.13, 2.97) *p* = 0.01 I^2=85% **SS in favour of olanzapine**	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 (very serious limitations) Consistency: -1 (high heterogeneity) Directness: ok Imprecision: ok

The systematic review from Ma 2014(23) compared olanzapine with placebo for the risk of CVA in patients with BPSD. Two RCT's (Deberdt 2005(35), Schneider 2006(37)) with a study duration of 10-12 weeks were included.

One study had an intermediate risk of bias mainly due to unclear risk for sequence generation and a high dropout rate.(35) The second study had a poor rating for quality with a Jadad score of 1/5 (single blind, no similar groups at baseline, outcome assessor not masked).(37).

There were **significantly more extrapyramidal symptoms** for olanzapine compared to placebo in patients with BPSD.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

6.4.1.3 Quetiapine versus placebo

Quetiapine versus placebo for BPSD – extrapyramidal symptoms			
Bibliography: Ma 2014(23), including Paleacu 2008(41), Schneider 2006(37)/Sultzer 2008(38), Tariot 2006(42), Zhong 2004(43)/Zhong 2007(44)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Extrapyramidal symptoms	799 (4) 6-12 weeks	26/446 vs 23/353 OR 0.82 (95%CI: 0.45, 1.51) I^2=13% NS	⨁⨁⊖⊖ **LOW** Study quality: -2 (very serious limitations) Consistency: ok Directness: ok Imprecision: ok (~wide CI)

The systematic review from Ma 2014(23) compared quetiapine with placebo for the risk of extrapyramidal symptoms in patients with BPSD. Four RCT's (Paleacu 2008(41), Schneider 2006(37), Tariot 2006(42), Zhong 2007(44)) with a study duration between 6 and 12 weeks were included.

The largest study had of poor rating for quality with a Jadad score of 1/5 (single blind, no similar groups at baseline, outcome assessor not masked).(37) Two other studies had overall a low risk of bias.(42),(44). One study with a small sample size (n=40) had an intermediate risk of bias due to an unclear risk for sequence generation.(41) The dropout rate was overall high across the studies.

There was **no difference** between quetiapine and placebo for **extrapyramidal symptoms** in patients with BPSD.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

6.4.1.4 Risperidone versus placebo

Risperidone versus placebo for BPSD – extrapyramidal symptoms
Bibliography: Ma 2014(23),

including Brodaty 2003(45)/Brodaty 2005(46), Deberdt 2005(35), De Deyn 1999(47), Katz 1999(48), Mintzer 2006(49)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Extrapyramidal symptoms	2181 (5) 8-12 weeks	247/1260 vs 89/921 OR 2.10 (95%CI: 1.59, 2.76) $p < 0.00001$ I^2=27% **SS in favour of risperidone**	⨁⨁⊖⊖ **LOW** Study quality: -2 (very serious limitations) Consistency: ok Directness: ok Imprecision: ok

The systematic review from Ma 2014(23) compared risperidone with placebo for the risk of extrapyramidal symptoms in patients with BPSD. Five RCT's (Brodaty 2003(45), Deberdt 2005(35), De Deyn 1999(47), Mintzer 2006(49)) were included. The study duration varied between 8 and 12 weeks.

Two studies had overall an intermediate risk of bias mainly due to unclear risk for sequence generation (35),Mintzer, 2006 #192} One study had overall an intermediate risk of bias mainly due to unclear risk for sequence generation and allocation concealment.(47) The dropout rate was high (>20%) across all studies.

There was **significant higher risk of extrapyramidal symptoms** for risperidone compared to placebo in patients with BPSD.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

6.4.1.5 SGA as group versus placebo

SGA versus placebo for BPSD – extrapyramidal symptoms			
Bibliography: Ma 2014(23), including De Deyn 2005(31), Mintzer 2007(30), Streim 2008(33), Deberdt 2005(35), Schneider 2006(37)/Sultzer 2008(38), Paleacu 2008(41), Tariot 2006(42), Zhong 2004(43)/Zhong 2007(44), Brodaty 2003(45)/Brodaty 2005(46), De Deyn 1999(47), Katz 1999(48), Mintzer 2006(49)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Extrapyramidal symptoms	4471 (12) 6-12 weeks	397/2613 vs 157/1858 OR 1.74 (95%CI: 1.41, 2.14) $p < 0.00001$ I^2=40% **SS in favour of SGA**	⨁⨁⊖⊖ **LOW** Study quality: -2 (very serious limitations) Consistency: ok (I^2=40%) Directness: ok Imprecision: ok

The systematic review from Ma 2014(23) compared for SGA as group (aripiprazole, olanzapine, quetiapine, risperidone) with placebo for the risk of extrapyramidal symptoms in patients with BPSD. A total of 12 RCT's were included. The study duration varied between 6 and 12 weeks.

Several studies suffered from risk of bias (see individual comparisons). The dropout rate was overall high (>20%) across studies.

There was a **significant higher risk of extrapyramidal symptoms** for SGA as group (aripiprazole, olanzapine, quetiapine, risperidone) compared to placebo in patients with BPSD.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

6.4.2 SGA versus haloperidol for BPSD

The AHRQ 2011(6) review treated each SGA separately and (in general) did not group them together as a class. Separate results for the number of patients with extrapyramidal symptoms in very small sample sizes were reported for olanzapine, quetiapine, and risperidone versus haloperidol in patients with BPSD. None of the comparisons were statistically significant. References are not added in the AHRQ 2011 adverse events analysis and we could therefore not always verify the data for this outcome with absolute certainty. Even after having checked each included study comparing SGA with FGA in patients with BPSD. (50),(51),(52),(42),(47)

GRADE: Insufficient evidence

6.4.3 SGA versus SGA for BPSD

The AHRQ 2011(6) review treated each SGA separately and (in general) did not group them together as a class. References are not added in the AHRQ 2011 adverse events analysis and we could therefore not always verify the data for **extrapyramidal symptoms** in patients with BPSD with absolute certainty. Even after having checked each included study comparing risperidone with olanzapine (Deberdt 2005(35), Schneider 2006(37)/Sultzer 2008(38)) or each study comparing risperidone with quetiapine (Rainer 2007(53)Schneider 2006(37)/Sultzer 2008(38)). Our verification of the results was also further complicated by the various ways extrapyramidal symptoms are reported in each study. Because of the uncertainty of the referred studies and other methodological problems in the studies (e.g. sparse data), we rated the quality of the results as "insufficient evidence".

The AHRQ 2011(6) review included three studies for their comparison of extrapyramidal symptoms between **risperidone and olanzapine** in patients with BPSD. However, there were only two possible studies for this comparison. We could not verify the studies their results were based on.

There was no significant difference for extrapyramidal symptoms between risperidone and olanzapine in patients with BPSD.
GRADE: Insufficient evidence

The AHRQ 2011(6) review included two studies for their comparison of extrapyramidal symptoms between **risperidone and quetiapine** in patients with BPSD. Their results are likely based on data from Rainer2007(53) and Schneider 2006(37)/Sultzer 2008(38).

There was a lower risk for extrapyramidal symptoms for risperidone compared to quetiapine in patients with BPSD.
GRADE: Insufficient evidence

6.5 Safety: Falls

6.5.1 SGA versus placebo for BPSD

6.5.1.1 Aripiprazole versus placebo

The systematic review of Ma 2014(23) found no studies comparing aripiprazole with placebo in patients with BPSD.

GRADE: Insufficient evidence

6.5.1.2 Olanzapine versus placebo

Olanzapine versus placebo for BPSD - Falls			
Bibliography: Ma 2014(23), including Deberdt 2005(35)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Falls	297 (1) 10 weeks	4/203 vs 2/94 OR 0.92 (95%CI: 0.17, 5.14) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (high dropout, unclear sequence generation) Consistency: NA Directness: ok Imprecision: -1 (sparse data)

The systematic review from Ma 2014(23) included one RCT by Deberdt 2005(35) that compared falls between olanzapine and placebo in patients with BPSD. The study duration was 10 weeks.

There was overall a medium risk of bias mainly due to an unclear sequence generation and high dropout rate (>20%).

There was **no difference** between olanzapine and placebo for **the risk of falls** in patients with BPSD.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

6.5.1.3 Quetiapine versus placebo

Quetiapine versus placebo for BPSD - Falls			
Bibliography: Ma 2014(23), including Paleacu 2008(41), Tariot 2006(42), Zhong 2007(44)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Falls	563 (3) 6-10 weeks	89/352 vs 54/211 OR 0.96 (95%CI: 0.64, 1.45) I^2=0% NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (high dropout) Consistency: ok Directness: ok Imprecision: ok

The systematic review from Ma 2014(23) included three RCTs (Paleacu 2008, Tariot 2006, Zhong 2007)(41),(42),(44) comparing falls between quetiapine and placebo in patients with BPSD. The study duration varied between 6 and 10 weeks. There was overall a medium risk of bias in this study with a study duration of 10 weeks.

The two largest studies had overall a low risk of bias.(42),(44)

There was **no difference** between quetiapine and placebo for **the risk of falls** in patients with BPSD.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

6.5.1.4 Risperidone versus placebo

Risperidone versus placebo for BPSD - Falls			
Bibliography: Ma 2014(23), including Brodaty 2003(45), Deberdt 2005(35), Katz 1999(48), Mintzer 2006(49)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Falls	1725 (4) 8-12 weeks	152/1060 vs 111/665 OR 0.86 (95%CI: 0.65, 1.14) I^2=0% NS	⨁⨁⨀⨀ **LOW** Study quality: -2 (high dropout, unclear sequence generation) Consistency: ok Directness: ok Imprecision: ok

The systematic review from Ma 2014(23) included four RCTs (Brodaty 2003, Deberdt 2005, Katz 1999, Mintzer 2006)(45),(35),(48),(49) comparing falls between risperidone and placebo in patients with BPSD. The study duration varied between 8 and 12 weeks.

Two studies had overall an intermediate risk of bias mainly due to an unclear risk for sequence generation and high dropout rate (>20%). (35), (49)

There was **no difference** between risperidone and placebo for **the risk of falls** in patients with BPSD.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

6.5.1.5 SGA as group versus placebo

SGA versus placebo for BPSD - Falls			
Bibliography: Ma 2014(23), including Brodaty 2003(45), Deberdt 2005(35), Katz 1999(48), Mintzer 2006(49), Paleacu 2008(41), Tariot 2006(42), Zhong 2007(44)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Falls	2585 (7) 6-12 weeks	245/1615 vs 167/970 OR 0.89 (95%CI: 0.71, 1.12) I^2=0% NS	⨁⨁⨁⨀ **MODERATE** Study quality: -1 (high dropout) Consistency: ok Directness: ok Imprecision: ok

The systematic review from Ma 2014(23) included seven RCTs(45), (35),(48),(49),(41),(42),(44) comparing falls between SGA as a group (olanzapine, quetiapine, risperidone) and placebo in patients with BPSD. The study duration varied between 6 and 12 weeks.

From the seven studies, three studies had overall a intermediate risk of bias due to an unclear risk for sequence generation.(35),(49),(41) One of the aforementioned studies had a small sample size (n=40).(41) Furthermore, the dropout rate was overall high across the studies.

There was **no difference** between SGA as a group and placebo for **the risk of falls** in patients with BPSD.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

6.5.2 SGA versus haloperidol for BPSD

SGA versus haloperidol for BPSD - Falls			
Bibliography: AHRQ 2011(6) including Tariot 2006(42)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Falls	346 (1) 10 weeks	26/91 (28.6%) vs 27/94 (28.7%) NS	⨁⨁⨀⨀ **LOW** Study quality: -1 (high dropout) Consistency: NA Directness: ok Imprecision: -1 (sparse data)

The AHRQ 2011(6) review does not report results for falls. We therefore checked all included studies that compared SGA with haloperidol in the AHRQ 2011 review individually for the outcome falls.(50),(51),(52),(42),(47)

The study by Tariot 2006(42) reports falls for quetiapine versus haloperidol in patients with BPSD. The study duration was 10 weeks. There was overall a low risk of bias in this study but the dropout rate was high (>20%).

No other RCTs were found comparing falls between other SGA and haloperidol.

There was **no difference** between quetiapine and haloperidol for **the risk of falls** in patients with BPSD.
GRADE: LOW quality of evidence

We have low confidence that the results of the studies reflect the true effect.

6.5.3 SGA versus SGA for BPSD

SGA versus SGA for BPSD - Falls			
Bibliography: AHRQ 2011(6) including Deberdt 2005(35)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Falls	494 (1) 10 weeks	11.3% vs 9.2% vs 6.4% NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (high dropout, unclear sequence generation) Consistency: NA Directness: ok Imprecision: -1 (sparse data)

The AHRQ 2011 review(6) does not report results for falls. We therefore checked each included study comparing SGA with SGA in the AHRQ 2011 review for the outcome falls.(35),(37),(38),(53)

The study by Deberdt 2005(35) reports falls for olanzapine versus risperidone versus placebo in patients with BPSD. No separate analysis without the placebo group was reported. The study duration was 10 weeks. There was overall a medium risk of bias in this study mainly due to an unclear risk of bias for sequence generation and a high dropout rate.

No other RCT's were found comparing falls between other SGA.

There was **no difference** between olanzapine, risperidone, and placebo for **the risk of falls** in patients with BPSD.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

6.6 Safety: endocrine adverse events (diabetes, hyperprolactinemia)

6.6.1 SGA versus placebo for BPSD

6.6.1.1 Risperidone versus placebo

Risperidone versus placebo for BPSD – diabetes
Bibliography: AHRQ 2011(6), including Mintzer 2006(49)

Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
Diabetes	473 (1) 8 weeks	1.7% (4/235) vs 2.1% (5/238) OR 0.81 (95%CI: 0.16, 3.80) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (serious limitations) Consistency: NA Directness: ok Imprecision: -1 (wide CI)

The AHRQ 2011 review(6) compared risperidone with placebo for diabetes in patients with BPSD. One RCT's with a study duration of 8 weeks was included.

The study by Mintzer 2006(49) had overall an intermediate risk of bias mainly due to unclear risk sequence generation. The dropout rate was high (>20%).

There was **no difference** between risperidone and placebo for the development of **diabetes** in patients with BPSD.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

Risperidone versus placebo for BPSD – Hyperprolactinemia			
Bibliography: AHRQ 2011(6), including Mintzer 2006(49)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Prolactin	473 (1) 8 weeks	0/235 vs 0/238 Not estimable	Insufficient evidence

The AHRQ 2011 review(6) compared risperidone with placebo for hyperprolactinemia in patients with BPSD. One RCT's with a study duration of 8 weeks was included.

The study by Mintzer 2006(49) had overall an intermediate risk of bias mainly due to unclear risk sequence generation.

GRADE: insufficient evidence

6.6.1.2 Other SGA versus placebo

The AHRQ 2011 review(6) found no studies comparing other SGA besides risperidone with placebo for the development of diabetes or hyperprolactinemia in patients with BPSD.

GRADE: Insufficient evidence

6.6.2 SGA versus haloperidol for BPSD

6.6.2.1 Olanzapine versus haloperidol

Olanzapine vs haloperidol for BPSD – endocrine adverse events			
Bibliography: AHRQ 2011(6), including Moretti 2005(50), ?Verhey 2006(51)?			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Diabetes	386 (2) 5 weeks – 12 months	2/193 vs 3/193 OR 1.50 (95%CI: 0.17, 18.14) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 (very serious limitations) Consistency: ok Directness: ok Imprecision: -1 (wide CI)

The AHRQ 2011(6) review treated each SGA separately and (in general) did not group them together as a class. References are not added in the AHRQ 2011 adverse events analysis and we could therefore not always verify the data for this outcome with absolute certainty. Even after having checked each included study comparing SGA with FGA in patients with BPSD.(50),(51),(52),(42),(47)

The AHRQ 2011 review included two studies (Moretti 2005(50) and likely Verhey 2006(51)) comparing the development of diabetes between olanzapine and haloperidol in patients with BPSD. The study by Moretti 2005(50) compared olanzapine with FGA (60 patients receiving promazine chloridrate and 113 patients receiving haloperidol). No separate results were reported for haloperidol and promazine chloridrate.

The study duration was 12 months in one study(50) and 5 weeks in the other study(51).

The study by Moretti 2005(50) did not meet our inclusion criterion for study type (open label). However, we decided to retain the results of this study for the outcome diabetes. This study had a poor rating for quality with a jadad score of 0/5. The study by Verhey 2006(51) had an intermediate risk of bias mainly due to an unclear risk for sequence generation and allocation concealment.

There was **no difference** between olanzapine and FGA for **diabetes** in patients with BPSD.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

6.6.2.2 Risperidone versus haloperidol

Risperidone vs haloperidol for BPSD – endocrine adverse events			
Bibliography: AHRQ 2011(6), including ?De Deyn 1999(47)?			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Diabetes	344 (1) 12 weeks	0/20 vs 0/20 Not estimable	Insufficient data

The AHRQ 2011(6) review treated each SGA separately and (in general) did not group them together as a class. References are not added in the AHRQ 2011 adverse events analysis and we could therefore not always verify the data for this outcome with absolute certainty. Even after having checked each included study comparing SGA with FGA in patients with BPSD.(50),(51),(52),(42),(47)

The AHRQ 2011 review included one study comparing the development of diabetes between risperidone and haloperidol in patients with BPSD. This is very likely the study by De Deyn 1999(47) since no other RCT for this comparison was included. The study by De Deyn 1999 compared olanzapine with haloperidol and had a study duration of 12 weeks.

The study by De Deyn 1999(47) had overall a low risk of bias but the dropout rate was high. This study (n=344) reported this outcome for only a total of 40 patients.

GRADE: Insufficient evidence

6.6.3 SGA versus SGA for BPSD

The AHRQ 2011(6) review included one study comparing the development of diabetes between risperidone and olanzapine in patients with BPSD. References are not added in the AHRQ 2011 adverse events analysis and we could therefore not verify the data for this outcome.

The AHRQ 2011 review included two studies (Deberdt 2005(35), Schneider 2006(37)/Sultzer 2008(38)) comparing risperidone with olanzapine. Even after having checked both studies, we could not verify which one was used by AHRQ 2011 for their diabetes results. Although the two studies had a total sample size (including other arms) of 494 and 421 respectively, the diabetes results in the AHRQ 2011 analysis were reported for a total of 40 patients.

GRADE: Insufficient evidence

6.6.4 Observational studies: antipsychotic-induced diabetes

We found no observational studies assessing the development of diabetes mellitus in patients with BPSD on antipsychotics.

6.7 Safety: urinary tract infections

6.7.1 SGA versus placebo for BPSD

6.7.1.1 Aripiprazole versus placebo

Aripiprazole versus placebo for BPSD - Urinary tract infections			
Bibliography: Ma 2014(23), including De Deyn 2005(31), Mintzer 2007(30), Streim 2008(33)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Urinary tract infection	951 (3) 10 weeks	89/603 vs 39/348 OR 1.18 (95%CI: 0.77, 1.79) I^2=18% NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (high dropout, unclear sequence generation) Consistency: ok Directness: ok Imprecision: ok

The systematic review by Ma 2014(23) compared urinary tract infections between aripiprazole and placebo in patients with BPSD. Three RCT's (De Deyn 2005(31), Mintzer 2007(30), Streim 2008(33) with a study duration of 10 weeks were included.

Two studies had overall a medium risk of bias mainly due an unclear risk for sequence generation. (30),(31) The dropout rate was high (>20%) in two studies.(30),(33)

There was **no difference** for **urinary tract infections** between aripiprazole and placebo in patients with BPSD.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

6.7.1.2 Quetiapine versus placebo

Quetiapine versus placebo for BPSD - Urinary tract infections			
Bibliography: Ma 2014(23), including Tariot 2006(42), Zhong 2007(44)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Urinary tract infection	523 (2) 10 weeks	40/332 vs 12/191 OR 1.96 (95%CI: 0.99, 3.87) I^2=0% NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (high dropout) Consistency: ok Directness: ok Imprecision: ok

The systematic review by Ma 2014(23) compared urinary tract infections between quetiapine and placebo in patients with BPSD. Two RCT's (Tariot 2006(42), Zhong 2007(44) with a study duration of 10 weeks were included.

Both studies had overall a low risk of bias but a high dropout rate.

There was **no difference** for **urinary tract infections** between quetiapine and placebo in patients with BPSD.
GRADE: Moderate quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

6.7.1.3 *Risperidone versus placebo*

Risperidone versus placebo for BPSD - Urinary tract infections			
Bibliography: Ma 2014(23), including Brodaty 2003(45), Katz 1999(48), Mintzer 2006(49)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Urinary tract infection	1435 (3) 8-12 weeks	139/864 vs 70/571 OR 1.34 (95%CI: 0.97, 1.84) I^2= 17% NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (high dropout, unclear sequence generation) Consistency: ok Directness: ok Imprecision: ok

The systematic review by Ma 2014(23) compared urinary tract infections between risperidone and placebo in patients with BPSD. Three RCT's (Brodaty 2003(45), Katz 1999(48), Mintzer 2006(49)) were included. The study duration varied between 8 weeks and 12 weeks.

One larger study had overall an intermediate risk of bias mainly due to an unclear risk of bias for sequence generation.(49) The dropout rate was high (>20%) in the three included studies.

There was **no difference** for **urinary tract infections** between risperidone and placebo in patients with BPSD.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

6.7.1.4 *SGA as group versus placebo*

SGA versus placebo for BPSD - Urinary tract infections			
Bibliography: Ma 2014(23), including De Deyn 2005(31), Mintzer 2007(30), Streim 2008(33), Tariot 2006(42), Zhong 2007(44), Brodaty 2003(45), Katz 1999(48), Mintzer 2006(49)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Urinary tract infection	2909 (8) 8-12 weeks	268/1799 vs 121/1110 OR 1.35 (95%CI: 1.07, 1.71) p = 0.01 I^2=0% **SS in favour of SGA**	⊕⊕⊖⊖ **LOW** Study quality: -2 (high dropout, unclear sequence generation) Consistency: ok Directness: ok Imprecision: ok

The systematic review by Ma 2014(23) compared urinary tract infections between SGA as a group (aripiprazole, quetiapine, risperidone) and placebo in patients with BPSD. A total of eight RCT's were included.(31),(30),(33),(42),(44),(45),(48),(49) The study duration varied between 8 and 12 weeks.

Three studies had overall a medium risk of bias mainly due an unclear risk for sequence generation. (30),(49),(31) The dropout rate was overall high (>20%).

There were **significantly more urinary tract infections** for SGA as group compared to placebo in patients with BPSD.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

6.7.2 SGA versus haloperidol for BPSD

SGA versus haloperidol for BPSD – urinary tract infections			
Bibliography: AHRQ 2011(6), including Tariot 2006(42)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Urinary tract infections	n= 284 (Tariot 2006) 10 weeks	11/91 (12.1%) vs 10/94 (10.6%) NS	⨁⨁⊖⊖ **LOW** Study quality: -1 (high dropout) Consistency: NA Directness: ok Imprecision: -1 (sparse data)

The AHRQ 2011 review(6) reports results for urinary symptoms for the comparison olanzapine versus FGA and risperidone versus FGA. Results were based on data from 2 studies and 1 study respectively. Since we focused on the outcome urinary tract infection and since the AHRQ 2011 review seems to group urinary symptoms together (urinary incontinence and urinary tract infection) we could not use these data. Furthermore, references are not added in the AHRQ 2011 adverse events analysis. We therefore checked each included study comparing SGA with FGA in the AHRQ 2011 review for urinary tract infections.(50),(51),(52),(42),(47)

Tariot 2006(42) compared urinary tract infections between quetiapine versus haloperidol in patients with BPSD. The study had a duration of 10 weeks. Overall, there was a low risk of bias in this study but the dropout rate was high (>20%).

We found no other RCTs comparing urinary tract infections between other SGA and haloperidol in patients with BPSD.

There was **no difference** between quetiapine and haloperidol for urinary tract infections in patients with BPSD.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

6.7.3 SGA versus SGA for BPSD

The AHRQ 2011 review(6) reports results for urinary symptoms for the comparison risperidone versus olanzapine or quetiapine. Results were based on 1 study for each comparison.(35),(53) Since we focused on the outcome urinary tract infection and since the AHRQ 2011 review seems to group urinary symptoms together (urinary incontinence and urinary tract infection), we could not use these data. We therefore checked both studies individually for urinary tract infections. However both studies only report urinary incontinence and not urinary tract infections.

GRADE: Insufficient evidence

6.8 Discontinuation of antipsychotics in patients with BPSD

Withdrawal from antipsychotics vs continuation of antipsychotics			
Bibliography: Van Leeuwen 2018(56) including Ballard 2004(57), Ballard 2008(58), Bergh 2011(59), Bridges-Parlet 1997(60), Devanand 2011(61), Devanand 2012(62), Findlay 1989(63), van Reekum 2002(64), Ruths 2008(65).			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Success of withdrawal defined as number of non-completers	575 (9) 1 to 12 months	In 7 studies: **no overall difference** in the different outcomes In two study: **SS in favour of continuation** <u>Devanand 2011:</u> **Time to relapse:** 5.8 weeks (SD 6.7) vs 8.0 weeks (SD 6.7) Chi^2= 4.1 p = 0.04 <u>Devanand 2012:</u> **Drop out due to symptomatic relapse:**	⨁⨁⨀⨀ **LOW** Study quality: -1 (reporting/attrition bias) Consistency: 0 Directness: -1 (outcome, population) Imprecision: 0

		24/40 (60%) vs 23/70 (33%) HR 1.94 (95% CI 1.09 to 3.45) P = 0.02 13/27 (48%) vs 2/13 (15%) HR 4.88 (95%CI 1.08 to 21.98) p=0.02 In one small study: <u>Bergh 2011:</u> **Dropout rate:** 7/9 vs 0/10	
Behavioural and psychological Symptoms	519 (7) 1 to 12 months 265 (194 reported events) (2)	In five non-pooled studies: **no difference** in most of the outcomes . <u>In van Reekum 2002:</u> **Apathy:** No supporting data, p = 0.04 **reported as SS in favour of discontinuation** Two pooled studies (NPI to assess NPS): MD -1.49 (95% CI -5.39 to 2.40) NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-1 (data not reported) Consistency: 0 Directness: -1 (population) Imprecision: -1 (CI-population size)
Withdrawal symptoms/syndrome		No data	**Insufficient evidence**
Adverse events attributable to antipsychotics	381 (5) 1 to 12 months	N**o evidence of a difference**	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 (drop out) Consistency: 0 Directness: -1 (diverse outcomes, population) Imprecision: -1 (population size)
Quality of life	119 (2) 3 months to 25 weeks	N**o evidence of a difference**	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 (reporting and attrition bias) Consistency: 0 Directness: -1 (population) Imprecision: -1 (population size)
Cognitive function	365 (5) 1 to 12 months	In 5 studies: **no evidence of a difference** in overall cognitive function using different scales. <u>In Ballard 2008:</u> **FAS (verbal fluency):** 0.6 (SD 6.2) improvement vs 3.2 (SD 6.6) deterioration MD -4.5 (95% CI -7.3 to -1.7) p = 0.002 **SS favouring discontinuation**	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 (reporting bias) Consistency: 0 Directness: -1 (population) Imprecision: -1 (population size)
Use of physical restraint	1	**No difference** No supporting data provided	**Insufficient evidence**

	(36) 1 month		
Mortality	275 (2) 4 to 36 months	Up to 12 months: **no evidence of a difference.** <u>In Ballard 2008:</u> **Probability of survival (**36 months): 59% vs 30 % not details reported **reported as SS favouring discontinuation**	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 (important drop out) Consistency: 0 Directness: -1 population Imprecision:-1 (few events)
Time until prescription of any psychotropic agent except APs	30 (1) 1 month	**No difference** No supporting data provided.	**Insufficient evidence**
Global functioning	329 (4) 1 to 12 months	**No evidence of a difference.**	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 (reporting bias) Consistency: 0 Directness: -1 (population) Imprecision: -1 (population size)
Sleep	66 (2) 1 month	**No evidence of a difference.**	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 (reporting bias) Consistency: 0 Directness: -1 (population) Imprecision: -1 (population size)
Clinical global impression	311 (3) 1 to 12 months	**No difference** No supporting data provided	**Insufficient evidence**

The Cochrane review from Van Leeuwen 2018(56) compared **withdrawal from antipsychotics vs continuation of antipsychotics** in adults aged 65 and older with dementia. RCTs with patients who were treated with antipsychotics for at least 3 months were included. Studies used either abrupt, tapered or mixed withdrawal schedules.

A total of 10 studies with study durations between 1 to 36 months was included: Ballard 2004(57), Ballard 2008(58), Bergh 2011(59), Bridges-Parlet 1997(60), Devanand 2011(61), Devanand 2012(62), Findlay 1989(63), van Reekum 2002(64), Ruths 2008(65), Cohen-Mansfield 1999)(66). The Cochrane review could not use the data from one crossover RCT (Cohen-Mansfield 1999) due to the lack of separate outcome data for the different medications discontinued (benzodiazepine as well as antipsychotics).

The authors were unable to pool data due to the clinical heterogeneity and considerable discrepancies in measured outcomes. Pooling was only possible for behavioural outcomes assessed by neuropsychiatric inventory score (NPI). It is important to note that there is a lack of consistency

regarding study participants, types and dosages of antipsychotics used before withdrawal, method of withdrawal, and times of assessment among the individual studies.

Five studies had a small sample size (n= 19 to 36): Bergh 2011(59), Bridges-Parlet 1997(60), Devanand 2011(61), Findlay 1989(63), and van Reekum 2002(64). For several outcomes, no raw data were found from the original RTC's limiting our confidence in any conclusions. Participants' average age was 80 years or over and residing in nursing facilities in most studies, reflecting indirectness in rating strength of evidence. Ballard 2008(58), Devanand 2011(61), Devanad 2012(62) and van Reekum 2002(64) reported high dropout rates. A high dropout rate with unequal numbers across the groups was reported in Bergh 2011 resulting in a high risk of attrition bias.

In seven studies: discontinuation of the antipsychotic drug made **no difference** to the ability of participants to complete the study (Defined criteria for **success of withdrawal**).
In three studies: there was **some evidence in favour of the continuation group**.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

In seven studies: discontinuation may make **no difference to behavioural and psychological symptoms.**

GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

In five studies: Discontinuation may make little or **no difference to adverse events of antipsychotics.**

GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

In two studies: Discontinuation may make **no difference to quality of life.**

GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

In five studies: Discontinuation may make **no difference to overall cognitive functions**. One trial found that **discontinuation of antipsychotics improves measures of verbal fluency** compared to continuation.

GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

In two studies: There is **no evidence of a difference** between discontinuation and continuation of antipsychotics **for mortality**. In one study the probability of survival was increased in the discontinuation group compared to continuation group but no statistics were provided.

GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

In four studies: Discontinuation may make **no difference to global functioning.**

GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

In two studies: Discontinuation may make **no difference to sleep**.

GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

7 Antipsychotics for the treatment of delirium: summary and conclusions from the literature review

7.1 Antipsychotics versus nonantipsychotics/placebo

Antipsychotics versus placebo/non-antipsychotic drugs for delirium in non-ICU patients			
Bibliography: Burry 2018(25), including Agar 2016(26), Breitbart 1996(70), Hu 2004(71), Tahir 2010(72)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Total duration of delirium (days)		No trial data	Insufficient data
Delirium severity	494 (4) 3-10 days	SMD -1.08 (95% CI -2.55 to 0.39) I^2= 97% NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 (serious limitation) Consistency: -1 (high heterogeneity) Directness: ok Imprecision: -1
Delirium resolution	247 (3) 6-10 days	66/191 vs 15/56 RR 0.95 (95% CI 0.30 to 2.98) I^2= 83% NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 (serious limitation) Consistency: -1 (high heterogeneity) Directness: ok Imprecision: -1
Mortality	319 (3) 3-10 days	36/208 vs 14/111 RR 1.29 (95% CI 0.73 to 2.27) I^2= 0.0% NS	⨁⨁⊖⊖ **LOW** Study quality: -1 (serious limitation) Consistency: ok Directness: ok Imprecision: -1
Hospital length of stay (days)		No trial data	Insufficient data
Hospital discharge disposition (e.g. rehabilitation, chronic care facility, home)		No trial data	Insufficient data
Health-related quality of life		No trial data	Insufficient data
Extrapyramidal symptoms	247 (3) 6-10 days	26/191 vs 3/56 RR 1.70 (95% CI 0.04 to 65.57) I^2= 77% NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 (serious limitation) Consistency: -1 (high heterogeneity) Directness: ok Imprecision: -1

The Cochrane review from Burry 2018 included four studies in various populations (e.g. patients receiving palliative care, patients with HIV) comparing antipsychotics with non-antipsychotics/placebo for delirium in hospitalized non-ICU patients. The study duration varied between 3 days and 10 days. Two studies had 3 arms comparing a SGA (risperidone or olanzapine), haloperidol, and placebo. One study without a placebo group had 3 arms comparing 2 FGA (haloperidol and chlorpromazine (not available in Belgium)) and a benzodiazepine (lorazepam). One study compared a SGA (quetiapine) with placebo. All studies used titrated study drug according to symptom response.

There were no reported data to determine whether antipsychotics altered the duration of delirium, length of hospital stay, or health-related quality of life as studies did not report on these outcomes. No trials reported the use of physical restraints.

Only one study (Agar 2016) (26) was scored as low risk of bias across all domains. Two studies scored unclear risk of bias in one (Tahir 2010) (72) or more domains (Breitbart 1996) (70). The remaining study (Hu 2004) (71) had a high risk of bias across two domains (blinding and incomplete outcome data) and unclear risk of bias across three other domains.

Guidelines suggest antipsychotics only be considered after failure of non-drug strategies in distressed patients. Only half of the studies reported that non-drug strategies were used during the study period and details of the intervention applied were not provided. Also, the use of rescue therapies for agitation, such as benzodiazepines, was not consistently reported. Physical restraint use was not reported in any trial. Use of chemical and physical restraint as rescue therapy presents an opportunity to introduce bias. These methodological problems limit our confidence in the results.

For the outcomes, severity and resolution of delirium, variable tools were used, different definition or thresholds were applied, and the outcomes were assessed at different time points.

There was **no difference** between antipsychotics and non-antipsychotics/placebo for the treatment of **delirium severity** in non-ICU patients.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

We note that the definition of delirium varied in the studies.

There was **no difference** between antipsychotics and non-antipsychotics/placebo for the treatment of **delirium resolution** in non-ICU patients.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

Mortality was measured at study day three (Agar 2016) (26),within one week of study completion Breitbart 1996(70), and at day 30 (Tahir 2010) (72).

There was **no difference** between antipsychotics and non-antipsychotics/placebo for **mortality** in non-ICU patients treated for delirium.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no difference** between antipsychotics and non-antipsychotics/placebo for **extrapyramidal symptoms** in non-ICU patients treated for delirium.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

7.2 SGA versus FGA

FGA versus SGA for delirium in non-ICU patients			
Bibliography: Burry 2018(25), including Agar 2016(26), Grover 2011(73), Grover 2016(74), Han 2004(75), Hu 2004(71), Lin 2008(76), Maneeton 2013(77)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Total duration of delirium (days)		No trial data	Insufficient data
Delirium severity	542 (7) 3-7 days	SMD -0.17 (95% CI -0.37 to 0.02) I^2= 16% NS	⨁⨁⨀⨀ **LOW** Study quality: -1 (serious limitation) Consistency: -1 Directness: ok Imprecision: ok
Delirium resolution	349 (5) 6-7 days	62/185 vs 50/164 RR 1.10 (95%CI 0.79 to 1.52) I^2= 2% NS	⨁⨁⨀⨀ **LOW** Study quality: -1 (serious limitation) Consistency: -1 Directness: ok Imprecision: ok
Mortality	342 (4) 3-7 days	17/181 vs 10/161 RR 1.71 (95% CI 0.82 to 3.53) I^2= 0.0% NS	⨁⨁⨀⨀ **LOW** Study quality: -1 (serious limitation) Consistency: ok Directness: ok Imprecision: -1 (sparse data)
Hospital length of stay (days)		No trial data	Insufficient data
Hospital discharge disposition (e.g. rehabilitation, chronic care facility, home)		No trial data	Insufficient data

Health-related quality of life		No trial data	Insufficient data
Extrapyramidal symptoms	198 (2) 7 days	24/100 vs 0/98 RR 12.16 (95% CI 0.55 to 269.52) I^2 = 54% NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 (serious limitation) Consistency: -1 (moderate heterogeneity) Directness: ok Imprecision: -1

The Cochrane review from Burry 2018 included a total of seven studies in various populations (e.g. patients receiving palliative care, older patients) comparing FGA with SGA for delirium in hospitalized non-ICU patients. The study duration varied between 3 days and 7 days. The studied SGA included risperidone, olanzapine, and quetiapine. Haloperidol was studied as FGA in every included study. All studies used titrated study drug according to symptom response.

None of the included studies evaluated duration of delirium, use of physical restraints, length of hospital stay, or health-related quality of life.

Six studies were scored a high risk of bias for incomplete outcome data. One study (Hu 2004)(71) had an additional high risk of bias for blinding. With the exception of one study (Agar 2016) (26), all other studies had an unclear risk of bias in one or more domains.
Guidelines suggest antipsychotics only be considered after failure of non-drug strategies in distressed patients. As pointed out by Burry 2018, only half of the total identified trials reported that non-drug strategies were used during the study period and details of the interventions applied were not provided. Also, the use of rescue therapies for agitation, such as benzodiazepines, was not consistently reported. Physical restraint use was not reported in any trial. Use of chemical and physical restraint as rescue therapy presents an opportunity to introduce bias.
These methodological problems limit our confidence in the results.

For the outcomes, severity and resolution of delirium, variable tools were used, different definition or thresholds were applied, and the outcomes were assessed at different time points.

There was **no difference** between SGA and haloperidol for the treatment of **delirium severity** in non-ICU patients.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

We note that the definition of delirium varied in the studies.

There was **no difference** between SGA and haloperidol for the treatment of **delirium resolution** in non-ICU patients.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Mortality was measured at study day three (Agar 2016) (26) and within one week of study enrolment (Grover 2011, Grover 2016, Maneeton 2013).(73),(74),(77)

There was **no difference** between SGA and haloperidol for **mortality** in non-ICU patients treated for delirium.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no difference** between SGA and haloperidol for **extrapyramidal symptoms** in non-ICU patients treated for delirium.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

7.3 SGA versus SGA

The AHRQ 2019 review by Neufeld 2019(27) searched for RCTs comparing SGA with SGA in patients with delirium. The authors found 3 RCTs (Grover D 2011(73), Kim SW 2010(78), Lee KU 2005(79)) comparing SGA with SGA that could not be pooled. One study(78) compared amisulpride with quetiapine. Amisulpride is classified as a FGA by the BCFI. None of these three studies met our inclusion criteria for study type or sample size.

GRADE: insufficient evidence

8 Antipsychotics for insomnia: summary and conclusions from the literature review

8.1 Haloperidol versus placebo/active comparator

The review of Schroeck 2016 focusing on an older population did not discuss any study comparing haloperidol or any other FGA with placebo/active comparator for insomnia.(67)

We found no other RCTs comparing haloperidol to placebo/active comparator for insomnia.

GRADE: insufficient evidence

8.2 SGA versus placebo/active comparator for insomnia

8.2.1 Olanzapine versus placebo/active comparator

The systematic review of Thompson 2016 found no studies comparing olanzapine to placebo/active comparator for insomnia.(68)

GRADE: insufficient evidence

8.2.2 Quetiapine versus placebo/active comparator

The systematic review of Thompson 2016(68) found one double-blind RCT comparing quetiapine with placebo for 2 weeks. This study (n= 16) did not meet our inclusion criterion for sample size (n>40 for each arm).(69)

GRADE: insufficient evidence

8.2.3 Risperidone versus placebo/active comparator

The systematic review of Thompson 2016 found no studies comparing risperidone to placebo/active comparator for insomnia. (68)

GRADE: insufficient evidence

8.3 Withdrawal of antipsychotics in patients with insomnia

We found no RCTs evaluating the withdrawal of antipsychotics in patients with insomnia.

GRADE: insufficient evidence

9 Safety of antipsychotics in children: summary and conclusions from the literature review

9.1 Antipsychotics vs control

AP versus control			
Bibliography: Ray 2019(80); Jeon 2021**(81)**			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality *(classified as deaths due to injury, suicide or unexpected deaths)*	219481 (1 study) *control group: 123005 person-years* *AP group: 27345 person-years*	**RR: 1.80 (95%CI 1.06 to 3.07)** **SS more deaths with AP** **NNH 2283 (888 to 30097)**	⨁⨁⊖⊖ **LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: ok
Unexpected deaths	219481 (1 study) *control group: 123005 person-years* *AP group: 27345 person-years*	**RR 3.51 (1.54 to 7.96)** **SS more unexpected deaths with AP** **NNH 2229 (802 to 10288)**	⨁⨁⊖⊖ **LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: ok
Death due to injury or suicide	219481 (1 study) *control group: 123005 person-years* *AP group: 27345 person-years*	RR 1.03 (0.53 to 2.01) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: -1
Movement disorders	10969 (1 study) +/- 2yrs	**HR 8.17 (95%CI 7.16 to 9.33)** SS more movement disorders during exposure vs non-exposure to AP	⨁⨁⊖⊖ **LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: ok

A retrospective cohort study compared the risk of mortality in children and young adults (5-24 years of age) between current, new use of antipsychotics and the use of control medications (ADHD medication, antidepressants and mood stabilizers).

As we have information from observational data only, the quality of evidence is assessed as low.

In children and young adults, current, new use of antipsychotics resulted in **more deaths** compared to use of control medications.
GRADE: LOW quality of evidence

In children and young adults, current, new use of antipsychotics resulted in **more unexpected deaths** compared to use of control medications.
GRADE: LOW quality of evidence

In children and young adults, there was **no difference in number of deaths due to injury or suicide** with new use of antipsychotics compared to use of control medications.
GRADE: LOW quality of evidence

Our second search update found one retrospective cohort study (Jeon 2021**(81)**) that compared periods of exposure to antipsychotics including haloperidol, risperidone, aripiprazole, olanzapine and quetiapine, with periods of no exposure to antipsychotics, in children diagnosed with a psychiatric disorder and newly receiving antipsychotics.

There are some methodological problems that limit our confidence in the estimate of the results: only observational data was found, and there were some disparities between the results in the text of the publication versus the results presented in the figures.

In children, there were **more movement disorders** during periods of exposure vs periods of no exposure to antipsychotics.
GRADE: LOW quality of evidence

9.2 FGA versus SGA

FGA versus SGA			
Bibliography: AHRQ 2017(3)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Weight (kg)	506 (14 studies) <6 months	**MD -2.67 (95% CrI -4.61 to -0.70)** **SS less weight gain with FGA**	⨁⨁⨁⊖ **MODERATE** Study quality: -1 risk of incomplete outcome, no blinding in larger study Consistency: unable to assess Directness: ok Imprecision: ok
Sedation	345 (7 studies) <6 months	70/160 vs 79/185 RR 1.05 (95%CrI 0.75 to 1.89) NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1 risk of incomplete outcome, no blinding in larger study Consistency: unable to assess Directness: ok Imprecision: ok

Sedation (12+ months)	160 (3 studies) >12 months	18/87 vs 5/73 RR 2.84 (95% CrI 0.34 to 92.81) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: observational study Consistency: unable to assess Directness: ok Imprecision: -1
Somnolence	83 (3 studies) <6 months	15/41 vs 26/42 RR 0.53 (95% CrI 0.14 to 1.75) NS	⨁⨁⊖⊖ **LOW** Study quality:-1 risk of incomplete outcome Consistency: unable to assess Directness: ok Imprecision: -1

This AHRQ systematic review and meta-analysis by Pillay 2017 searched for all RCTs and cohort studies that compared first generation antipsychotics to second generation antipsychotics in children and adolescents (≤24yrs).

There are some methodological problems that limit our confidence in the estimate of the results: a high risk of incomplete outcome data, a large study without blinding, and one outcome for which only observational data was found.

In children and young adults, first generation antipsychotics resulted in **less weight gain** compared to second generation antipsychotics.
GRADE: MODERATE quality of evidence

In children and young adults, there was **no difference in sedation** with **short term use** of first generation antipsychotics or second generation antipsychotics.
GRADE: MODERATE quality of evidence

In children and young adults, there was **no difference in sedation** with **long term use** of first generation antipsychotics or second generation antipsychotics.
GRADE: VERY LOW quality of evidence

In children and young adults, there was **no difference in somnolence** with first generation antipsychotics or second generation antipsychotics.
GRADE: LOW quality of evidence

FGA versus SGA			
Bibliography: Chung 2019(82)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Occurrence of cardiometabolic events	29030 (1 study) +/- 2yrs	HR 0.98 (95% CI 0.56 to 1.70) NS	⨁⨁⊖⊖ **LOW** Study quality: observational study Consistency: NA

type 2 diabetes mellitus, hypertension, dyslipidemia and major adverse cardiovascular events (MACE), including AMI, IHD, ischemic stroke, and cardiac death.			Directness: ok Imprecision: ok
Type 2 diabetes melllitus	29030 (1 study) +/- 2yrs	HR 0.42 (95% CI 0.09–2.02) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: -1
Hypertension	29030 (1 study) +/- 2yrs	HR 1.39 (95% CI 0.66–2.91) NS	⨁⨁⊖⊖ **LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: ok
Dyslipidemia	29030 (1 study) +/- 2yrs	HR 0.74 (95% CI 0.25–2.20) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: observational study outcome Consistency: NA Directness: ok Imprecision: -1
MACE AMI, ischemic heart disease, ischemic stroke, and cardiac death	29030 (1 study) +/- 2yrs	HR 2.64 (95% CI 0.16–42.62) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: observational study outcome Consistency: NA Directness: ok Imprecision: -1

Our updated search (update 1) found one retrospective cohort study (Chung 2019(82)) that compared several antipsychotics, with risperidone used as the reference comparator, in children diagnosed with a psychiatric disorder and newly receiving antipsychotics.

There are some methodological problems that limit our confidence in the estimate of the results: only observational data was found, and the rarity of some of the endpoints resulted in imprecise results.

In children, there was **no difference in the occurrence of cardiometabolic events** between haloperidol (FGA) and risperidone (SGA).
GRADE: LOW quality of evidence

In children, there was **no difference in type 2 diabetes mellitus** between haloperidol (FGA) and risperidone (SGA).
GRADE: VERY LOW quality of evidence

In children, there was **no difference in hypertension** between haloperidol (FGA) and risperidone (SGA).
GRADE: LOW quality of evidence

In children, there was **no difference in dyslipidemia** between haloperidol (FGA) and risperidone (SGA).
GRADE: VERY LOW quality of evidence

In children, there was **no difference in MACE** between haloperidol (FGA) and risperidone (SGA).
GRADE: VERY LOW quality of evidence

haloperidol vs risperidone			
Bibliography: Jeon 2021**(81)**			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Movement disorders	10969 (1 study) +/- 2yrs	**HR 2.14 (1.57 to 2.91)** SS more movement disorders with haloperidol vs risperidone	⨁⨁⨀⨀ **LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: ok

Our second search update found one retrospective cohort study (Jeon 2021) that compared exposure to antipsychotics including haloperidol, aripiprazole, olanzapine and quetiapine, to exposure to risperidone as the reference comparator, in children diagnosed with a psychiatric disorder and newly receiving antipsychotics.

There are some methodological problems that limit our confidence in the estimate of the results: only observational data was found, and there were some disparities between the results in the text of the publication versus the results presented in the figures.

In children, there were **more movement disorders** with haloperidol versus risperidone.
GRADE: LOW quality of evidence

9.3 FGA vs placebo

No studies met our inclusion criteria.

9.4 SGA vs placebo

All SGA versus placebo			
Bibliography: AHRQ 2017(3), Chen 2016 (83), Xing 2017(84), Chen 2018(85), Patel 2017(86)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	2247 (13 studies) <6 months	0/1635 vs 0/812 *Insufficient data*	*Insufficient data*
Cardiac arrhythmia	2425 (14 studies) <6 months	19/1490 vs 9/935 *No statistical testing*	*Insufficient data*
Cardiovascular events	74700 (1 study) 2 yrs	**RR: 1.55 (95% CI 1.09 to 2.21)** **SS more cardiovascular events with SGA**	⨁⨁⨀⨀ **LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: ok
Development of type 2 diabetes	703 (3 studies) <6 months	21/436 vs 4/267 *No statistical testing*	⨁⨁⨀⨀ **LOW** Study quality: -2 incomplete outcome, observational studies Consistency: unable to assess Directness: ok Imprecision: ok
	43287 (1 study) >12 months	**25.3 vs. 7.8 cases per 10,000 person-years follow-up** **HR 2.89 (95% CI 1.64 to 5.10)** **SS more diabetes cases with SGA**	
	30550 (1 study) 2-9 yrs	**Short-term user (<1 yr) vs nonuser** HR 1.39 (0.94 to 3.02) NS	

		Long-term user (>1 yr) vs nonuser **HR 2.35 (1.23 to 4.50)** **SS more DM II with long-term users**	
	982214 (1 study) 384 days	**SGA vs non-SGA :** **HR 1.71 (95%CI 1.33 to 2.20)** **SS more DM II with SGA use**	
	107847 (1 study) 2-9 yrs	**Short-term user vs nonuser** HR 1.51 (95% CI 0.76 to 2.99) NS **Long-term user vs nonuser** **HR 2.73 (95%CI 1.50 to 4.99)** **SS more DM II with long-term use**	
Increased fasting glucose	1204 (7 studies) <6 months	10/797 vs 5/407 RR 0.85 (95%CrI 0.26-2.76) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 incomplete outcome Consistency: unable to assess Directness: ok Imprecision: -1
Weight (kg)	3919 (37 studies) <6 months	MD 1.53 (95% CI 1.11 to 1.98) **SS more weight gain with SGA**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 incomplete outcome Consistency: unable to assess Directness: ok Imprecision: ok
BMI (kg/m^2)	2462 (16 studies) <6 months 5391 (1 study) 12 months	MD 0.66 (95% CI 0.44 to 0.91) **SS more weight gain with SGA** **0.09 (0.02 to 0.17)** **SS more weight gain with atypical antipsychotic therapy**	⊕⊕⊕⊖ **MODERATE** Study quality:-1 incomplete outcome, unclear randomization Consistency: unable to assess Directness: ok Imprecision: ok
≥7% increase in weight	3057 (17 studies) <6 months	337/2023 vs 42/1034 **RR 3.53 (95%CrI 2.49 to 5.23)** **SS more participants with ≥7% increase in weight with SGA**	⊕⊕⊕⊖ **MODERATE** Study quality:-1 incomplete outcome Consistency: unable to assess Directness: ok Imprecision: ok

Hyperprolactinemia	2009 (12 studies) <6 months	231/1261 vs 98/748 RR 2.04 (95% CrI 0.82 to 5.44) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 incomplete outcome Consistency: unable to assess Directness: ok Imprecision:-1
Increased total cholesterol	643 (6 studies) <6 months	92/410 vs 13/233 **RR 3.17 (95% CI 1.29 to 9.13)** **SS more participants with increased total cholesterol with SGA**	⊕⊕⊖⊖ **LOW** Study quality:-2 incomplete outcome, unclear randomization Consistency: unable to assess Directness: ok Imprecision: ok
Increased triglycerides	1383 (10 studies) <6 months	130/897 vs 38/486 **RR 1.64 (95% CrI 1.09 to 2.63)** **SS more participants with increased triglycerides with SGA**	⊕⊕⊖⊖ **LOW** Study quality:-2 incomplete outcome, unclear randomization Consistency: unable to assess Directness: ok Imprecision: ok
Tardive dyskinesia	570 (5 studies) <6 months	0/336 vs 2/234 *No statistical testing*	*Insufficient data*
Any EPS	2730 (15 studies) <6 months	233/1757 vs 40/973 **RR 2.94 (95%CI 2.02 to 4.27)** **SS more EPS with SGA**	⊕⊕⊖⊖ **LOW** Study quality:-2 incomplete outcome, unclear randomization, unclear blinding Consistency: unable to assess Directness: ok Imprecision: ok
Any EPS (6-12 months)	629 (2 studies) 6-12 months	Study 1: 62/197 vs 7/97 **RR 4.36 (95%CI 2.08 to 9.17)** **SS more EPS with SGA** Study 2: 3/172 vs 1/163 RR 2.84 (95%CI 0.30 to 27.06) NS	⊕⊖⊖⊖ **VERY LOW** Study quality:-2 incomplete outcome, unclear randomization Consistency: -1 Directness: ok Imprecision: ok
Akathisia	3638 (21 studies) <6 months	151/2433 vs 56/1205 RR 1.29 (95%CrI 0.81 to 2.27) NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1 incomplete outcome Consistency: unable to assess Directness: ok Imprecision: ok
Akathisia (6-12 months)	629 (2 studies) 6-12 months	Study 1: 20/197 vs 2/97 **RR 4.92 (95%CI 1.17 to 20.64)** **SS more akathisia with SGA**	⊕⊖⊖⊖ **VERY LOW** Study quality: :-2 incomplete outcome, unclear randomization Consistency:-1 Directness: ok Imprecision: ok

		Study 2: 0/172 vs 0/163 *Not estimable*	
Dystonia	1497 (6 studies) <6 months	21/1032 vs 4/465 RR 1.65 (95%CrI 0.44 to 6.07) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 unclear blinding, randomization Consistency: unable to assess Directness: ok Imprecision: -1
Dystonia (6-12 months)	629 (2 studies) 6-12 months	Study 1: 7/197 vs 2/97 RR 1.72 (95%CI 0.36 to 8.14) NS Study 2: 2/172 vs 1/163 RR 1.90 (95%CI 0.17 to 20.70) NS	⊕⊖⊖⊖ **VERY LOW** Study quality:-2 incomplete outcome, unclear randomization Consistency: unable to assess Directness: ok Imprecision: -1
Sedation	2710 (21 studies) <6 months	288/1696 vs 79/1014 **RR 2.19 (95%CrI 1.50 to 3.41)** **SS more sedation with SGA**	⊕⊕⊖⊖ **LOW** Study quality:-2 incomplete outcome Consistency: unable to assess Directness: ok Imprecision: ok
Somnolence	3942 (26 studies) <6 months	560/2481 vs 119/1461 **RR 2.91 (95%CrI 2.27 to 3.86)** **SS more somnolence with SGA**	⊕⊕⊖⊖ **LOW** Study quality:-2 incomplete outcome, unclear blinding Consistency: unable to assess Directness: ok Imprecision: ok
Somnolence (6-12 months)	545 (2 studies) 6-12 months	Study 1: 3/172 vs 2/163 RR 1.42 (95%CI 0.24 to 8.40) NS Study 2: 6/146 vs 0/64 RR 5.75 (95% CI 0.33 to 100.53) NS	⊕⊖⊖⊖ **VERY LOW** Study quality:-2 incomplete outcome, unclear randomization Consistency: unable to assess Directness: ok Imprecision:-1

This AHRQ systematic review and meta-analysis by Pillay 2017 searched for all RCTs and cohort studies that compared second generation antipsychotics to placebo in children and adolescents (≤24yrs).

There are some methodological problems that limit our confidence in the estimate of the results: the most important of which were a number of larger studies with a high risk of incomplete outcome data, and some outcomes for which only (or mainly) observational data was found.

Detailed tables with outcomes of individual antipsychotics versus placebo can be found in the appendix.

We have insufficient data to compare the risk of mortality in SGA versus placebo.

We have insufficient data to compare the risk of cardiac arrhythmia in SGA versus placebo.

We have insufficient data to compare the risk of tardive dyskinesia in SGA versus placebo.

In children and young adults, second generation antipsychotics resulted in **more cardiovascular events** compared to placebo.
GRADE: LOW quality of evidence

In children and young adults, long-term use of second generation antipsychotics resulted in **more development of diabetes** compared to placebo.
GRADE: LOW quality of evidence

In children and young adults, there was **no difference in increased fasting glucose** between second generation antipsychotics and placebo.
GRADE: LOW quality of evidence

In children and young adults, second generation antipsychotics resulted in **more weight gain** compared to placebo.
GRADE: MODERATE quality of evidence

In children and young adults, second generation antipsychotics resulted in **more BMI gain** compared to placebo.
GRADE: MODERATE quality of evidence

In children and young adults, second generation antipsychotics resulted in **more participants with ≥7% increase in weight** compared to placebo.
GRADE: MODERATE quality of evidence

In children and young adults, there was **no difference in participants with hyperprolactemia** between second generation antipsychotics and placebo.
GRADE: LOW quality of evidence

In children and young adults, second generation antipsychotics resulted in **more participants with increased total cholesterol** compared to placebo.
GRADE: LOW quality of evidence

In children and young adults, second generation antipsychotics resulted in **more participants with increased triglycerides** compared to placebo.

GRADE: LOW quality of evidence

In children and young adults, short-term second generation antipsychotics resulted in **more extrapyramidal symptoms** compared to placebo.
GRADE: LOW quality of evidence

In children and young adults, there was **no difference in akathisia** between short-term use of second generation antipsychotics and placebo.
GRADE: MODERATE quality of evidence

In children and young adults, 6-12 months use of second generation antipsychotics resulted in **more akathisia** compared to placebo.
GRADE: VERY LOW quality of evidence

In children and young adults, there was **no difference in dystonia** between second generation antipsychotics and placebo.
GRADE: LOW quality of evidence

In children and young adults, there was **no difference in dystonia** between 6-12 months use of second generation antipsychotics and placebo.
GRADE: VERY LOW quality of evidence

In children and young adults, second generation antipsychotics resulted in **more sedation** compared to placebo.
GRADE: LOW quality of evidence

In children and young adults, short-term second generation antipsychotics resulted in **more somnolence** compared to placebo.
GRADE: LOW quality of evidence

In children and young adults, there was **no difference in somnolence** between 6-12 months use of second generation antipsychotics and placebo.
GRADE: VERY LOW quality of evidence

9.5 SGA vs SGA

9.5.1 Aripiprazole vs olanzapine

Aripiprazole vs olanzapine			
Bibliography: AHRQ 2017(3), Yoon 2016(87), Al-Dhaher 2016(88)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**

Weight	99 (1 study) <6 months	**MD -4.12 (95% CI -5.50 to -2.74)** **SS less weight gain with aripiprazole**	⊕⊕⊖⊖ **LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: ok
≥7% increase in weight	86 (1 study) <6 months	**24/41 vs 38/45** **RR 0.69 (95% CI 0.52 to 0.92)** **SS fewer patients with ≥7% increase in weight with aripiprazole**	⊕⊕⊖⊖ **LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: ok
BMI (kg/m^2)	99 (1 study) <6 months	**MD -1.34 (95% CI -1.85 to -0.83)** **SS Less weight gain with aripiprazole**	⊕⊕⊖⊖ **LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: ok
BMI z-score change **>12 months**	202 (1 study) >12 months	**0.39 (0.08 to 0.70)** **SS more weight gain with olanzapine**	⊕⊕⊖⊖ **LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: ok
Akathisia	124 (1 study) <6 months	5/66 vs 3/58 RR 1.46 (95%CI 0.37 to 5.86) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: -1
Sedation	86 (1 study) 3 months	No between-group difference	⊕⊕⊖⊖ **LOW** Study quality: -1 unclear blinding Consistency: NA Directness: ok Imprecision: -1 unclear

This AHRQ systematic review and meta-analysis by Pillay 2017 searched for all RCTs and cohort studies that compared aripiprazole to olanzapine in children and adolescents (≤24yrs).

There are some methodological problems that limit our confidence in the estimate of the results: only observational data was found for most of the outcomes.

In children and young adults, aripiprazole resulted in **less weight gain** compared to olanzapine.
GRADE: LOW quality of evidence

In children and young adults, aripiprazole resulted in **fewer participants with ≥7% increase in weight** compared to olanzapine.
GRADE: LOW quality of evidence

In children and young adults, aripiprazole resulted in **less BMI gain** compared to olanzapine.

GRADE: LOW quality of evidence

In children and young adults, aripiprazole resulted in **less BMI-z score gain** compared to olanzapine.
GRADE: LOW quality of evidence

In children and young adults, there was **no difference in akathisia** between aripiprazole and olanzapine.
GRADE: VERY LOW quality of evidence

In children and young adults, there was **no difference in sedation** between aripiprazole and olanzapine.
GRADE: LOW quality of evidence

9.5.2 Aripiprazole vs paliperidone

Aripiprazole vs paliperidone			
Bibliography: AHRQ 2017(3)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	228 (1 study)	0/115 vs 0/113	*Insufficient data*
Weight (kg)	226 (1 study) <6 months	**MD -1.28 (95% CI -1.95 to -0.61)** **SS less weight gain with aripiprazole**	⨁⨁⨁⊖ **MODERATE** Study quality:-1 unclear allocation concealment Consistency: NA Directness: ok Imprecision: ok
BMI (kg/m^2)	226 (1 study) <6 months	**MD -0.50 (95% CI -0.74 to -0.26)** **SS less weight gain with aripiprazole**	⨁⨁⨁⊖ **MODERATE** Study quality:-1 unclear allocation concealment Consistency: NA Directness: ok Imprecision: ok
Weight (6-12 months)	226 (1 study) 6-12 months	**MD -1.90 (95% CI -2.96 to -0.84)** **SS less weight gain with aripiprazole**	⨁⨁⨁⊖ **MODERATE** Study quality:-1 unclear allocation concealment Consistency: NA Directness: ok Imprecision: ok
BMI (kg/m^2) (6-12 months)	226 (1 study) 6-12 months	**MD -0.70 (95% CI -1.07 to -0.33)** **SS less weight gain with aripiprazole**	⨁⨁⨁⊖ **MODERATE** Study quality:-1 unclear allocation concealment Consistency: NA Directness: ok Imprecision: ok
≥7% increase in weight	226 (1 study) <6 months	20/114 vs 29/112 RR 0.68 (95% CI 0.41 to 1.12)	⨁⨁⨁⊖ **MODERATE** Study quality:-1 unclear allocation concealment Consistency: NA

		NS	Directness: ok Imprecision: ok
Hyperprolactinemia (6-12 months)	227 (1 study) 6-12 months	5/114 vs 59/113 **RR 0.04 (95% CI 0.02 to 0.11)** **SS less hyperprolactinemia with aripiprazole**	⊕⊕⊕⊖ **MODERATE** Study quality:-1 unclear allocation concealment Consistency: NA Directness: ok Imprecision: ok
Akathisia (6-12 months)	226 (1 study) 6-12 months	6/114 vs 7/112 RR 0.84 (95%CI 0.29 to 2.43) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 unclear allocation concealment Consistency: NA Directness: ok Imprecision:-1
Sedation	227 (1 study) <6 months	3/114 vs 6/113 RR 0.50 (95%CI 0.13 to 1.93) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 unclear allocation concealment Consistency: NA Directness: ok Imprecision:-1
Somnolence	227 (1 study) <6 months	12/114 vs 12/113 RR 0.99 (95%CI 0.47 to 2.11) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 unclear allocation concealment Consistency: NA Directness: ok Imprecision:-1

This AHRQ systematic review and meta-analysis by Pillay 2017 searched for all RCTs and cohort studies that compared aripiprazole to paliperidone in children and adolescents (≤24yrs).

We have insufficient data to compare the risk of mortality in aripiprazole versus paliperidone.

Our confidence in the estimate of the results is limited by unclear allocation concealment in the only study that was found for this comparison.

In children and young adults, aripiprazole resulted in **less weight gain** compared to paliperidone.
GRADE: MODERATE quality of evidence

In children and young adults, aripiprazole resulted in **less BMI gain** compared to paliperidone.
GRADE: MODERATE quality of evidence

In children and young adults, there was **no difference in number of participants with ≥7% increase in weight** between aripiprazole and paliperidone.
GRADE: MODERATE quality of evidence

In children and young adults, aripiprazole resulted in **fewer participants with hyperprolactinemia** compared to paliperidone.
GRADE: MODERATE quality of evidence

In children and young adults, there was **no difference in number of participants with akathisia** between aripiprazole and paliperidone.
GRADE: LOW quality of evidence

In children and young adults, there was **no difference in number of participants with sedation** between aripiprazole and paliperidone.
GRADE: LOW quality of evidence

In children and young adults, there was **no difference in number of participants with somnolence** between aripiprazole and paliperidone.
GRADE: LOW quality of evidence

9.5.3 Aripiprazole vs quetiapine

Aripiprazole vs quetiapine			
Bibliography: AHRQ 2017(3), Jensen 2019(89), Yoon 2016(87), Pagsberg 2017(90), Al-Dhaher 2016(88), Jensen 2018(91)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
QTc change (ms)	113 (1 study) 12 weeks	**Quetiapine 6.8 ±20.2** **Aripiprazole -3.4 ± 18.9** **Between-group difference p =0.004** **SS shorter QTc with aripiprazole**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 only 1 RCT 12-17 yr/psychosis Imprecision: ok
Weight (kg)	92 (1 study) <6 months 113 (1 study) 12 weeks	**MD -1.63 (95% CI -3.01 to -0.25)** **SS less weight gain with aripiprazole** ---- Quetiapine **4.88 (3.92 to 5.83)** Aripiprazole **1.97 (0.97 to 2.97)** **Between-group difference 2.91 (1.54 to 4.29)** **SS more weight gain with quetiapine**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 RCT + observational study Consistency: ok Directness: ok Imprecision: ok

BMI (kg/m^2)	92 (1 study) <6 months 113 (1 study) 12 weeks	MD -0.45 (95% CI -0.96 to 0.06) NS ---- Quetiapine **1.48 (1.16 to 1.81)** Aripiprazole **0.45 (0.11 to 0.80)** **Between-group difference 1.03 (0.56 to 1.50)** **SS more weight gain with quetiapine**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 RCT + observational study Consistency: ok Directness: ok Imprecision: -1
BMI z-score change **>12 months**	202 (1 study) >12 months	0.22 (-0.01 to 0.46) NS	⊕⊕⊖⊖ **LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: ok
Change in systolic BP (mmHg)	113 (1 study) 12 weeks	Quetiapine 2.15 (-0.85 to 5.15) Aripiprazole -2.91 (-5.86 to 0.03) **Between-group difference 5.06 (1.13 to 8.99)** **SS more rise in systolic BP with quetiapine**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness:-1 single study/psychosis Imprecision: ok
Change in diastolic BP (mmHg)	113 (1 study) 12 weeks	Quetiapine **2.88 (0.46 to 5.31)** Aripiprazole -3.94 (-6.34 to -1.55) **Between-group difference 6.83 (3.72 to 9.93)** **SS more rise in diastolic BP with quetiapine**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness:-1 single study/psychosis Imprecision: ok
Change in glucose (mmoL/L)	113 (1 study) 12 weeks	Quetiapine 0.02 (-0.01 to 0.04) Aripiprazole 0.01 (-0.01 to 0.04) **Between-group difference** 0.01 (-0.03 to 0.04) NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness:-1 single study/psychosis Imprecision: ok
Change in total cholesterol (mmoL/L)	113 (1 study) 12 weeks	Quetiapine **0.10 (0.06 to 0.15)**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA

		Aripiprazole -0.02 (-0.06 to 0.02) **Between-group difference 0.12 (0.07 to 0.18)** **SS more rise in total cholesterol with quetiapine**	Directness:-1 single study/psychosis Imprecision: ok
Change in triglycerides (mmoL/L)	113 (1 study) 12 weeks	Quetiapine **0.24 (0.12 to 0.35)** Aripiprazole -0.01 (-0.12 to 0.11) **Between-group difference 0.24 (0.09 to 0.39)** **SS more rise in triglycerides with quetiapine**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness:-1 single study/psychosis Imprecision: ok
Akathisia	132 (1 study) <6 months	5/66 vs 1/66 RR 5.00 (95% CI 0.60 to 41.65) NS ---	⊕⊕⊖⊖ **LOW** Study quality:-1 RCT+ observational study Consistency: unable to assess Directness: ok Imprecision: -1
	113 (1 study) 12 weeks	Quetiapine 15/47 (32%) Aripiprazole 13/48 (27%) **Between-group difference p=0.0023** **SS more akathisia with quetiapine**	
Sedation	113 (1 study) 12 weeks	Quetiapine 34/47 (72%) Aripiprazole 44/48 (92%) **Between-group difference p=0.012** **SS more sedation with aripiprazole**	⊕⊕⊕⊖ **MODERATE** Study quality:-1 RCT + observational study Consistency: unable to assess Directness: ok Imprecision: ok
	77 (1 study) 3 months	No between-group difference	

This AHRQ systematic review and meta-analysis by Pillay 2017 searched for all RCTs and cohort studies that compared aripiprazole to quetiapine in children and adolescents (≤24yrs).

In children and young adults, aripiprazole resulted in a **shorter QTc** compared to quetiapine.

GRADE: MODERATE quality of evidence

In children and young adults, aripiprazole resulted in **less weight gain** compared to quetiapine.
GRADE: MODERATE quality of evidence

In children and young adults, aripiprazole compared to quetiapine resulted in **less BMI gain** in one RCT, and in **no difference in BMI change** in one observational study.
GRADE: MODERATE quality of evidence

In children and young adults, there was **no difference in BMI z-score change** between aripiprazole and quetiapine.
GRADE: LOW quality of evidence

In children and young adults, aripiprazole resulted in **less rise in systolic blood pressure** compared to quetiapine.
GRADE: MODERATE quality of evidence

In children and young adults, aripiprazole resulted in **less rise in diastolic blood pressure** compared to quetiapine.
GRADE: MODERATE quality of evidence

In children and young adults, there was **no difference in glucose change** between aripiprazole and quetiapine.
GRADE: MODERATE quality of evidence

In children and young adults, aripiprazole resulted in **less rise in total cholesterol** compared to quetiapine.
GRADE: MODERATE quality of evidence

In children and young adults, aripiprazole resulted in **less rise in triglycerides** compared to quetiapine.
GRADE: MODERATE quality of evidence

In children and young adults, aripiprazole compared to quetiapine resulted in **less akathisia** in one RCT, and in **no difference in akathisia** in one observational study.
GRADE: LOW quality of evidence

In children and young adults, aripiprazole compared to quetiapine resulted in **more sedation** in one RCT, and in **no difference in sedation** in one observational study.
GRADE: MODERATE quality of evidence

9.5.4 Aripiprazole vs risperidone

Aripiprazole vs risperidone			
Bibliography: AHRQ 2017(3), Yoon 2016(87), Schoemakers 2019(92), Al-Dhaher 2016(88)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Weight (kg)	215 (1 study) <6 months	MD -0.90 (95% CI -1.81 to 0.01) NS	⨁⨁⨀⨀ **LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: ok
≥7% increase in weight	176 (1 study) <6 months	24/41 vs 87/135 RR 0.91 (95% CI 0.68 to 1.21) NS	⨁⨁⨀⨀ **LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: ok
BMI (kg/m^2)	215 (1 study) <6 months	MD -0.25 (95% CI -0.62 to 0.12) NS	⨁⨁⨀⨀ **LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision:
BMI (kg/m^2) (>12 months)	142 (1 study) >12 months	MD -0.31 (95%CI -1.78 to 1.16) NS	⨁⨁⨀⨀ **LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision:
BMI z-score change **>12 months**	202 (1 study) >12 months 131 (1 study) 12 months	-0.04 (-0.23 to 0.15) NS ---- **Risperidone** 0.37 (0.21 to 0.53) **Aripiprazole** 0.30 (0.07 to 0.53) **Risperidone vs aripiprazole** No significant difference between groups p= 0.973	⨁⨁⨀⨀ **LOW** Study quality: observational study Consistency: ok Directness: ok Imprecision:
Akathisia	203 (1 study) <6 months	5/66 vs 7/137 RR 1.48 (95% CI 0.49 to 4.50) NS	⨁⨀⨀⨀ **VERY LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: -1

Akathisia (6-12 months)	114 (1 study) <6 months	5/62 vs 3/52 RR 1.40 (95%CI 0.35 to 5.57) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: -1
Sedation	114 (1 study) 6-12 months	1/62 vs 2/52 RR 0.42 (95%CI 0.04 to 4.49) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: observational study Consistency: unable to assess Directness: ok Imprecision: -1
	176 (1 study) 3 months	No between-group difference	

This AHRQ systematic review and meta-analysis by Pillay 2017 searched for all RCTs and cohort studies that compared aripiprazole to risperidone in children and adolescents (≤24yrs).

There are some methodological problems that limit our confidence in the estimate of the results: only observational data was found for this comparison.

In children and young adults, there was **no difference in weight change** between aripiprazole and risperidone.
GRADE: LOW quality of evidence

In children and young adults, there was **no difference in number of participants with ≥7% increase in weight** between aripiprazole and risperidone.
GRADE: LOW quality of evidence

In children and young adults, there was **no difference in BMI change** between aripiprazole and risperidone.
GRADE: LOW quality of evidence

In children and young adults, there was **no difference in BMI z-score change** between aripiprazole and risperidone.
GRADE: LOW quality of evidence

In children and young adults, there was **no difference in number of participants with akathisia** between aripiprazole and risperidone.
GRADE: VERY LOW quality of evidence

In children and young adults, there was **no difference in number of participants with sedation** between aripiprazole and risperidone.
GRADE: VERY LOW quality of evidence

Aripiprazole vs risperidone			
Bibliography: Chung 2019(82)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Occurrence of cardiometabolic events type 2 diabetes mellitus, hypertension, dyslipidemia and major adverse cardiovascular events (MACE), including AMI, IHD, ischemic stroke, and cardiac death.	29030 (1 study) +/- 2yrs	HR 0.90 (95%CI 0.54–1.48) NS	⨁⨁⊖⊖ **LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: ok
Type 2 diabetes melllitus	29030 (1 study) +/- 2yrs	HR 0.39 (95%CI 0.10–1.81) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: -1
Hypertension	29030 (1 study) +/- 2yrs	HR 1.16 (95%CI 0.60–2.23) NS	⨁⨁⊖⊖ **LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: -1
Dyslipidemia	29030 (1 study) +/- 2yrs	HR 0.67 (95%CI 0.26–1.69) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: observational study outcome Consistency: NA Directness: ok Imprecision: -1

Our updated search found one retrospective cohort study (Chung 2019(82)) that compared several antipsychotics, with risperidone used as the reference comparator, in children diagnosed with a psychiatric disorder and newly receiving antipsychotics.

There are some methodological problems that limit our confidence in the estimate of the results: only observational data was found, and the rarity of some of the endpoints resulted in imprecise results.

In children, there was **no difference in the occurrence of cardiometabolic events** between aripiprazole and risperidone.
GRADE: LOW quality of evidence

In children, there was **no difference in type 2 diabetes mellitus** between aripiprazole and risperidone.
GRADE: VERY LOW quality of evidence

In children, there was **no difference in hypertension** between aripiprazole and risperidone.
GRADE: LOW quality of evidence

In children, there was **no difference in dyslipidemia** between aripiprazole and risperidone.
GRADE: VERY LOW quality of evidence

aripiprazole vs risperidone			
Bibliography: Jeon 2021**(81)**			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Movement disorders	10969 (1 study) +/- 2yrs	HR 0.88 (0.67 to 1.15) NS	⨁⨁⊖⊖ **LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: ok

Our second search update found one retrospective cohort study (Jeon 2021**(81)**) that compared exposure to antipsychotics including haloperidol, aripiprazole, olanzapine and quetiapine, to exposure to risperidone as the reference comparator, in children diagnosed with a psychiatric disorder and newly receiving antipsychotics.

There are some methodological problems that limit our confidence in the estimate of the results: only observational data was found, and there were some disparities between the results in the text of the publication versus the results presented in the figures.

In children, there was **no difference in the occurrence of movement disorders** between aripiprazole and risperidone.
GRADE: LOW quality of evidence

9.5.5 Clozapine vs olanzapine

Clozapine vs olanzapine			
Bibliography: AHRQ 2017(3)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**

Weight (kg)	136 (5 studies) <6 months	MD -1.56 (95% CrI -5.12 to 1.57) NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-2 2 observational studies, RCT with high risk of incomplete data Consistency: unable to assess Directness: ok Imprecision: -1
BMI (kg/m^2)	87 (3 studies) <6 months	MD -0.66 (95% CrI -2.59 to 1.23) NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-2 1 observational study, RCT with high risk of incomplete data Consistency: unable to assess Directness: ok Imprecision: -1
Somnolence	96 (3 studies) <6 months	20/46 to 21/50 RR 1.09 (95%CrI 0.41 to 2.75) NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-2 1 observational study, RCT with high risk of incomplete data Consistency: unable to assess Directness: ok Imprecision: -1

This AHRQ systematic review and meta-analysis by Pillay 2017 searched for all RCTs and cohort studies that compared clozapine to olanzapine in children and adolescents (≤24yrs).

There are some methodological problems that limit our confidence in the estimate of the results: mainly observational data was found for this comparison, and one RCT with high risk of incomplete outcome data.

In children and young adults, there was **no difference in weight change** between clozapine and olanzapine.
GRADE: VERY LOW quality of evidence

In children and young adults, there was **no difference in BMI change** between clozapine and olanzapine.
GRADE: VERY LOW quality of evidence

In children and young adults, there was **no difference number of participants with somnolence** between clozapine and olanzapine.
GRADE: VERY LOW quality of evidence

9.5.6 Olanzapine vs quetiapine

Olanzapine vs quetiapine			
Bibliography: AHRQ 2017(3), Yoon 2016(87), Al-Dhaher 2016(88), Alda 2016(93)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**

QTc interval	216 (1 study) 12 months	Olanzapine – quetiapine p=0.528 NS	⊕⊕⊖⊖ **LOW** Study quality: observational study Consistency: NA Directness: unable to assess Imprecision: unable to assess
Weight (kg)	232 (3 studies) <6 months	MD 4.00 (95% CrI -1.67 to 10.79) NS	⊕⊕⊖⊖ **VERY LOW** Study quality: observational studies Consistency: unable to assess Directness: ok Imprecision: -1
Weight (kg) (6-12 months)	185 (3 studies) 6-12 months	**MD 7.91 (95% CrI 3.65 to 12.29)** **SS more weight gain with olanzapine**	⊕⊕⊖⊖ **LOW** Study quality: observational studies Consistency: unable to assess Directness: ok Imprecision: ok
≥7% increase in weight	192 (3 studies) <6 months	72/99 vs 47/93 RR 1.41 (95% CrI 0.65 to 2.83) NS	⊕⊕⊖⊖ **LOW** Study quality: observational studies Consistency: unable to assess Directness: ok Imprecision: ok
≥7% increase in weight (6-12 months)	91 (1 study) <6 months	18/44 vs 22/47 RR 0.87 (95% CI 0.55 to 1.40) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: observational study with small sample size Consistency: NA Directness: ok Imprecision:-1
BMI (kg/m^2)	232 (3 studies) <6 months	MD 1.36 (95% CrI -0.29 to 3.40) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: observational studies Consistency: unable to assess Directness: ok Imprecision: -1
BMI (kg/m^2) (6-12 months)	203 (4 studies) 6-12 months	**MD 2.68 (95% CrI 0.96 to 4.27)** **SS more weight gain with olanzapine**	⊕⊕⊖⊖ **LOW** Study quality: observational studies Consistency: unable to assess Directness: ok Imprecision: ok
BMI z-score change **>12 months**	202 (1 study) >12 months	**0.62 (0.27 to 0.96)** **SS more weight gain with olanzapine**	⊕⊕⊖⊖ **LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: ok
Akathisia	194 (3 studies) <6 months	13/94 vs 8/100 RR 1.65 (95%CrI 0.42 to 8.06) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: observational study and RCTs with serious limitations (incomplete outcome, blinding) Consistency: unable to assess Directness: ok Imprecision:-1
Sedation	81 (1 study) 3 months	No between-group difference	⊕⊖⊖⊖ **VERY LOW** Study quality: observational study Consistency: NA Directness: ok

	Imprecision: -1

This AHRQ systematic review and meta-analysis by Pillay 2017 searched for all RCTs and cohort studies that compared olanzapine to quetiapine in children and adolescents (≤24yrs).

There are some methodological problems that limit our confidence in the estimate of the results: only or mainly observational data was found for most of the outcomes.

In children and young adults, there was **no difference in QTc interval** between olanzapine and quetiapine.
GRADE: LOW quality of evidence

In children and young adults, there was **no difference in weight change** between short-term treatment with olanzapine and quetiapine.
GRADE: VERY LOW quality of evidence

In children and young adults, 6-12 months treatment with olanzapine resulted in **more weight gain** compared to quetiapine.
GRADE: LOW quality of evidence

In children and young adults, there was **no difference in number of participants with ≥7% increase in weight** between short-term use of olanzapine and quetiapine.
GRADE: LOW quality of evidence

In children and young adults, there was **no difference in number of participants with ≥7% increase in weight** between 6-12 months of treatment with olanzapine and quetiapine.
GRADE: VERY LOW quality of evidence

In children and young adults, there was **no difference in BMI change** between short-term treatment with olanzapine and quetiapine.
GRADE: VERY LOW quality of evidence

In children and young adults, 6-12 months treatment with olanzapine resulted in **more BMI gain** compared to quetiapine.
GRADE: LOW quality of evidence

In children and young adults, >12 months treatment with olanzapine resulted in **more BMI z-score gain** compared to quetiapine.
GRADE: LOW quality of evidence

In children and young adults, there was **no difference in number of participants with akathisia** between olanzapine and quetiapine.
GRADE: VERY LOW quality of evidence

In children and young adults, there was **no difference in number of participants with sedation** between olanzapine and quetiapine.
GRADE: VERY LOW quality of evidence

9.5.7 Olanzapine vs risperidone

Olanzapine vs risperidone			
Bibliography: AHRQ 2017(3), Yoon 2016(87), Al-Dhaher 2016(88)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
QTc interval	216 (1 study) 12 months	Risperidone – olanzapine p=0.578 NS	⨁⨁⨀⨀ **LOW** Study quality: observational study Consistency: NA Directness: unable to assess Imprecision: unable to assess
Weight (kg)	936 (13 studies) <6 months	**MD 2.18 (95% CrI 1.13 to 3.25)** **SS more weight gain with olanzapine**	⨁⨁⨀⨀ **LOW** Study quality: -2 serious limitations: RCTs with high risk of incomplete data, observational studies Consistency: unable to assess Directness: ok Imprecision: ok
Weight (kg) (6-12 months)	295 (4 studies) 6-12 months	MD 4.40 (95% CrI -0.54 to 9.86) NS	⨁⨁⨀⨀ **LOW** Study quality: observational studies Consistency: unable to assess Directness: ok Imprecision: ok
≥7% increase in weight	504 (6 studies) <6 months	107/150 vs 188/354 RR 1.36 (95% CrI 0.93 to 3.42) NS	⨁⨁⨀⨀ **LOW** Study quality: observational studies Consistency: unable to assess Directness: ok Imprecision: ok
≥7% increase in weight (6-12 months)	264 (3 studies) 6-12 months	28/64 vs 64/200 RR 1.44 (95% CrI 0.55 to 5.50) NS	⨁⨁⨀⨀ **LOW** Study quality: observational studies Consistency: unable to assess Directness: ok Imprecision: ok
BMI (kg/m^2)	737 (9 studies) <6 months	**MD 0.94 (95% CrI 0.64 to 1.30)** **SS more weight gain with olanzapine**	⨁⨁⨀⨀ **LOW** Study quality:-2 observational studies, RCTs with serious limitations Consistency: unable to assess Directness: ok Imprecision: ok

BMI (kg/m^2) (6-12 months)	328 (5 studies) <6 months	**MD 1.66 (95% CrI 0.19 to 3.42)** **SS more weight gain with olanzapine**	⊕⊕⊖⊖ **LOW** Study quality: observational studies Consistency: unable to assess Directness: ok Imprecision: ok
BMI z-score change **>12 months**	202 (1 study) >12 months	**0.43 (0.12 to 0.74)** **SS more weight gain with olanzapine**	⊕⊕⊖⊖ **LOW** Study quality: observational study Consistency: unable to assess Directness: ok Imprecision: ok
Hyperprolactinemia	128 (3 studies) <6 months	7/49 vs 27/79 RR 0.46 (95% CrI 0.11 to 1.70) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: observational studies, RCT with serious limitations (incomplete outcome data) Consistency: unable to assess Directness: ok Imprecision:-1
Akathisia	507 (9 studies) <6 months	20/192 vs 24/315 RR 1.17 (95%CrI 0.59 to 2.40) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 observational studies, RCTs with serious limitations (incomlete data) Consistency: unable to assess Directness: ok Imprecision: ok
Dystonia	270 (5 studies) <6 months	10/108 vs 13/162 RR 1.65 (95% CrI 0.44 to 6.07) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 observational studies Consistency: unable to assess Directness: ok Imprecision: 1
Sedation	321 (7 studies) <6 months 180 (1 study) 3 months	35/133 vs 36/188 RR 1.19 (95% CrI 0.68 to 2.35) NS No between-group difference	⊕⊕⊖⊖ **LOW** Study quality: -2 observational studies, RCTs with serious limitations (incomplete outcome data) Consistency: unable to assess Directness: ok Imprecision: ok

This AHRQ systematic review and meta-analysis by Pillay 2017 searched for all RCTs and cohort studies that compared olanzapine to risperidone in children and adolescents (≤24yrs).

There are some methodological problems that limit our confidence in the estimate of the results: only or mainly observational data was found for most of the outcomes.

In children and young adults, there was **no difference in QTc interval** between olanzapine and risperidone.
GRADE: LOW quality of evidence

In children and young adults, short -term treatment with olanzapine resulted in **more weight gain** compared to risperidone.
GRADE: LOW quality of evidence

In children and young adults, there was **no difference in weight change** between 6-12 months treatment with olanzapine and risperidone.
GRADE: LOW quality of evidence

In children and young adults, there was **no difference in number of participants with ≥7% increase in weight** between olanzapine and risperidone.
GRADE: LOW quality of evidence

In children and young adults, treatment with olanzapine resulted in **more BMI gain** compared to risperidone.
GRADE: LOW quality of evidence

In children and young adults, treatment with olanzapine resulted in **more BMI z-score gain** compared to risperidone.
GRADE: LOW quality of evidence

In children and young adults, there was **no difference in number of participants with hyperprolactinemia** between olanzapine and risperidone.
GRADE: VERY LOW quality of evidence

In children and young adults, there was **no difference in number of participants with akathisia** between olanzapine and risperidone.
GRADE: LOW quality of evidence

In children and young adults, there was **no difference in number of participants with dystonia** between olanzapine and risperidone.
GRADE: VERY LOW quality of evidence

In children and young adults, there was **no difference in number of participants with sedation** between olanzapine and risperidone.
GRADE: LOW quality of evidence

Olanzapine vs risperidone
Bibliography: Chung 2019(82)

Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
Occurrence of cardiometabolic events type 2 diabetes mellitus, hypertension, dyslipidemia and major adverse cardiovascular events (MACE), including AMI, IHD, ischemic stroke, and cardiac death.	29030 (1 study) +/- 2yrs	HR 1.85 (95% CI 0.79–4.32) NS	⨁⨁⨀⨀ **LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: ok
Type 2 diabetes melllitus	29030 (1 study) +/- 2yrs	**HR 4.70 (95% CI 1.01–21.82)** **SS more diabetes with olanzapine**	⨁⨁⨀⨀ **LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: ok
Hypertension	29030 (1 study) +/- 2yrs	HR 1.92 (95% CI 0.58–6.39) NS	⨁⨀⨀⨀ **VERY LOW** Study quality: observational study outcome Consistency: NA Directness: ok Imprecision: -1
Dyslipidemia	29030 (1 study) +/- 2yrs	HR 1.18 (95% CI 0.16–8.92) NS	⨁⨀⨀⨀ **VERY LOW** Study quality: observational study outcome Consistency: NA Directness: ok Imprecision: -1

Our updated search found one retrospective cohort study (Chung 2019(82)) that compared several antipsychotics, with risperidone used as the reference comparator, in children diagnosed with a psychiatric disorder and newly receiving antipsychotics.

There are some methodological problems that limit our confidence in the estimate of the results: only observational data was found, and the rarity of some of the endpoints resulted in imprecise results.

In children, there was **no difference in the occurrence of cardiometabolic events** between olanzapine and risperidone.
GRADE: LOW quality of evidence

In children, there was **no difference in type 2 diabetes mellitus** between olanzapine and risperidone.
GRADE: VERY LOW quality of evidence

In children, there was **no difference in hypertension** between olanzapine and risperidone.
GRADE: LOW quality of evidence

In children, there was **no difference in dyslipidemia** between olanzapine and risperidone.
GRADE: VERY LOW quality of evidence

olanzapine vs risperidone			
Bibliography: Jeon 2021**(81)**			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Movement disorders	10969 (1 study) +/- 2yrs	HR 0.83 (0.56 to 1.23) NS	⨁⨁⨀⨀ **LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: ok

Our second search update found one retrospective cohort study (Jeon 2021**(81)**) that compared exposure to antipsychotics including haloperidol, aripiprazole, olanzapine and quetiapine, to exposure to risperidone as the reference comparator, in children diagnosed with a psychiatric disorder and newly receiving antipsychotics.

There are some methodological problems that limit our confidence in the estimate of the results: only observational data was found, and there were some disparities between the results in the text of the publication versus the results presented in the figures.

In children, there was **no difference in the occurrence of movement disorders** between olanzapine and risperidone.
GRADE: LOW quality of evidence

9.5.8 Quetiapine vs risperidone

Quetiapine vs risperidone			
Bibliography: AHRQ 2017(3), Yoon 2016(87), Biscontri 2017(94), Al-Dhaher 2016(88); Jeon 2021**(81)**			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
QTc interval	216 (1 study) 12 months	Risperidone – quetiapine p=0.216 NS	⨁⨁⨀⨀ **LOW** Study quality: observational study Consistency: NA Directness: unable to assess Imprecision: unable to assess
Weight (kg)	436 (3 studies) <6 months	MD 0.08 (95% CrI -3.77 to 3.14) NS	⨁⨁⨀⨀ **LOW** Study quality: observational studies Consistency: unable to assess Directness: ok

			Imprecision: ok
Weight (kg) (6-12 months)	295 (3 studies) 6-12 months	MD -1.48 (95% CI -4.16 to 1.18) NS	⊕⊕⊖⊖ **LOW** Study quality: observational studies Consistency: unable to assess Directness: ok Imprecision: ok
≥7% increase in weight	417 (4 studies) <6 months	55/104 vs 176/313 RR 0.91 (95% CrI 0.56 to 1.44) NS NS	⊕⊕⊖⊖ **LOW** Study quality: observational studies Consistency: unable to assess Directness: ok Imprecision: ok
≥7% increase in weight (6-12 months)	204 (1 study) 6-12 months	22/47 vs 56/157 RR 1.31 (95% CI 0.91 to 1.90) NS NS	⊕⊕⊖⊖ **LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: ok
BMI (kg/m^2)	436 (3 studies) <6 months	MD 0.04 (95% CrI -1.34 to 1.20) NS	⊕⊕⊖⊖ **LOW** Study quality: observational studies Consistency: unable to assess Directness: ok Imprecision: ok
BMI (kg/m^2) (6-12 months)	328 (4 studies) 6-12 months	MD -0.32 (95% CrI -1.56 to 1.12) NS	⊕⊕⊖⊖ **LOW** Study quality: observational studies Consistency: unable to assess Directness: ok Imprecision: ok
BMI z-score change **>12 months**	202 (1 study) >12 months	0.18 (-0.05 to 0.42) NS	⊕⊕⊖⊖ **LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: ok
EPS	2427 (1 study) 1 yr 10969 (1 study) +/- 2yrs	Quetiapine 8.76/100 person-years Risperidone 10.55/100 person-years **Quetiapine vs risperidone** **HR 0.53 (0.34 to 0.83)** **SS fewer EPS with quetiapine** **HR 0.49 (95% CI 0.34 to 0.71)** SS fewer movement disorders with quetiapine vs risperidone	⊕⊕⊖⊖ **LOW** Study quality: observational study Consistency: ok Directness: ok Imprecision: ok

Akathisia	203 (1 study) <6 months	1/66 vs 7/137 RR 0.30 (95%CI 0.04 to 2.36) NS NS	⨁⊖⊖⊖ **VERY LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: -1
Sedation	171 (1 study) 3 months	No between-group difference	⨁⊖⊖⊖ **VERY LOW** Study quality: observational study Consistency: NA Directness: ok Imprecision: -1

This AHRQ systematic review and meta-analysis by Pillay 2017 searched for all RCTs and cohort studies that compared quetiapine to risperidone in children and adolescents (≤24yrs).

There are some methodological problems that limit our confidence in the estimate of the results: only or mainly observational data was found for most of the outcomes.

Our second search update found one retrospective cohort study (Jeon 2021**(81)**) that compared **movement disorders** during exposure to antipsychotics including haloperidol, aripiprazole, olanzapine and quetiapine, to exposure to risperidone as the reference comparator, in children diagnosed with a psychiatric disorder and newly receiving antipsychotics.

There are some methodological problems that limit our confidence in the estimate of the results: only observational data was found, and there were some disparities between the results in the text of the publication versus the results presented in the figures.

In children and young adults, there was **no difference in QTc interval** between quetiapine and risperidone.
GRADE: LOW quality of evidence

In children and young adults, there was **no difference in weight change** between quetiapine and risperidone.
GRADE: LOW quality of evidence

In children and young adults, there was **no difference in number of participants with ≥7% increase in weight** between quetiapine and risperidone.
GRADE: LOW quality of evidence

In children and young adults, there was **no difference in BMI change** between quetiapine and risperidone.
GRADE: LOW quality of evidence

In children and young adults, there was **no difference in BMI z-score change** between quetiapine and risperidone.

GRADE: LOW quality of evidence

In children and young adults, quetiapine resulted in **fewer extrapyramidal symptoms** compared to risperidone.
GRADE: LOW quality of evidence

In children and young adults, there was **no difference in number of participants with akathisia** between quetiapine and risperidone.
GRADE: VERY LOW quality of evidence

In children and young adults, there was **no difference in number of participants with sedation** between quetiapine and risperidone.
GRADE: VERY LOW quality of evidence

Quetiapine vs risperidone			
Bibliography: Chung 2019(82)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Occurrence of cardiometabolic events type 2 diabetes mellitus, hypertension, dyslipidemia and major adverse cardiovascular events (MACE), including AMI, IHD, ischemic stroke, and cardiac death.	29030 (1 study) +/- 2yrs	HR 1.00 (95% CI 0.50–1.96) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: observational study outcome Consistency: NA Directness: ok Imprecision: -1
Type 2 diabetes melllitus	29030 (1 study) +/- 2yrs	HR 0.68 (95% CI 0.09–5.37) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: observational study outcome Consistency: NA Directness: ok Imprecision: -1
Hypertension	29030 (1 study) +/- 2yrs	HR 1.39 (95% CI 0.60–3.22) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: observational study outcome Consistency: NA Directness: ok Imprecision: -1
Dyslipidemia	29030 (1 study) +/- 2yrs	HR 0.33 (95% CI 0.04–2.44) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: observational study outcome Consistency: NA Directness: ok Imprecision: -1
MACE AMI, ischemic heart disease, ischemic	29030 (1 study) +/- 2yrs	HR 5.26 (95% CI 0.32–85.65) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: observational study outcome Consistency: NA

stroke, and cardiac death		Directness: ok Imprecision: -1

Our updated search found one retrospective cohort study (Chung 2019(82)) that compared several antipsychotics, with risperidone used as the reference comparator, in children diagnosed with a psychiatric disorder and newly receiving antipsychotics.

There are some methodological problems that limit our confidence in the estimate of the results: only observational data was found, and the rarity of the endpoints resulted in imprecise results.

In children, there was **no difference in the occurrence of cardiometabolic events** between quetiapine and risperidone.
GRADE: VERY LOW quality of evidence

In children, there was **no difference in type 2 diabetes mellitus** between quetiapine and risperidone.
GRADE: VERY LOW quality of evidence

In children, there was **no difference in hypertension** between quetiapine and risperidone.
GRADE: VERY LOW quality of evidence

In children, there was **no difference in dyslipidemia** between quetiapine and risperidone.
GRADE: VERY LOW quality of evidence

In children, there was **no difference in the occurrence of MACE** between quetiapine and risperidone.
GRADE: VERY LOW quality of evidence

10 Additional safety information from other sources

10.1 Contra-indications

10.1.1 Contra-indications of antipsychotics in general

- Conciousness disorders, coma.(1)
- Risk factors for prolongation of the QT interval (of genetic or medicinal origin), in particular in the event of parenteral use and at high doses, especially for the following antipsychotics: droperidol, pimozide, sertindole, sulpiride and high doses of haloperidol.(1)

10.1.2 Contra-indications of phenothiazines and thioxanthenes (prothipendyl,flupentixol, clotiapine)

- Prolactin-dependent tumors.(1)
- Those of anticholinergics. The main contra-indications of drugs with anticholinergic properties are: angle-closure glaucoma, reflux esophagitis, pylorus stenosis, intestinal atony, paralytic ileus, severe ulcerative colitis, myasthenia gravis. Caution is especially essential in children and the elderly because they are more sensitive to anticholinergic side effects; a decrease in dose may be indicated.(1)
- Other risk situations are prostatic hypertrophy, hyperthermia, tachycardia (e.g. due to hyperthyroidism or heart failure), high blood pressure and acute myocardial infarction.(1)

10.1.3 Contra-indications of second generation antipsychotics

- Cariprazine: concomitant administration of strong or moderate CYP3A4 inducers.(1)
- Clozapine (drug with a narrow therapeutic-toxic range): also heart disease, neutropenia, agranulocytosis, bone marrow depression, alcoholic or toxic psychosis, uncontrolled epilepsy, severe renal failure.(1)
- Clozapine and olanzapine possesses antimuscarinic properties and consequently it is contra-indicated in patients with paralytic ileus; it should also be used with caution in benign prostatic hyperplasia and angle-closure glaucoma.(2)
- Olanzapine is also not recommended in Parkinson's disease since its use has commonly been associated with an increase in parkinsonian symptoms and hallucinations.(2)
- Asenapine and sertindole: also liver failure.(1)
- Sertindole is contra-indicated in patients with a history of cardiovascular disease, heart failure, cardiac hypertrophy, arrhythmias, or bradycardia. Sertindole should not be given to patients with uncorrected hypokalaemia or hypomagnesaemia.(2)

10.2 Adverse events

10.2.1 Adverse events of antipsychotics in general

- Sedation, orthostatic hypotension, falls.(1)
- Early extrapyramidal symptoms such as dystonia, akathisia and parkinsonism; they are dose dependent.(1)
    - Dystonia: more common in younger patients, especially children and adolescents.
    - Parkinsonism: including rest tremors more common in elderly patients. The risk is probably lower for second generation antipsychotics than for first generation antipsychotics.(95)
- Tardive dyskinesia, sometimes irreversible, in the event of chronic use. (1)
    - This mainly manifested itself in involuntary orofacial and axial movements

- It occur with all antipsychotics, especially at high doses, but the risk is lower for clozapine, and probably also for other second generation antipsychotics than for first generation antipsychotics.

- Decreased convulsive threshold : probably more frequent with clozapine.(1)
- Hyperprolactinemia, which can lead, in case of prolonged treatment, to hypogonadism in men and women with amenorrhea, galactorrhea, gynecomastia and sexual disorders.(1)
- Metabolic side effects such as weight gain, hyperglycemia and dyslipidemia, in the event of chronic use of any antipsychotics but especially for clozapine and olanzapine.(1)
- Increased risk of deep vein thrombosis and pulmonary embolism (especially with clozapine and olanzapine).(1)
- Anticholinergic side effects, especially with phenothiazines, clozapine, haloperidol, olanzapine, pimozide and risperidone.(1)
    - Central anticholinergic undesirable effects mainly result in dizziness, rarely cognitive regression and delirium, with or without agitation.
    - Peripheral anticholinergic side effects appear mainly as dryness of the mouth (with increased risk of dental caries) and eyes, decreased sweating, nausea and constipation, mydriasis and disorders of the accommodation, urinary retention; rarely, tachycardia and arrhythmias.

      The decrease in salivary production promotes the emergence of dental caries. Attention has been drawn to drugs that expose dental caries, including drugs that cause dry mouth such as anticholinergic medication.(96)
- Increased number of strokes and increased mortality in the elderly with dementia.(1)
- Cognitive deterioration after prolonged use in patients with Alzheimer's disease.(1)
- Risk of sudden cardiac death: probably due to ventricular arrhythmias caused by a prolongation of the QT interval. QT interval prolongation has been described with several antipsychotics, especially droperidol, levomepromazine, pimozide, sertindole, sulpiride and high doses of haloperidol. Torsades de pointes can occur, especially in parenteral use and high doses, and in the presence of risk factors.(1)
- Malignant antipsychotic syndrome (previously called neuroleptic malignant syndrome (NMS)). The syndrome is characterized by the fairly sudden onset of extrapyramidal rigidity, involuntary movements and hyperthermia, often associated with dysarthria, dysphagia and acute impairment of renal function. Disorders of consciousness and disruption of the autonomic nervous system may also occur. Antipsychotic malignant syndrome is a rare but very serious side effect of antipsychotics. The syndrome can have a fatal outcome due to renal failure and hyperthermia associated with tachycardia.(1)
- Relaxation of the urethral sphincter which can cause urinary incontinence (second generation antipsychotics like clozapine are also a risk factor for nocturnal enuresis).(97)
- Occasionally: haematological disorders, including haemolytic anaemia, aplastic anaemia, thrombocytopenic purpura, eosinophilia, and a potentially fatal agranulocytosis; they may be manifestations of a hypersensitivity reaction.(2)
- Hyponatraemia has been reported to be associated with clozapine, as with other antipsychotics. A more recent review has also concluded that both classical and atypical antipsychotics may induce hyponatraemia. It was emphasised that hyponatraemia should be excluded as a possible trigger when considering the epileptogenic potential of clozapine.(2)
- Effects on sexual function: Phenothiazines can cause both impotence and ejaculatory dysfunction. There are also several reports of priapism with phenothiazines. Male sexual dysfunction, including priapism, has been reported only rarely with other classical antipsychotics such as the butyrophenones (haloperidol), diphenylbutylpiperidines, and thioxanthenes (clotiapine). Priapism has also been reported with clozapine and other atypical antipsychotics.(2)

10.2.2 Adverse events of phenothiazines and thioxanthene (prothipendyl, flupentixol, clotiapine)

- Orthostatic hypotension and sedation are common.(1)
- Hypersensitivity (rare): leukopenia most often reversible, cholestatic hepatitis or allergic dermatosis.(1)
- Skin pigmentation and photosensitivity.(1)
- Stronger anticholinergic effects for certain phenothiazines.(1)
- The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies flupentixol as possibly porphyrinogenic.(2)

10.2.3 Adverse events of butyrophenones (haloperidol)

Haloperidol is less likely to cause sedation, orthostatic hypotension, or antimuscarinic effects(2), than phenothiazines drugs, but is associated with a higher incidence of extrapyramidal effects.(1)

10.2.4 Adverse events of second generation antipsychotics

- Very common metabolic side effects: weight gain (especially during the first months of treatment), dyslipidemia, hyperglycemia occurring more frequently with clozapine and olanzapine than with other antipsychotics, but it is not clear whether this leads to an increased incidence of diabetes.(1)
- Aripiprazole: rarely, also compulsive behaviors (e.g. pathological gambling, hypersexuality, bulimia)(1). The US Food and Drug Administration (FDA) recently issued a warning regarding the possible occurrence of compulsive disorder with aripiprazole. Pathological gambling is already among the undesirable effects in the SPC of aripiprazole. Although compulsive behavior in patients treated with aripiprazole is uncommon, it should be taken into account when worsening or developing compulsive disorder.(98)
- Cariprazine: also visual disturbances (cataract) and gastrointestinal disturbances. Akathisia seems to occur more frequently than with other antipsychotics. Its long elimination half-life (one week) can complicate management in the event of adverse reactions. (1)
- Clozapine (medicine with a narrow therapeutic-toxic range):
    - Given its hematological (eosinophilia, anemia and thrombocytopenia)(2) and cardiac adverse effects, clozapine can only be used in patients who do not respond to other antipsychotics and the treatment must be established in a specialized environment, and closely monitored.(1)
    - Clozapine can cause reversible neutropenia which may progress to potentially fatal agranulocytosis.(2)
    - In addition, myocarditis and cardiomyopathy and anticholinergic effects.(1)
    - Additional adverse effects of clozapine include, hypersalivation (particularly at night), headache, nausea, vomiting, constipation (which, in a few cases, has led to gastrointestinal obstruction, fecal impaction, and paralytic ileus), urinary incontinence and retention, fatigue, and transient fever which must be distinguished from the signs of impending agranulocytosis.(2)
- Quetiapine: ischemic colitis(1), reduced hemoglobin and plasma-thyroid hormone concentrations(2).
- Sertindole is not a first-class antipsychotic given the risk of QT prolongation likely more pronounced than with other antipsychotics(1). Marketing of sertindole has been restricted because of cardiac arrhythmias and sudden cardiac deaths associated with its use(2).
- The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies risperidone as porphyrinogenic, and quetiapine as possibly porphyrinogenic.(2)

10.2.5 Adverse reactions related to withdrawal of antipsychotics

Stopping treatment with an antipsychotic abruptly may produce withdrawal symptoms, the most common of which are nausea, vomiting, anorexia, diarrhoea, rhinorrhoea, sweating, myalgias, paraesthesias, insomnia, restlessness, anxiety, and agitation. Patients may also experience vertigo, alternate feelings of warmth and coldness, and tremor. Symptoms generally begin within 1 to 4 days of withdrawal and abate within 7 to 14 days.(2)

Remarks regarding clozapine:

- Abrupt withdrawal of clozapine may be associated with symptoms that have been described as "cholinergic rebound" although the manifestations, which may include headache, profuse sweating, hypersalivation, bronchoconstriction, agitation, enuresis, and diarrhoea also have some common features with the serotonin syndrome; motor disorders and exacerbation of extrapyramidal disorders have also occurred. In addition, as with other antipsychotics, abrupt withdrawal of clozapine may be associated with rapid relapse of the original psychosis.(2)
- On planned withdrawal, the dose of clozapine should be reduced gradually over at least a 1- to 2-week period in order to avoid the risk of rebound psychosis and other withdrawal symptoms. If abrupt withdrawal is necessary then patients should be observed carefully(2)

10.3 Interactions

10.3.1 Interactions of antipsychotics in general

- Excessive sedation when used in combination with other sedative drugs or with alcohol.(1)
- Decreased effect of levodopa and dopamine agonists.(1)
- Increased risk of extrapyramidal symptoms when combined with SSRIs, gastroprokinetics or cholinesterase inhibitors.(1)
- Increased risk of extrapyramidal symptoms and neurotoxicity if combined with lithium.(1)
- Increased risk of seizures when used in combination with other medicines causing seizures.(1)
- Increased risk of torsade de pointes if used in combination with other drugs causing risk of QT interval prolongation.(1)
- Decreased effect of cholinesterase inhibitors.(1)
- Increased risk of anticholinergic effects when combined with other drugs with anticholinergic properties.(1)
- Chronic use of anticholinergics (e.g. used for extrapyramidal symptoms) could cause or worsen tardive dyskinesia.(1)

10.3.2 Interactions of butyrophenones (haloperidol)

- Haloperidol is a substrate of CYP2D6 and CYP3A4 and is itself an inhibitor of CYP2D6(1). It may increase the plasma concentrations of tricyclic antidepressants by inhibiting their metabolism(2).
- Haloperidol must be used with extreme caution in patients receiving lithium; an encephalopathic syndrome has been reported after their use together.(2)

10.3.3 Interactions of second generation antipsychotics

- Clozapine and olanzapine(99): increased risk of orthostatic hypotension in the event of alcohol consumption.(1)
- Clozapine: increased risk of bone marrow depression in combination with other drugs that depress bone marrow.(1)
- Olanzapine(2):
    - More common neutropenia when olanzapine is given with valproate.
    - Use with valproate has also been associated with an increased incidence of tremor, dry mouth, increased appetite, and weight gain.
- Risperidone(2):
    - Carbamazepine decreases the antipsychotic fraction (risperidone plus 9-hydroxyrisperidone) of risperidone and a similar effect may be seen with other enzyme inducers.
    - Fluoxetine may increase the plasma concentrations of the antipsychotic fraction by raising the concentration of risperidone.
    - Increased mortality has been reported in elderly patients with dementia who are given risperidone and furosemide. Caution is advised when using risperidone with furosemide or other potent diuretics.
- Aripiprazole and sertindole are substrates of CYP2D6 and CYP3A4.(1)
- Cariprazine is a substrate of CYP3A4, and an inhibitor of P-gp. (1)
- Clozapine and olanzapine are substrates of CYP1A2.(1)
- Paliperidone is a substrate for P-gp.(1)
- Quetiapine is a substrate for CYP3A4.(1)
- Risperidone is a substrate for CYP2D6.(1)

10.4 Precautions and monitoring

10.4.1 Precautions for antipsychotics in general

- Regarding metabolic effects, it is recommended to regularly monitor weight, blood pressure and certain metabolic parameters (blood sugar, lipids).(1)
- Caution is advised in the event of hepatic insufficiency.(1)
- In dementia with Lewy bodies, it is best to avoid antipsychotics because of the risk of frequent and severe extrapyramidal disorders.(1)
- Most antipsychotics may affect the performance of skilled tasks including driving.(2)

10.4.2 Specific precautions for butyrophenones (haloperidol)

- Haloperidol should be used with great care in children and adolescents as they may be at increased risk of severe dystonic reactions; patients with hyperthyroidism may also be at increased risk.(2)
- The risk of QT prolongation and/or ventricular arrhythmias may be increased with high doses or with parenteral use of haloperidol, particularly intravenous administration.(2)

10.4.3 Specific precautions for second generation antipsychotics

- Cariprazine: Due to the long half-life of cariprazine and its active metabolites, patients should be monitored for treatment response and adverse effects for several weeks after starting therapy and after each dose adjustment.(2)

- Clozapine: Monitor the blood count regularly (once a week at the start of treatment) and the ECG.(1)
- Quetiapine(2):
    - Asymptomatic changes in the lens of the eye have occurred in patients during long-term treatment with quetiapine. US licensed product information recommends that patients should have an eye examination to detect cataract formation when starting therapy with quetiapine and every 6 months during treatment.
    - Increases in blood pressure have been reported in children and adolescents; blood pressure should be measured at the beginning of, and periodically during, treatment with quetiapine.
- Sertindole(2):
    - Should not be given to patients with uncorrected hypokalemia or hypomagnesaemia. Baseline serum potassium and magnesium screening should be performed before starting sertindole therapy in patients who are at risk of significant electrolyte disturbances. Serum potassium should be monitored in patients with electrolyte disturbances, vomiting or diarrhoea, or receiving diuretics during sertindole treatment.
    - It is also recommended that blood pressure should be monitored during dose titration and in early maintenance therapy.

10.5 Notes on parenteral forms

- In case of parenteral use: cardio-respiratory depression which can be fatal. Monitoring of vital parameters is indicated.(1)
- Depot injection preparations(100):
    - may have a place in long-term treatment when the patient wishes or in case of therapeutic compliance problems with oral forms.
    - Depot preparations based on second generation antipsychotics (e.g. paliperidone palmitate) vs depot preparations based on first generation antipsychotics (e.g. haloperidol decanoate): more expensive, and not more effective. A randomized double-blind study (n = 311) in patients with schizophrenia or a schizoaffective disorder showed a comparable frequency of recurrences over a treatment period of 2 years. Weight gain and hyperprolactinemia occurred more frequently with paliperidone while akathisia was more common with haloperidol. The incidence of tardive dyskinesia was 10.6% in the paliperidone group and 15.4% in the haloperidol group; this difference is not statistically significant, which could be explained by the lack of statistical power of this study.

- Olanzapine in the form of depot injection preparation(101):
    - Post-injection syndrome (post injection delirium/sedation syndrome).(1)
    - In case of post-injection syndrome, the total dose scheduled for a period of 2 to 4 weeks, is released soon after the injection and acute intoxication (overdose) with olanzapine appears.
    - Symptoms of overdose can be: drowsiness, decreased consciousness, disorientation, hyperactivity, extrapyramidal symptoms, parkinsonism, agitation, delirium, hypo or hypertension, tachycardia, hypothermia, prolongation of the QT interval; in one case described in the “Nederlands Tijdschrift voor Geneeskunde” there was also talk of reduced oxygen saturation. Symptoms usually appear within an hour of the injection, rarely 1 to 3 hours after the injection and very rarely after more than 3 hours. Treatment is symptomatic and recovery occurs within 12 to 72 hours.

- Post-injection syndrome occurs in <0.1% of injections and in 2% of patients (incidence estimated on the basis of clinical studies); however, both a higher and a lower incidence is suggested. In a post-marketing study, the incidence was higher in men and at high doses (> 350 mg).
- To quickly limit or detect the risk of post-injection syndrome after administration of olanzapine pamoate, a number of precautionary measures are proposed:
  - Use of the correct injection technique.
  - After each injection, the patient should be monitored (i.e. checked, at least once an hour) for at least 3 hours, in a healthcare institution.
  - After leaving the care facility, the patient (or supervisor) should remain alert to symptoms of post-injection syndrome, and the patient should know where to go for help if symptoms occur. The patient should not drive a vehicle or operate a machine for the rest of the day.
- Contra-indicated also in case of ischemic heart disease, arrhythmias, hypotension.(1)

10.6 Children

10.6.1 General remarks

Dystonia usually occur within the first few days of treatment or after a dosage increase but may also develop on withdrawal. They are transitory, and are most common in children and young adults. Dystonic reactions may be controlled by antimuscarinics such as biperiden or procyclidine.(2)

10.6.2 Regarding first generation antipsychotics

- Few phenothiazines (e.g. prothipendyl) are recommended for use in children; in particular there have been concerns about the use of phenothiazine derivatives in infants (Sudden Infant Death Syndrome).(2)
- Haloperidol should be used with great care in children and adolescents as they may be at increased risk of severe dystonic reactions.(2)
- Symptoms of haloperidol overdosage in children have ranged from the expected, such as drowsiness, restlessness, confusion, marked extrapyramidal symptoms, and hypothermia, to unexpected reactions such as bradycardia (possibly secondary to hypothermia) and an episode of severe, delayed hypertension.(2)

10.6.3 Regarding second generation antipsychotics

- Use of the atypical antipsychotics aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone has been associated with case reports of neuroleptic malignant syndrome in children and adolescents aged 11 to 18 years; symptoms were consistent with those seen in adults.(2)
- Adverse effects such as increased appetite, extrapyramidal symptoms, and rises in prolactin concentrations may occur at a higher frequency in children and adolescents than in adults.(2)
- Increases in blood pressure have been reported in children and adolescents, and blood pressure should be measured at the beginning of, and periodically during, treatment with quetiapine.(2)

10.7 Elderly

- The risk of hip fracture has been reported to be increased in elderly patients given antipsychotics. It was suggested that antipsychotic-induced sedation or orthostatic hypotension could increase the risk of falls in elderly persons.(2)
- The use of antipsychotics to manage behavioural complications of dementia may increase the rate of cognitive decline. Elderly patients with dementia, especially Lewy-body dementia, are reported to be highly susceptible to the extrapyramidal adverse effects of antipsychotic drugs, and the reaction can be extremely serious, even fatal.(2)
- The use of second generation antipsychotics in such patients is not without risk and there is evidence of an increased death rate with their use.(2) An increased risk of death from the use of antipsychotics in the elderly with dementia has been reported in observational studies. When treated with antipsychotics for six months, in patients with dementia, there would be an additional 2-4% death. Quetiapine appears to be associated with a lower risk than other second generation antipsychotics, but it may be less effective on agitation and psychosis. For second generation antipsychotics, a higher dose seems to be associated with a higher risk of mortality.(102)
- Sertindole should be used with caution in the elderly.(2)
- Cerebrovascular adverse effects(2):
    - Risperidone in elderly patients with dementia appeared to be associated with an increased risk of cerebrovascular adverse effects such as stroke and transient ischaemic attacks. The UK CSM (Committee on Safety of Medicines) therefore recommended at the time that risperidone should not be used to treat behavioural problems in elderly patients with dementia (but see below).
    - Similarly, the CSM (Committee on Safety of Medicines) recommended that olanzapine should not be used to treat behavioural problems or dementia-related psychosis in elderly patients with dementia after analysis of placebo-controlled studies revealed a threefold increase in cerebrovascular adverse effects including stroke and a twofold increase in all-cause mortality. It was considered that the risk may not be confined to use in dementia and should be considered relevant to any patient with a history of stroke or transient ischaemic attack or other risk factors for cerebrovascular disease, including hypertension, diabetes, current smoking, or atrial fibrillation.
    - Licensed product information for aripiprazole also includes a warning about evidence of a dose-response relationship between cerebrovascular adverse events and the use of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease.
    - 3 large retrospective population-based studies in the elderly (1 involving 10 385 patients given atypicals and 1015 given classical antipsychotics, another involving 17 845 given atypicals and 14 865 given classical antipsychotics, and the third involving 24 359 given atypicals and 12 882 given classical antipsychotics), suggested that use of atypical antipsychotics was not associated with a statistically significant increased risk of stroke compared with the classical drugs.
- UK licensed product information states that a higher incidence of mortality was seen in elderly patients with dementia who were taking risperidone and furosemide when compared with those taking either drug alone. (2)
- More recently, the UK CHM (formerly the CSM) stated that analysis of 3 randomised studies showed a clear benefit for the short-term use of risperidone in the treatment of aggression in elderly patients with dementia. Indeed, risperidone is now licensed for such use in the UK but the balance of risks and benefits should be carefully assessed for every patient.(2)

10.8 Pregnancy and lactation

- Failure to treat severe psychotic symptoms during pregnancy can have detrimental effects on the mother and the child; however, the use of antipsychotics should be avoided as much as possible throughout the duration of pregnancy.(1)
- First trimester: a teratogenic effect cannot be excluded.(1)
- Third trimester and breastfeeding period: the use of antipsychotics by the mother can involve in the child a risk of extrapyramidal syndrome, sedation and, especially with phenothiazines, anticholinergic effects (excitation, sucking disorders and, less commonly, arrhythmias, bowel motility disorders and urinary retention).(1)

11 Appendix. Evidence tables: BPSD - Efficacy

11.1 Aripiprazole versus placebo for BPSD - efficacy

Meta-analysis:
AHRQ 2011(6): Maglione M, Ruelaz Maher A, Hu J, et al. Off-Label Use of Atypical Antipsychotics: An Update. Comparative Effectiveness Review No. 43.
Inclusion criteria:
"Only studies on humans were included. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. As single dose or short term trials (less than 6 weeks in length) are common for several of the new uses, we decided, at the TEP's suggestion, not to limit inclusion by study duration."
Search strategy:
"We conducted an initial update search on June 1, 2008, as part of a project to determine if Comparative Effectiveness Reviews (CERs) funded by AHRQ needed updating; this search included only the drugs aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Regular update searches continued through May 2011. The search for off-label use of the newly approved atypicals (iloperidone, paliperidone and asenapine) included all years available in the electronic databases through May 2011."

"Databases searched include: DARE (Database of Abstracts of Reviews of Effects), Cochrane Database of Systematic Reviews, CENTRAL (Cochrane Central Register of Controlled Trials), PubMed (National Library of Medicine, includes MEDLINE), Embase (biomedical and pharmacological bibliographic database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), and PsycINFO."
"Other sources of literature include clinicaltrials.gov, references of included studies, references of relevant reviews, and personal files from related topic projects. In addition, the AHRQ Effective Health Care Program Scientific Resource Center (SRC) at Oregon Health Sciences University requested unpublished studies from pharmaceutical manufacturers and searched the FDA and Health Canada databases."
Assessment of quality of included trials: yes, but seems incomplete
Other methodological remarks: see below tables

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2011(6) Design:	Aripiprazole Vs placebo	N= 3 n= 951 (Breder 2004/Mintzer	Efficacy for overall BPSD	SMD 0.20 (95%CI: 0.04, 0.35) I-squared=22.1%, p= 0.277

MA Search date: (May-2011)		2007, De Deyn 2005, Streim 2004/Streim 2008)		**SS in favour of aripiprazole**
		N= 3 n= 951 (Breder 2004/Mintzer 2007, De Deyn 2005, Streim 2004/Streim 2008)	Efficacy for psychosis	SMD 0.14 (95%CI: -0.02, 0.29) I-squared=18.8%, p= 0.292 NS
		N= 2 n= 743 (Breder 2004/Mintzer 2007, Streim 2004/Streim 2008)	Efficacy for agitation	SMD 0.31 (95%CI: 0.10, 0.52); **SS in favour of aripiprazole** SMD 0.30 (95%CI: 0.05, 0.55); **SS in favour of aripiprazole**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (Risk of Bias Assessment)
Mintzer 2007(30) RCT	487	Psychosis/psychotic features, Nursing home resident, NPI or NPI/NH >= 6 sum of hallucinations and delusional items, Age 55-95, MMSE= 6-22	10 weeks	Placebo vs Aripiprazole 2 mg/day vs Aripiprazole 5 mg/day vs Aripiprazole 10 mg/day	<u>Data from Yunusa et al. 2019</u> -Sequence generation (selection bias): unclear risk -Allocation concealment (selection bias): low risk

					-Blinding of participants and personnel: (performance bias): low risk -Blinding of outcome assessment (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Overall risk of bias: medium risk <u>Data from AHRQ 2011</u> -Jadad score: 3 -Withdrawals: 46.3% vs 34.7% vs 40.2% vs 45.2% -Withdrawals due to AE's: 13.2% vs 7.6% vs 18.0% vs 24.6% -ITT analysis: yes -Funding: Industry
De Deyn 2005(31) RCT	208	AD with psychosis Mean age 82; 28% male Allowed medication: Sedative/hypnotics, Acetylcholinesterase inhibitors, Rivastigmine, Tacrine, Antidepressants, Benztropine Assessed at baseline and 10 weeks: NPI, BPRS, CGI, MMSE, Extrapyramidal side effects	10 weeks	Placebo vs Aripiprazole 2–15 mg/day	<u>Data from Yunusa et al. 2019</u> -Sequence generation (selection bias): unclear risk -Allocation concealment (selection bias): low risk -Blinding of participants and personnel: (performance bias): low risk -Blinding of outcome assessment (detection bias): low risk -Incomplete outcome data (attrition bias): low risk

					-Selective outcome reporting (reporting bias): low risk -Overall risk of bias: medium risk <u>Data from AHRQ 2011:</u> data missing <u>Data retrieved from AHRQ 2006:</u> -Jadad score: 3 -Withdrawals: 17.6% vs 17.0% -Withdrawals due to AE's: 6.9% vs 9.4% -ITT analysis: yes -Funding: Industry
Streim 2008(33) RCT	256	AD with psychosis, Age 55-95, MMSE = 6-22, NPI or NPI/NH ≥ 6 sum of hallucinations and delusional items, hallucinations and delusions >=1 month Mean age 59	10 weeks	Placebo vs Aripiprazole 8.6 mg/day	<u>Data from Yunusa et al. 2019</u> -Sequence generation (selection bias): low risk -Allocation concealment (selection bias): low risk -Blinding of participants and personnel: (performance bias): low risk -Blinding of outcome assessment (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Overall risk of bias: low risk <u>Data from AHRQ 2011</u> -Jadad score: 3 -Run-in/wash-out period: Wash-out: No drug for 7 day(s)

					-Withdrawals: 48.8% vs 33.6% -Withdrawals due to AE's: 8.0% vs 13.0% -ITT analysis: yes -Funding: Industry

Remarks:

-"Total global score includes psychiatric symptoms of delusions, suspiciousness, dysphoria, anxiety, motor agitation, aggression, hostility, euphoria, disinhibition, irritability and apathy, as measured by the NPI. Psychosis was measured by subscales of the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), BPRS, and NPI, which focus primarily on delusions and hallucinations. Agitation was measured by subscales of the BEHAVE-AD, BPRS, NPI, and Cohen-Mansfield Agitation Inventory, and included the symptoms physical aggression, verbal aggression, excitability, oppositional behaviors, and excessive motor ability.

Several PCTs contained more than one treatment arm; these studies compared different doses of atypicals. For our main efficacy analyses, we pooled these arms together and present one resulting intervention outcome for each trial. This was most often done for aripiprazole trials that included a 2, 5, and 10 mg arm."

-In case of two publications of the same study, we reported the risk of bias assessment of the most recent publication.

Author's conclusions:

"2011 Findings:
Overall – In our meta-analysis of PCTs, aripiprazole, olanzapine, and risperidone were superior to placebo as treatment of behavioral symptoms as measured by total
scores on BEHAVE-AD, BPRS, and NPI. Effect sizes were generally considered to be "small" in magnitude.
Psychosis – In our meta-analysis risperidone was superior to placebo, as measured by the psychosis subscales of the BEHAVE-AD, BPRS, and NPI. Results for aripiprazole did not meet conventional levels of statistical significance.
Agitation – In our meta-analysis, aripiprazole, olanzapine and risperidone were superior to placebo, as measured by the agitation subscales of the BEHAVE-AD, BPRS, NPI,
and CMAI."

"2011 conclusions: Aripiprazole, olanzapine, and risperidone have efficacy as treatment for behavioral symptoms of dementia."

11.2 Asenapine versus placebo for BPSD - efficacy

Meta-analysis:
Yunusa I, Alsumali A, Garba AE, et al. 2019. Assessment of reported comparative effectiveness and safety of atypical antipsychotics in the treatment of behavioral and psychological symptoms of dementia: a network meta-analysis.(4)
Inclusion criteria:
"Only randomized clinical trials comparing identified AAPs with placebo or head-to-head comparisons of different AAPS in adults 65 years or older with BPSD were included. We evaluated trials that compared at least 2 of the following AAPs with each other: aripiprazole, olanzapine, quetiapine, and risperidone. Trials that compared 1 of those AAPs with placebo were also included. Exclusion criteria were study designs other than randomized clinical trials, active-controlled trials comparing AAPs with any other medication, studies with less than 6 weeks of follow-up, and non-English articles."
Search strategy:
"We searched the literature using the Cochrane Library, Embase, MEDLINE/PubMed, and PsychINFO databases from their inception to May 31, 2018, for studies evaluating the effectiveness and safety of AAPS for the treatment of BPSD. Key search terms included dementia, atypical antipsychotics, aripiprazole, olanzapine, risperidone, quetiapine, asenapine, clozapine, iloperidone, lurasidone, paliperidone, and ziprasidone."
Assessment of quality of included trials: yes
Other methodological remarks: only network meta-analysis

Remarks
This network meta-analysis by Yunusa 2019(4) found no eligible RCT's comparing asenapine versus placebo in patients with BPSD.

11.3 Clozapine versus placebo for BPSD - efficacy

Meta-analysis:
Yunusa I, Alsumali A, Garba AE, et al. 2019. Assessment of reported comparative effectiveness and safety of atypical antipsychotics in the treatment of behavioral and psychological symptoms of dementia: a network meta-analysis.(4)
Inclusion criteria:
"Only randomized clinical trials comparing identified AAPs with placebo or head-to-head comparisons of different AAPS in adults 65 years or older with BPSD were included. We evaluated trials that compared at least 2 of the following AAPs with each other: aripiprazole, olanzapine, quetiapine, and

risperidone. Trials that compared 1 of those AAPs with placebo were also included. Exclusion criteria were study designs other than randomized clinical trials, active-controlled trials comparing AAPs with any other medication, studies with less than 6 weeks of follow-up, and non-English articles."
Search strategy:
"We searched the literature using the Cochrane Library, Embase, MEDLINE/PubMed, and PsychINFO databases from their inception to May 31, 2018, for studies evaluating the effectiveness and safety of AAPS for the treatment of BPSD. Key search terms included dementia, atypical antipsychotics, aripiprazole, olanzapine, risperidone, quetiapine, asenapine, clozapine, iloperidone, lurasidone, paliperidone, and ziprasidone."
Assessment of quality of included trials: yes
Other methodological remarks: only network meta-analysis

Remarks
This network meta-analysis by Yunusa 2019(4) found no eligible RCT's comparing clozapine versus placebo in patients with BPSD.

11.4 Olanzapine versus placebo for BPSD - efficacy

Meta-analysis:
AHRQ 2011(6) - Maglione M, Ruelaz Maher A, Hu J, et al. Off-Label Use of Atypical Antipsychotics: An Update. Comparative Effectiveness Review No. 43.
Inclusion criteria:
"Only studies on humans were included. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. As single dose or short term trials (less than 6 weeks in length) are common for several of the new uses, we decided, at the TEP's suggestion, not to limit inclusion by study duration."
Search strategy:
"We conducted an initial update search on June 1, 2008, as part of a project to determine if Comparative Effectiveness Reviews (CERs) funded by AHRQ needed updating; this search included only the drugs aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Regular update searches continued through May 2011. The search for off-label use of the newly approved atypicals (iloperidone, paliperidone and asenapine) included all years available in the electronic databases through May 2011."

"Databases searched include: DARE (Database of Abstracts of Reviews of Effects), Cochrane Database of Systematic Reviews, CENTRAL (Cochrane Central Register of Controlled Trials), PubMed (National Library of Medicine, includes MEDLINE), Embase (biomedical and pharmacological bibliographic database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), and PsycINFO."

"Other sources of literature include clinicaltrials.gov, references of included studies, references of relevant reviews, and personal files from related topic projects. In addition, the AHRQ Effective Health Care Program Scientific Resource Center (SRC) at Oregon Health Sciences University requested unpublished studies from pharmaceutical manufacturers and searched the FDA and Health Canada databases."
Assessment of quality of included trials: yes
Other methodological remarks: see below tables

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2011(6) Design: MA Search date: (May-2011)	Olanzapine vs placebo	N= 4 n= 1773 (De Deyn 2004, Deberdt 2005, Schneider 2006/Sultzer 2008, Street 2000)	Efficacy for overall BPSD	SMD 0.12 (95%CI: 0.00, 0.25) I-squared=0.0%, p= 0.485 **SS in favour of olanzapine**
		N= 5 n= 2041 (De Deyn 2004, Deberdt 2005, Kennedy 2005, Schneider 2006/Sultzer 2008, Street 2000)	Efficacy for psychosis	SMD 0.05 (95%CI: -0.07, 0.17) I-squared=14.7%, p= 0.321 NS
		N= 4 n= 1773	Efficacy for agitation	SMD 0.19 (95%CI: 0.07, 0.31)

		(De Deyn 2004, Deberdt 2005, Schneider 2006/Sultzer 2008, Street 2000)		I-squared=0.0%, p= 0.454 **SS in favour of olanzapine**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (Risk of Bias Assessment)
De Deyn 2004(34) RCT	652	Age >= 40, Hospitalized/institutionalized, Psychosis/psychotic features, MMSE = 5-26 Mean age 77, 25% male Allowed medication: benzodiazepines, sedative/hypnotics Assessed at baseline and 10 weeks: NPI-NH, CGI, BPRS, MMSE, SIB	10 weeks	Placebo vs Olanzapine 1.0 mg/day vs Olanzapine 2.5 mg/day vs Olanzapine 5.0 mg/day vs Olanzapine 7.5 mg/day	<u>Data from Yunusa et al. 2019</u> -Sequence generation (selection bias): unclear risk -Allocation concealment (selection bias): low risk -Blinding of participants and personnel: (performance bias): low risk -Blinding of outcome assessment (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Overall risk of bias: medium risk <u>Data from AHRQ 2011:</u> data missing <u>Data retrieved from AHRQ 2006:</u>

					-Jadad score: 2 -method for randomization and allocation? NR -outcome assessors masked? NR -Run-in period reported -Washout: NR -Withdrawals: 29.5% vs 34.1% vs 24.6% vs 24.8% vs 28.8% -Withdrawals due to AE's: 3.9% vs 9.3% vs 6.7% vs 7.2% vs 9.8% -ITT analysis: no -Funding: Industry
Deberdt 2005(35) RCT	494	Age >= 40, AD, vascular or mixed dementia, NPI or NPI/NH >= 6 sum of hallucinations and delusional items Mean age 79; 34% male Allowed medication: Anticholinergics, benzodiazepines Assessed at baseline and 10 weeks: NPI, CGI, NPI- NH, CMAI, BPRS, CSDD, PDS, MMSE	10 weeks	Placebo vs Olanzapine 5.2 mg vs Risperidone 1.0 mg	Data from Yunusa et al. 2019 -Sequence generation (selection bias): unclear risk -Allocation concealment (selection bias): low risk -Blinding of participants and personnel: (performance bias): low risk -Blinding of outcome assessment (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Overall risk of bias: medium risk Data from AHRQ 2011: data missing Data retrieved from AHRQ 2006: -Jadad score: 2

					-method for randomization and allocation? NR -outcome assessors masked? NR -Run-in: NR -Washout period reported -Withdrawals: 20.2% vs 37.7% vs 31.1% -Withdrawals due to AE's: 3.2% vs 16.2% vs 8.7% -ITT analysis: yes -Funding: Industry
Kennedy 2005(36) RCT	268	Age ≥ 40, MMSE 14-26 Allowed medication: benzodiazepines, hypnotics Mean age 78; 44% male Assessed at baseline and 26 weeks: NPI, MMSE, ADAS-cog, Extrapyramidal side effects, CIBIC	26 weeks	Placebo vs Olanzapine 2.5-7.5 mg/day	Not included in Yunusa et al. 2019 Data missing in AHRQ 2011 Data retrieved from AHRQ 2006: -Jadad score: 3 -Run-in: NR -Washout period reported -Withdrawals: 26.7% vs 38.2% -Withdrawals due to AE's: 4.4% vs 12.4% -ITT analysis: yes -Funding: Industry
Schneider 2006(37)/Sultzer 2008(38) Randomized, controlled, double blind trial	421	AD or probable AD, MMSE 5-26, psychosis, aggression, or agitation previous week or at least intermittently for 4 weeks, had a severity rating of at least "moderate" for conceptual disorganization, suspiciousness, or hallucinatory behavior on BPRS, ambulatory and living at home or in an assisted-living facility	12 weeks	Placebo vs Olanzapine 5.5mg/day vs Quetiapine 56.5 mg/day vs Risperidone 1.0 mg/day	Data from Yunusa et al. 2019 -Sequence generation (selection bias): low risk -Allocation concealment (selection bias): low risk -Blinding of participants and personnel: (performance bias): low risk -Blinding of outcome assessment (detection bias): low risk

					-Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Overall risk of bias: low risk <u>Data from AHRQ 2011</u> -Jadad score: 1 -Single blind, patient -No similar groups at baseline -Outcome assessor and care provider not masked -dropout rate with reason not described; but acceptable dropout rate. -ITT analysis: yes -Funding: Government
Street 2000(39) RCT	206	Possible or probable AD, NPI/NH ≥ 3 Assessed at baseline and 6 weeks: NPI-NH, BPRS, MMSE Allowed other medication: benzodiazepines Mean age 83 (61-97); 39% male	6 weeks	Placebo vs Olanzapine 5 mg/day vs Olanzapine 10 mg/day vs Olanzapine 15 mg/day	<u>Data from Yunusa et al. 2019</u> -Sequence generation (selection bias): low risk -Allocation concealment (selection bias): low risk -Blinding of participants and personnel: (performance bias): low risk -Blinding of outcome assessment (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Overall risk of bias: low risk

					Data from AHRQ 2011: Data missing Data retrieved from AHRQ 2006: -Jadad score: 5 -Run-in: NR -Washout: NR -Withdrawals: 23.4% vs 19.6% vs 28.0% vs 34.0% -Withdrawals due to AE's: 4.3% vs 10.7% vs 8.0% vs 17.0% -ITT analysis: yes -Funding: Government, Industry & Private

Remarks:

-"Total global score includes psychiatric symptoms of delusions, suspiciousness, dysphoria, anxiety, motor agitation, agression, hostility, euphoria, disinhibition, irritability and apathy, as measured by the NPI. Psychosis was measured by subscales of the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), BPRS, and NPI, which focus primarily on delusions and hallucinations. Agitation was measured by subscales of the BEHAVE-AD, BPRS, NPI, and Cohen-Mansfield Agitation Inventory, and included the symptoms physical aggression, verbal aggression, excitability, oppositional behaviors, and excessive motor ability.

Several PCTs contained more than one treatment arm; these studies compared different doses of atypicals. For our main efficacy analyses, we pooled these arms together and present one resulting intervention outcome for each trial. This was most often done for aripiprazole trials that included a 2, 5, and 10 mg arm."

-In case of two publications of the same study, we reported the risk of bias assessment of the most recent publication.

Author's conclusions:

"2011 Findings:

Overall – In our meta-analysis of PCTs, aripiprazole, olanzapine, and risperidone were superior to placebo as treatment of behavioral symptoms as measured by total
scores on BEHAVE-AD, BPRS, and NPI. Effect sizes were generally considered to be “small” in magnitude.
Psychosis – In our meta-analysis risperidone was superior to placebo, as measured by the psychosis subscales of the BEHAVE-AD, BPRS, and NPI. Results for aripiprazole did not meet conventional levels of statistical significance.
Agitation – In our meta-analysis, aripiprazole, olanzapine and risperidone were superior to placebo, as measured by the agitation subscales of the BEHAVE-AD, BPRS, NPI,
and CMAI.”

“2011 conclusions: Aripiprazole, olanzapine, and risperidone have efficacy as treatment for behavioral symptoms of dementia.”

11.5 Paliperidone versus placebo for BPSD - efficacy

Meta-analysis:
Yunusa I, Alsumali A, Garba AE, et al. 2019. Assessment of reported comparative effectiveness and safety of atypical antipsychotics in the treatment of behavioral and psychological symptoms of dementia: a network meta-analysis.(4)
Inclusion criteria:
“Only randomized clinical trials comparing identified AAPs with placebo or head-to-head comparisons of different AAPS in adults 65 years or older with BPSD were included. We evaluated trials that compared at least 2 of the following AAPs with each other: aripiprazole, olanzapine, quetiapine, and risperidone. Trials that compared 1 of those AAPs with placebo were also included. Exclusion criteria were study designs other than randomized clinical trials, active-controlled trials comparing AAPs with any other medication, studies with less than 6 weeks of follow-up, and non-English articles.”
Search strategy:
“We searched the literature using the Cochrane Library, Embase, MEDLINE/PubMed, and PsychINFO databases from their inception to May 31, 2018, for studies evaluating the effectiveness and safety of AAPS for the treatment of BPSD. Key search terms included dementia, atypical antipsychotics, aripiprazole, olanzapine, risperidone, quetiapine, asenapine, clozapine, iloperidone, lurasidone, paliperidone, and ziprasidone.”
Assessment of quality of included trials: yes
Other methodological remarks: only network meta-analysis

Remarks

This network meta-analysis by Yunusa 2019(4) found no eligible RCT's comparing paliperidone versus placebo in patients with BPSD.

11.6 Quetiapine versus placebo for BPSD - efficacy

Meta-analysis:
AHRQ 2011(6) - Maglione M, Ruelaz Maher A, Hu J, et al. Off-Label Use of Atypical Antipsychotics: An Update. Comparative Effectiveness Review No. 43.
Inclusion criteria:
"Only studies on humans were included. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. As single dose or short term trials (less than 6 weeks in length) are common for several of the new uses, we decided, at the TEP's suggestion, not to limit inclusion by study duration."
Search strategy:
"We conducted an initial update search on June 1, 2008, as part of a project to determine if Comparative Effectiveness Reviews (CERs) funded by AHRQ needed updating; this search included only the drugs aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Regular update searches continued through May 2011. The search for off-label use of the newly approved atypicals (iloperidone, paliperidone and asenapine) included all years available in the electronic databases through May 2011."

"Databases searched include: DARE (Database of Abstracts of Reviews of Effects), Cochrane Database of Systematic Reviews, CENTRAL (Cochrane Central Register of Controlled Trials), PubMed (National Library of Medicine, includes MEDLINE), Embase (biomedical and pharmacological bibliographic database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), and PsycINFO."
"Other sources of literature include clinicaltrials.gov, references of included studies, references of relevant reviews, and personal files from related topic projects. In addition, the AHRQ Effective Health Care Program Scientific Resource Center (SRC) at Oregon Health Sciences University requested unpublished studies from pharmaceutical manufacturers and searched the FDA and Health Canada databases."
Assessment of quality of included trials: yes, but seems incomplete
Other methodological remarks: see below tables

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2011(6) Design: MA Search date: (May-2011)	Quetiapine Vs Placebo	N= 3 n= 1038 (Schneider 2006/Sultzer 2008, Tariot 2006, Zhong 2004/Zhong 2007)	Efficacy for overall BPSD	SMD 0.13 (95%CI: -0.03, 0.28) I-squared=0.0%, p= 0.610 NS
		N= 3 n= 1038 (Schneider 2006/Sultzer 2008, Tariot 2006, Zhong 2004/Zhong 2007)	Efficacy for psychosis	SMD 0.04 (95%CI: -0.11, 0.19) I-squared=0.0%, p= 0.558 NS
		N= 5 n= 1171 (Ballard 2005, Paleacu 2008, Schneider 2006/Sultzer 2008, Tariot 2006, Zhong 2004/Zhong 2007)	Efficacy for agitation	SMD 0.05 (95%CI: -0.14, 0.25) I-squared=38.4%, p= 0.165 NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (Risk Of Bias assessment)
Ballard 2005(40) RCT	93	CMAI >= 39, Age>= 60, NPI >= 4 Mean age 83, 19% male	26 weeks	Placebo vs Rivastigmine min 9 mg/day vs Quetiapine 100 mg/day	Data from Yunusa et al. 2019 -Sequence generation (selection bias): low risk -Allocation concealment (selection bias): low risk -Blinding of participants and personnel: (performance bias): low risk -Blinding of outcome assessment (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Overall risk of bias: low risk Data from AHRQ 2011: data missing Data retrieved from AHRQ 2006: -Jadad score: 4 -Withdrawals: 3.2% vs 32.3% vs 25.8% -Withdrawals due to AE's: not reported -ITT analysis: yes -Funding: Industry and private
Paleacu 2008(41) RCT	40	AD with BPSD, age > 50, MMSE <24, NPI > 6 on any item	6 weeks	Placebo vs Quetiapine 50- 300 mg/day	Data from Yunusa et al. 2019 -Sequence generation (selection bias): unclear risk

					-Allocation concealment (selection bias): low risk -Blinding of participants and personnel: (performance bias): low risk -Blinding of outcome assessment (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Overall risk of bias: medium risk <u>Data from AHRQ 2011</u> --Jadad score: 3 -Withdrawals: 40.0% vs 25.0% -Withdrawals due to AE's: 5.0% vs 5.0% -ITT analysis: yes -Funding: Industry
Schneider 2006(37)/Sultzer 2008(38) RCT	421	AD or probable AD, MMSE 5-26, psychosis, aggression, or agitation previous week or at least intermittently for 4 weeks, had a severity rating of at least "moderate" for conceptual disorganization, suspiciousness, or hallucinatory behavior on BPRS, ambulatory and living at home or in an assisted-living facility Mean age 78	12 weeks	Placebo vs Olanzapine 5.5mg/day vs Quetiapine 56.5 mg/day vs Risperidone 1.0 mg/day	<u>Data from Yunusa et al. 2019</u> -Sequence generation (selection bias): low risk -Allocation concealment (selection bias): low risk -Blinding of participants and personnel: (performance bias): low risk -Blinding of outcome assessment (detection bias): low risk -Incomplete outcome data (attrition bias): low risk

					-Selective outcome reporting (reporting bias): low risk -Overall risk of bias: low risk <u>Data from AHRQ 2011</u> -Jadad score: 1 -Single blind, patient -No similar groups at baseline -Outcome assessor not masked -dropout rate with reason not described; but acceptable dropout rate. -ITT analysis: yes -Funding: Government
Tariot 2006(42) RCT	284	Diagnosed with DSM-IV AD, > 64 years old, not bedridden, nursing home residents for >= 2 weeks, presence of psychosis, BPRS scores >=24, CGIS scores >=4, scores of >= 3 on two or more BPRS items, frequency scores of >= 3 on at least one of the two psychosis items of the NPINH, scores of >= 5 on MMSE	10 weeks	Placebo vs Haloperidol 0.5- 12 mg/day vs Quetiapine 25- 600 mg/day	<u>Data from Yunusa et al. 2019</u> -Sequence generation (selection bias): low risk -Allocation concealment (selection bias): low risk -Blinding of participants and personnel: (performance bias): low risk -Blinding of outcome assessment (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Overall risk of bias: low risk <u>Data from AHRQ 2011</u> -Jadad score: 4

					-Withdrawals: 36.4% vs 41.5% vs 31.9% -Withdrawals due to AE's: 13.1% vs 18.1% vs 11.0% -ITT analysis: yes -Funding: Government
Zhong 2007(44) RCT	333	Institutionalized, diagnosed possible AD or vascular dementia, age >= 55, ambulatory, agitation that didn't result directly from participants medical condition, PANSS-EC total >= 14, one of the 5 PANSS-EC items >= 4. Setting: Multi-center, Long-term care facilities	10 weeks	Placebo vs Quetiapine 100 mg/day vs Quetiapine 200 mg/day	<u>Data from Yunusa et al. 2019</u> -Sequence generation (selection bias): low risk -Allocation concealment (selection bias): low risk -Blinding of participants and personnel: (performance bias): low risk -Blinding of outcome assessment (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Overall risk of bias: low risk <u>Data from AHRQ 2011</u> -Jadad score: 5 -Withdrawals: 34.8% vs 34.7% vs 36.8% -Withdrawals due to AE's: 9.8% vs 8.1% vs 14.5% -ITT analysis: yes -Funding: Government

Remarks:

-“Total global score includes psychiatric symptoms of delusions, suspiciousness, dysphoria, anxiety, motor agitation, agression, hostility, euphoria, disinhibition, irritability and apathy, as measured by the NPI. Psychosis was measured by subscales of the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), BPRS, and NPI, which focus primarily on delusions and hallucinations. Agitation was measured by subscales of the BEHAVE-AD, BPRS, NPI, and Cohen-Mansfield Agitation Inventory, and included the symptoms physical aggression, verbal aggression, excitability, oppositional behaviors, and excessive motor ability.

Several PCTs contained more than one treatment arm; these studies compared different doses of atypicals. For our main efficacy analyses, we pooled these arms together and present one resulting intervention outcome for each trial. This was most often done for aripiprazole trials that included a 2, 5, and 10 mg arm.”

-In case of two publications of the same study, we reported the risk of bias assessment of the most recent publication.

Author’s conclusions:

“2011 Findings:
Overall – In our meta-analysis of PCTs, aripiprazole, olanzapine, and risperidone were superior to placebo as treatment of behavioral symptoms as measured by total
scores on BEHAVE-AD, BPRS, and NPI. Effect sizes were generally considered to be “small” in magnitude.
Psychosis – In our meta-analysis risperidone was superior to placebo, as measured by the psychosis subscales of the BEHAVE-AD, BPRS, and NPI. Results for aripiprazole did not meet conventional levels of statistical significance.
Agitation – In our meta-analysis, aripiprazole, olanzapine and risperidone were superior to placebo, as measured by the agitation subscales of the BEHAVE-AD, BPRS, NPI,
and CMAI.”

“2011 conclusions: Aripiprazole, olanzapine, and risperidone have efficacy as treatment for behavioral symptoms of dementia.”

11.7 Risperidone versus placebo for BPSD - efficacy

Meta-analysis:
AHRQ 2011(6) - Maglione M, Ruelaz Maher A, Hu J, et al. Off-Label Use of Atypical Antipsychotics: An Update. Comparative Effectiveness Review No. 43.
Inclusion criteria:
"Only studies on humans were included. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. As single dose or short term trials (less than 6 weeks in length) are common for several of the new uses, we decided, at the TEP's suggestion, not to limit inclusion by study duration."
Search strategy:
"We conducted an initial update search on June 1, 2008, as part of a project to determine if Comparative Effectiveness Reviews (CERs) funded by AHRQ needed updating; this search included only the drugs aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Regular update searches continued through May 2011. The search for off-label use of the newly approved atypicals (iloperidone, paliperidone and asenapine) included all years available in the electronic databases through May 2011."

"Databases searched include: DARE (Database of Abstracts of Reviews of Effects), Cochrane Database of Systematic Reviews, CENTRAL (Cochrane Central Register of Controlled Trials), PubMed (National Library of Medicine, includes MEDLINE), Embase (biomedical and pharmacological bibliographic database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), and PsycINFO."
"Other sources of literature include clinicaltrials.gov, references of included studies, references of relevant reviews, and personal files from related topic projects. In addition, the AHRQ Effective Health Care Program Scientific Resource Center (SRC) at Oregon Health Sciences University requested unpublished studies from pharmaceutical manufacturers and searched the FDA and Health Canada databases."
Assessment of quality of included trials: yes
Other methodological remarks: see below tables

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2011(6) Design: MA	Risperidone Vs placebo	N= 6 n= 2702 (Brodaty 2003/Brodaty 2005, Deberdt 2005, De Deyn 1999, Katz	Efficacy for overall BPSD	SMD 0.19 (95%CI: 0.00, 0.38) I-squared=74.6%, p= 0.001 **SS in favour of risperidone**

Search date: (May-2011)		1999, Mintzer 2006, Schneider 2006/Sultzer 2008)		
		N= 5 n= 2358 (Brodaty 2003/Brodaty 2005, Deberdt 2005, Katz 1999, Mintzer 2006, Schneider 2006/Sultzer 2008)	Efficacy for psychosis	SMD 0.20 (95%CI: 0.05, 0.36) I-squared=55.0%, p= 0.064 **SS in favour of risperidone**
		N= 6 n= 2702 (Brodaty 2003/Brodaty 2005, Deberdt 2005, De Deyn 1999, Katz 1999, Mintzer 2006, Schneider 2006/Sultzer 2008)	Efficacy for agitation	SMD 0.22 (95%CI: 0.09, 0.35) I-squared=43.7%, p= 0.114 **SS in favour of risperidone**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (Risk Of Bias assessment)
Brodaty 2003/Brodaty 2005(45) RCT	345	Age >= 55, FAST > = 4,MMSE< = 23, CMAI score of >= 4 on at least 1 aggressive item or a score of 3 on at least 2 aggressive items, or a score of 2 on at least 3 aggressive items, or 2 aggressive items occurring at a frequency of 2 and 1 at a frequency of 3, Nursing home resident, Resident >= 1 month prior to enrollment Mean age 83, 28% male Assessed at baseline and 12 weeks: CMAI, BEHAVE-AD, FAST, MMSE, CGI	12 weeks	Placebo 1.06 mg/day vs Risperidone 0.95 mg/day	<u>Data from Yunusa et al. 2019</u> -Sequence generation (selection bias): low risk -Allocation concealment (selection bias): low risk -Blinding of participants and personnel: (performance bias): low risk -Blinding of outcome assessment (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Overall risk of bias: low risk <u>Data from AHRQ 2011:</u> data missing <u>Data retrieved from AHRQ 2006:</u> -Jadad score: 3 -Withdrawals: 32.9% vs 26.9% -Withdrawals due to AE's: 8.2% vs 13.2% -ITT analysis: yes -Funding: Industry
Deberdt 2005(35) RCT	494	Age >= 40, AD, vascular or mixed dementia, NPI or NPI/NH >= 6 sum of hallucinations and delusional items Mean age 79, 34% male	10 weeks	Placebo vs Olanzapine 5.2 mg vs Risperidone 1.0 mg	<u>Data from Yunusa et al. 2019</u> -Sequence generation (selection bias): unclear risk -Allocation concealment (selection bias): low risk

		Assessed at baseline and 10 weeks: NPI, CGI, NPI- NH, CMAI, BPRS, CSDD, PDS, MMSE			-Blinding of participants and personnel: (performance bias): low risk -Blinding of outcome assessment (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Overall risk of bias: intermediate risk <u>Data from AHRQ 2011: d</u>ata missing <u>Data retrieved from AHRQ 2006:</u> -Jadad score: 2 -method for randomization and allocation? NR -outcome assessors masked? NR -Funding: Industry -Withdrawals: 20.2% vs 37.7% vs 31.1% -Withdrawals due to AE's: 3.2% vs 16.2% vs 8.7% -ITT analysis: yes
De Deyn 1999(31) RCT	344	Age >= 55, Hospitalized/institutionalized, FAST >=4, MMSE <= 23, BEHAVE-AD behavior pathology > 1, BEHAVE-AD >= 8 Assessed at baseline and 12 weeks: BEHAVE- AD, CMAI, CGI	12 weeks	Placebo vs Haloperidol 1.2 mg/day vs Risperidone 1.1 mg/day	<u>Data from Yunusa et al. 2019</u> -Sequence generation (selection bias): unclear risk -Allocation concealment (selection bias): unclear risk -Blinding of participants and personnel: (performance bias): low risk

					-Blinding of outcome assessment (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Overall risk of bias: intermediate risk <u>Data from AHRQ 2011: d</u>ata missing <u>Data retrieved from AHRQ 2006:</u> -Jadad score: 4 -Withdrawals: 35.1% vs 29.6% vs 40.9% -Withdrawals due to AE's: not reported -ITT analysis: no -Funding: Industry
Katz 1999(48) RCT	625	Age >= 55, FAST>= 4, MMSE <=23, BEHAVE-AD>= 8, BEHAVE-AD global rating >= 1 Mean age 83, 32% male Assessed at baseline and 12 weeks: BEHAVE-AD, CMAI, CGI, MMS	12 weeks	Placebo vs Risperidone 0.5 mg/day vs Risperidone 1 mg/day vs Risperidone 2 mg/day	<u>Data from Yunusa et al. 2019</u> -Sequence generation (selection bias): low risk -Allocation concealment (selection bias): low risk -Blinding of participants and personnel: (performance bias): low risk -Blinding of outcome assessment (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk

					-Overall risk of bias: low risk <u>Data from AHRQ 2011: d</u>ata missing <u>Data retrieved from AHRQ 2006:</u> -Jadad score: 4 -Withdrawals: 27.0% vs 21.5% vs 30.4% vs 41.8% -Withdrawals due to AE's: 12.3% vs 8.1% vs 16.2% vs 24.2% -ITT analysis: yes -Funding: Industry
Mintzer 2006(49) RCT	473	>= 55 years old, residents of nursing homes or long-term care facilities, mobile, met the criteria for psychosis of AD, in need of treatment with an atypical antipsychotic, scored >=2 on any item of the BEHAVE-AD psychosis subscale, MMSE 5-23 Mean age 83	8 weeks	Placebo vs Risperidone 0.5-2.5 mg/day	<u>Data from Yunusa et al. 2019</u> -Sequence generation (selection bias): unclear risk -Allocation concealment (selection bias): low risk -Blinding of participants and personnel: (performance bias): low risk -Blinding of outcome assessment (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Overall risk of bias: intermediate risk <u>Data from AHRQ 2011</u> -Jadad score: 3 **-**Run-in/wash-out period: Run-in: Placebo for 1-16 day(s).

					Patients still eligible after washout were randomized. -Withdrawals: 24.8% vs 25.1% -Withdrawals due to AE's: 10.1% vs 10.6% -ITT analysis: yes -Funding: Industry
Sultzer 2008(38) RCT	421	AD or probable AD, MMSE 5-26, psychosis, aggression, or agitation previous week or at least intermittently for 4 weeks, had a severity rating of at least "moderate" for conceptual disorganization, suspiciousness, or hallucinatory behavior on BPRS, ambulatory and living at home or in an assisted-living facility	12 weeks	Placebo vs Olanzapine 5.5mg/day vs Quetiapine 56.5 mg/day vs Risperidone 1.0 mg/day	<u>Data from Yunusa et al. 2019</u> -Sequence generation (selection bias): low risk -Allocation concealment (selection bias): low risk -Blinding of participants and personnel: (performance bias): low risk -Blinding of outcome assessment (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Overall risk of bias: low risk <u>Data from AHRQ 2011</u> -Jadad score: 1 -Single blind, patient -No similar groups at baseline -Outcome assessor not masked -dropout rate with reason not described; but acceptable dropout rate. -ITT analysis: yes

					-Funding: Government

Remarks:

Total global score includes psychiatric symptoms of delusions, suspiciousness, dysphoria, anxiety, motor agitation, agression, hostility, euphoria, disinhibition, irritability and apathy, as measured by the NPI. Psychosis was measured by subscales of the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), BPRS, and NPI, which focus primarily on delusions and hallucinations. Agitation was measured by subscales of the BEHAVE-AD, BPRS, NPI, and Cohen-Mansfield Agitation Inventory, and included the symptoms physical aggression, verbal aggression, excitability, oppositional behaviors, and excessive motor ability.

Several PCTs contained more than one treatment arm; these studies compared different doses of atypicals. For our main efficacy analyses, we pooled these arms together and present one resulting intervention outcome for each trial. This was most often done for aripiprazole trials that included a 2, 5, and 10 mg arm.

Author's conclusions:

"2011 Findings:
Overall – In our meta-analysis of PCTs, aripiprazole, olanzapine, and risperidone were superior to placebo as treatment of behavioral symptoms as measured by total
scores on BEHAVE-AD, BPRS, and NPI. Effect sizes were generally considered to be "small" in magnitude.
Psychosis – In our meta-analysis risperidone was superior to placebo, as measured by the psychosis subscales of the BEHAVE-AD, BPRS, and NPI. Results for aripiprazole did not meet conventional levels of statistical significance.
Agitation – In our meta-analysis, aripiprazole, olanzapine and risperidone were superior to placebo, as measured by the agitation subscales of the BEHAVE-AD, BPRS, NPI,
and CMAI."

"2011 conclusions: Aripiprazole, olanzapine, and risperidone have efficacy as treatment for behavioral symptoms of dementia."

11.8 SGA versus haloperidol for BPSD - efficacy

Meta-analysis:
AHRQ 2011(6) - Maglione M, Ruelaz Maher A, Hu J, et al. Off-Label Use of Atypical Antipsychotics: An Update. Comparative Effectiveness Review No. 43.
Inclusion criteria:
"Only studies on humans were included. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. As single dose or short term trials (less than 6 weeks in length) are common for several of the new uses, we decided, at the TEP's suggestion, not to limit inclusion by study duration."
Search strategy:
"We conducted an initial update search on June 1, 2008, as part of a project to determine if Comparative Effectiveness Reviews (CERs) funded by AHRQ needed updating; this search included only the drugs aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Regular update searches continued through May 2011. The search for off-label use of the newly approved atypicals (iloperidone, paliperidone and asenapine) included all years available in the electronic databases through May 2011."

"Databases searched include: DARE (Database of Abstracts of Reviews of Effects), Cochrane Database of Systematic Reviews, CENTRAL (Cochrane Central Register of Controlled Trials), PubMed (National Library of Medicine, includes MEDLINE), Embase (biomedical and pharmacological bibliographic database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), and PsycINFO."
"Other sources of literature include clinicaltrials.gov, references of included studies, references of relevant reviews, and personal files from related topic projects. In addition, the AHRQ Effective Health Care Program Scientific Resource Center (SRC) at Oregon Health Sciences University requested unpublished studies from pharmaceutical manufacturers and searched the FDA and Health Canada databases."
Assessment of quality of included trials: yes
Other methodological remarks: see below tables

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2011(6) Design: MA	SGA Vs Haloperidol	N= 5 n=972 (Moretti 2005, Verhey 2006, Savaskan 2006, Tariot	Efficacy for overall BPSD	SMD 0.16 (95%CI: -0.16, 0.47) I-squared= 74.6%, p=0.003 NS

Search date: (May-2011)		2006, Dedeyn 1999)		
		N= 4 n= 716 (Verhey 2006, Savaskan 2006, Tariot 2006, Dedeyn 1999)	Efficacy for agitation	SMD 0.03 (95%CI: -0.15, 0.21) I-squared= 0.0%, p=0.815 NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (Risk of Bias Assessment)
Moretti 2005(50) Controlled Clinical Trial only	256	DSM-IV for dementia, MMSE>=14, probable VaD, 71-92	12 months	Typical antipsychotics 10 drops/day vs Olanzapine 2.5-7.5 mg/day	This study did not meet our inclusion criterion for study type (open label). <u>Data from AHRQ 2011</u> --Jadad score: 0 -Funding: not reported -Withdrawals: 0.0% vs 0.0% -Withdrawals due to AE's: 0.0% vs 0.0%

Verhey 2006(51) Randomized, controlled trial only	58	Age >= 60 years, diagnosis of dementia according to DSM-IV, agitation level requiring antipsychotic treatment, no use of antipsychotic treatment within 3 days of inclusion CMAI score >=45	5 weeks	Haloperidol 1-3 mg/day vs Olanzapine 2.5-7.5 mg/day	This study did not meet our inclusion criterion for sample size. <u>Data from AHRQ 2011</u> -Jadad score: 3 -Withdrawals: 0.0% vs 10.0% -Funding: not reported
Savaskan 2006(52) Open-label, comparative study	30	AD, behavioral symptoms > 65	5 weeks	Haloperidol 0.5-4 mg/day vs Quetiapine 25-200 mg/day	This study did not meet our inclusion criteria for study type (open label) and sample size. <u>Data from AHRQ 2011</u> -Jadad score: 2 -Withdrawals due to AE's: 18.2% (2/11) vs 18.2% (2/11) -Funding: Government, Industry
Tariot 2006(42) Randomized, controlled, double blind trial	284	Diagnosed with DSM-IV AD, > 64 years old, not bedridden, nursing home residents for >= 2 weeks, presence of psychosis, BPRS scores >=24, CGIS scores >=4, scores of >= 3 on two or more BPRS items, frequency scores of >= 3 on at least one of the two psychosis items of the NPINH, scores of >= 5 on MMSE	10 weeks	Placebo vs Haloperidol 0.5- 12 mg/day vs Quetiapine 25- 600 mg/day	<u>Data from Yunusa et al. 2019</u> -Sequence generation (selection bias): low risk -Allocation concealment (selection bias): low risk -Blinding of participants and personnel:

					(performance bias): low risk -Blinding of outcome assessment (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Overall risk of bias: low risk <u>Data from AHRQ 2011</u> -Jadad score: 4 -Withdrawals: 36.4% vs 41.5% vs 31.9% -Withdrawals due to AE's: 13.1% vs 18.1% vs 11.0% -ITT analysis: yes -Funding: Government
De Deyn 1999(47) RCT	344	Age >= 55, Hospitalized/institutionalized, FAST >=4, MMSE <= 23, BEHAVE-AD behavior pathology > 1, BEHAVE-AD >= 8 Assessed at baseline and 12 weeks: BEHAVE-AD, CMAI, CGI	12 weeks	Placebo vs Haloperidol 1.2 mg/day vs Risperidone 1.1 mg/day	<u>Data from Yunusa et al. 2019</u> -Sequence generation (selection bias): unclear risk -Allocation concealment (selection bias): unclear risk -Blinding of participants and

					personnel: (performance bias): low risk -Blinding of outcome assessment (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Overall risk of bias: intermediate risk <u>Data from AHRQ 2011:</u> <u>d</u>ata missing <u>Data retrieved from AHRQ 2006:</u> -Jadad score: 4 -Withdrawals: 35.1% vs 29.6% vs 40.9% -Withdrawals due to AE's: not reported -ITT analysis: no -Funding: Industry

<u>Remarks:</u>

Three studies of this meta-analysis did not meet our inclusion criteria (study design and/or sample size). However, due to the paucity of data we decided to retain this meta-analysis as a whole. The studied typical antipsychotics in the study of Moretti 2005 comprised of haloperidol or promazine.

Author's conclusions:

"We conducted a meta-analysis by pooling five trials that compared atypicals to haloperidol on total score. Difference between atypicals and haloperidol was not significant. There were too few trials to pool results separately by drug. Regarding psychosis symptoms, we found one trial which showed no difference in efficacy between olanzapine and haloperidol."

11.9 Risperidone versus olanzapine for BPSD - efficacy

Meta-analysis:
AHRQ 2011(6) - Maglione M, Ruelaz Maher A, Hu J, et al. Off-Label Use of Atypical Antipsychotics: An Update. Comparative Effectiveness Review No. 43.
Inclusion criteria:
"Only studies on humans were included. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. As single dose or short term trials (less than 6 weeks in length) are common for several of the new uses, we decided, at the TEP's suggestion, not to limit inclusion by study duration."
Search strategy:
"We conducted an initial update search on June 1, 2008, as part of a project to determine if Comparative Effectiveness Reviews (CERs) funded by AHRQ needed updating; this search included only the drugs aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Regular update searches continued through May 2011. The search for off-label use of the newly approved atypicals (iloperidone, paliperidone and asenapine) included all years available in the electronic databases through May 2011."

"Databases searched include: DARE (Database of Abstracts of Reviews of Effects), Cochrane Database of Systematic Reviews, CENTRAL (Cochrane Central Register of Controlled Trials), PubMed (National Library of Medicine, includes MEDLINE), Embase (biomedical and pharmacological bibliographic database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), and PsycINFO."
"Other sources of literature include clinicaltrials.gov, references of included studies, references of relevant reviews, and personal files from related topic projects. In addition, the AHRQ Effective Health Care Program Scientific Resource Center (SRC) at Oregon Health Sciences University requested unpublished studies from pharmaceutical manufacturers and searched the FDA and Health Canada databases."
Assessment of quality of included trials: yes
Other methodological remarks: /

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2011(6) Design: MA	Risperidone Vs Olanzapine	N= 2 n= 915 (Deberdt 2005, Schneider 2006/Sultzer 2008)	Efficacy for overall BPSD	SMD 0.10 (95%CI: -0.10, 0.30); NS SMD -0.27 (95%CI: -0.56, 0.02); NS

Search date: (May-2011)		N= 2 n= 915 (Deberdt 2005, Schneider 2006/Sultzer 2008))	Efficacy for psychosis	SMD -0.03 (95%CI: -0.23, 0.17); NS SMD -0.27 (95%CI: -0.56, 0.02); NS
		N= 2 n= 915 (Deberdt 2005, Schneider 2006/Sultzer 2008))	Efficacy for agitation	SMD -0.04 (95%CI: -0.24, 0.16); NS SMD 0.17 (95%CI: -0.12, 0.46); NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (Risk of Bias Assessment)
Deberdt 2005(35) RCT	494	Age >= 40, AD, vascular or mixed dementia, NPI or NPI/NH >= 6 sum of hallucinations and delusional items Mean age 79; 34% male Allowed medication: Anticholinergics, benzodiazepines	10 weeks	Placebo vs Olanzapine 5.2 mg vs Risperidone 1.0 mg	<u>Data from Yunusa et al. 2019</u> -Sequence generation (selection bias): unclear risk -Allocation concealment (selection bias): low risk -Blinding of participants and personnel: (performance bias): low risk -Blinding of outcome assessment (detection bias): low risk -Incomplete outcome data (attrition bias): low risk

		Assessed at baseline and 10 weeks: NPI, CGI, NPI- NH, CMAI, BPRS, CSDD, PDS, MMSE			-Selective outcome reporting (reporting bias): low risk -Overall risk of bias: medium risk Data from AHRQ 2011: data missing Data retrieved from AHRQ 2006: -Jadad score: 2 -Funding: Industry -Withdrawals: 20.2% vs 37.7% vs 31.1% -Withdrawals due to AE's: 3.2% vs 16.2% vs 8.7% -ITT analysis: yes
Schneider 2006(37)/Sultzer 2008(38) Randomized, controlled, double blind trial	421	AD or probable AD, MMSE 5-26, psychosis, aggression, or agitation previous week or at least intermittently for 4 weeks, had a severity rating of at least "moderate" for conceptual disorganization, suspiciousness, or hallucinatory behavior on BPRS, ambulatory and living at home or in an assisted-living facility	12 weeks	Placebo vs Olanzapine 5.5mg/day vs Quetiapine 56.5 mg/day vs Risperidone 1.0 mg/day	Data from Yunusa et al. 2019 -Sequence generation (selection bias): low risk -Allocation concealment (selection bias): low risk -Blinding of participants and personnel: (performance bias): low risk -Blinding of outcome assessment (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Overall risk of bias: low risk Data from AHRQ 2011 -Jadad score: 1 -Funding: Government

					-Single blind, patient -No similar groups at baseline -Outcome assessor not masked -dropout rate with reason not described; but acceptable dropout rate. -ITT analysis: yes

Remarks: /

Author's conclusions:

"Three head to head trials compared atypicals; none was found superior."

11.10 Risperidone versus quetiapine for BPSD - efficacy

Meta-analysis:
AHRQ 2011(6) - Maglione M, Ruelaz Maher A, Hu J, et al. Off-Label Use of Atypical Antipsychotics: An Update. Comparative Effectiveness Review No. 43.
Inclusion criteria:
"Only studies on humans were included. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. As single dose or short term trials (less than 6 weeks in length) are common for several of the new uses, we decided, at the TEP's suggestion, not to limit inclusion by study duration."
Search strategy:
"We conducted an initial update search on June 1, 2008, as part of a project to determine if Comparative Effectiveness Reviews (CERs) funded by AHRQ needed updating; this search included only the drugs aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Regular update searches continued through May 2011. The search for off-label use of the newly approved atypicals (iloperidone, paliperidone and asenapine) included all years available in the electronic databases through May 2011."

"Databases searched include: DARE (Database of Abstracts of Reviews of Effects), Cochrane Database of Systematic Reviews, CENTRAL (Cochrane Central Register of Controlled Trials), PubMed (National Library of Medicine, includes MEDLINE), Embase (biomedical and pharmacological bibliographic database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), and PsycINFO."

"Other sources of literature include clinicaltrials.gov, references of included studies, references of relevant reviews, and personal files from related topic projects. In addition, the AHRQ Effective Health Care Program Scientific Resource Center (SRC) at Oregon Health Sciences University requested unpublished studies from pharmaceutical manufacturers and searched the FDA and Health Canada databases."
Assessment of quality of included trials: yes, but seems incomplete
Other methodological remarks: /

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2011(6) Design: MA Search date: (May-2011)	Risperidone Vs Quetiapine	N= 2 n= 493 (Rainer 2007, Schneider 2006/Sultzer 2008)	Efficacy for overall BPSD	SMD -0.06 (95%CI: -0.55, 0.43); NS SMD -0.24 (95%CI: -0.53, 0.06); NS
		N= 1 n= 421 (Schneider 2006/Sultzer 2008)	Efficacy for psychosis	SMD -0.24 (95%CI: -0.54, 0.05); NS
		N= 2 n= 493 (Rainer 2007, Schneider 2006/Sultzer 2008)	Efficacy for agitation	SMD -0.17 (95%CI: -0.66, 0.32); NS SMD 0.10 (95%CI: -0.20, 0.39); NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (Risk of Bias Assessment)
Rainer 2007(53) Randomized, controlled trial; rater-blinded	72	55-85 years old, dementia, MMSE score 10-26, have an NPI part I score in subitems relating to delusions, hallucinations, agitation/aggression	8 weeks	Quetiapine 50-400 mg/day vs Risperidone 0.5-4 mg/day	<u>Data from Yunusa et al. 2019</u> -Sequence generation (selection bias): low risk -Allocation concealment (selection bias): low risk -Blinding of participants and personnel: (performance bias): unclear risk -Blinding of outcome assessment (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Overall risk of bias: medium risk <u>Data from AHRQ 2011</u> -Jadad score: 3 -Funding: Industry -Blinding: care provider and patients were not masked. -Withdrawals: 10.5% vs 8.8% -Withdrawals due to AE's: 5.3% vs 2.9% -ITT analysis: yes

Schneider 2006(37)/Sultzer 2008(38) Randomized, controlled, double blind trial	421	AD or probable AD, MMSE 5-26, psychosis, aggression, or agitation previous week or at least intermittently for 4 weeks, had a severity rating of at least "moderate" for conceptual disorganization, suspiciousness, or hallucinatory behavior on BPRS, ambulatory and living at home or in an assisted-living facility	12 weeks	Placebo vs Olanzapine 5.5mg/day vs Quetiapine 56.5 mg/day vs Risperidone 1.0 mg/day	<u>Data from Yunusa et al. 2019</u> -Sequence generation (selection bias): low risk -Allocation concealment (selection bias): low risk -Blinding of participants and personnel: (performance bias): low risk -Blinding of outcome assessment (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Overall risk of bias: low risk <u>Data from AHRQ 2011</u> -Jadad score: 1 -Funding: Government -Single blind, patient -No similar groups at baseline -Outcome assessor not masked -dropout rate with reason not described; but acceptable dropout rate. -ITT analysis: yes

<u>Remarks:</u> /

<u>Author's conclusions:</u>

"Three head to head trials compared atypicals; none was found superior."

11.11 Discontinuation of antipsychotics in patients with BPSD

Antipsychotic withdrawal strategy versus continuation of antipsychotics

Meta-analysis: Van Leeuwen 2018(56), Cochrane review, Withdrawal versus continuation of long-term antipsychotic drug use for behavioural and psychological symptoms in older people with dementia.

Inclusion criteria: Randomized, controlled trials comparing an antipsychotic withdrawal strategy to continuation of antipsychotics in older people (> 65 years of age) with dementia living in the community or in nursing homes and and treated with an antipsychotic drug at fixed dose for at least three months.

Search strategy: Specialized Register of the Cochrane Dementia and Cognitive Improvement Group (ALOIS), the Cochrane Library, MEDLINE, Embase, PsycINFO, CINAHL, LILACS, clinical trials registries and grey literature sources were searched up to 11 January 2018.

Assessment of quality of included trials: yes using GRADE

ITT analysis: ITT analyses used where possible

Other methodological remarks: Trials that did not report comparable outcomes were considered
clinically heterogeneous and results were not pooled in meta-analysis. In this case, we performed critical interpretive synthesis of data from individual studies.

Ref	Comparison	N/n	Outcomes	Result
Van Leeuwen 2018 MA	withdraw from antipsychotics vs continuation of antipsychotics	N= 9 n= 575 (Ballard 2004, Ballard 2008, Bergh 2011,	Success of withdrawal over short-term (≤ 4 weeks) and long-term (> 4 weeks) follow-up (number of non-completers).	Ballard 2008: **Discontinuation (total number of participants):** 45/82 (56%) vs 43/83 (51%), NS Ballard 2004: **Discontinuation (total number of participants):**

Search date: Jan- 2018		Bridges-Parlet 1997, Devanand 2011, Devanand 2012, Findlay 1989, van Reekum 2002, Ruths 2008)		14/46 (30%) vs 14/54 (26%), p = 0.62, NS Discontinuation (behavioral deterioration): 6/46 vs 5/54, p = 0.55, NS Bergh 2011: **Dropout rate:** 7/9 vs 0/10 Bridges-Parlet 1997: **Discontinuation (total number of participants):** 2/22 (9%) vs 0/14 **Successful completion:** $Chi^2 > 0.05$, NS Devanand 2011: **Drop out due to symptomatic relapse:** 8/10 (80%) vs 4/10 (40%) **Relapse rates:** $Chi^2 = 3.3$, P = 0.07, NS **Time to relapse:** 5.8 weeks (SD 6.7) vs 8.0 weeks (SD 6.7), $Chi^2 = 4.1$, P = 0.04 **SS in favour of continuation .** Devanand 2012: **Drop out (total number of participants):** first 16 weeks : 27/40 vs 30/70 **Drop out due to symptomatic relapse:** first 16 weeks: 24/40 (60%) vs 23/70 (33%), HR 1.94 (95% CI 1.09 to 3.45), P = 0.02, **SS in favour of continuation** 16 following weeks: 13/27 (48%) vs 2/13 (15%) HR 4.88 (95%CI 1.08 to 21.98), P = 0.02, **SS in favour of continuation** **Relapse rate:** first 16 weeks: 6.5 % vs 3.0 % 16 following weeks: 4.3% vs 1.1% Findlay 1989:

				No events found van Reekum 2002: **Discontinuation (total number of participants):** 10/17 vs 6/17 RR 1.57 (95%CI 0.76 to 3.26), NS **Discontinuation (behavioral deterioration):** 4/17 vs 3/17, p > 0.1, NS Ruths 2008: **Discontinuation (total number of participants):** 4/27 vs 3/28 (2 due to behavioural deterioration), p = 0.7, NS
		N = 7 n = 519 (Ballard 2004, Ballard 2008, Bergh 2011, Bridges-Parlet 1997, Devanand 2012, Ruths 2008, van Reekum 2002)	Behavioural and psychological Symptoms (agitation, aggression and psychotic symptoms)	Bergh 2011: **NPI-10 score :** -3.50 (SD 13.53) vs - 5.40 (SD10.78), p = 0.76, NS **depression (CSDD):** Deterioration of 5.83 points (SD 36.40) vs improvement of 5.30 points (SD 11.25), p = 0.375, NS Devanand 2012: NPI score was not reported Ruths 2008: **Stable or decreased NPI-Q scores:** 18/27 vs 24/28, P = 0.18, NS van Reekum 2002: NPI data not reported BEHAVE-AD (measuring behaviour) and ROAS (measuring physical aggression towards themselves or others), P > 0.05, NS **Apathy:** P = 0.04, **SS in favour of discontinuation** -"…not all of the study authors' conclusions were supported by data reported." Bridges-Parlet 1997: **physically aggressive behaviour:** 1.27 (SD 3.95) vs 4.50 (SD 8.83), P > 0.05, NS

		Pooled results (NPI to assess NPS): N=2 n=265 (194 reported events) (Ballard 2004, Ballard 2008)		Two studies used the NPI to assess NPS and were considered suitable to pool for meta-analysis: MD -1.49 (95% CI -5.39 to 2.40) NS
		N = 5 N = 381 (Ballard 2008, Bridges-Parlet 1997, Devanand 2012, Findlay 1989, van Reekum 2002)	Adverse events attributable to antipsychotics	Ballard 2008: **Parkinsonism:** 0.4 (SD 3.2) improvement vs 0.8 (SD 4.1) deterioration MD 1.1 (95% CI 0.4 to 2.6) (favouring placebo), P = 0.1, NS Bridges-Parlet 1997: 3 events (2 participants had behaviour deterioration and 1 had tardive dyskinesia) vs 0 Findlay 1989: …reported numerical data for mobility, range of mobility, transferring, response to chest pushing and balance and position sense, vibration sense, reading of a sway for the participants standing with eyes open, systolic and diastolic blood pressure and heart rate, lying and standing blood pressure and heart rate, the sum of the mobility outcomes, balance while standing, balance on turning head, balance on turning whole body through 360 °. Only means, ranges and numbers of observations were reported for each of these outcomes. The study authors concluded that discontinuation had no apparent effect on mental

				function, mobility or balance, and that the drugs had few side effects. van Reekum 2002: **Extrapyramidal signs**: Similarity on the assessment measures-data not reported Devanand 2012: see supplemental S table below: NS
		N = 2 n = 119 (Ballard 2004, Bergh 2011)	Quality of life	Ballard 2004: -0.18 (SD 1.72) vs 0.35 (SD 2.41), MD -0.53 (95% CI -1.42 to 0.36), NS Bergh 2011: No differences in QoL-AD -No data were provided
		N = 5 n= 365 (Ballard 2008, Devanand 2011, Devanand 2012, Findlay 1989, van Reekum2002)	Cognitive function (e.g. short-term memory, frontal executive function, language)	Ballard 2008: **FAS (verbal fluency):** 0.6 (SD 6.2) improvement vs 3.2 (SD 6.6) deterioration, MD -4.5 (95% CI -7.3 to -1.7), P = 0.002, **SS favouring discontinuation** **SIB (overall cognition**): deterioration of 5.7 (SD 14.2) vs deterioration of 6.2 (SD 16.0), MD -0.4, (95% CI -6.4 to 5.5), P = 0.9, NS **SMMSE (overall cognition):** deterioration of 1.0 (SD 4.2) vs deterioration of 1.8 (SD 3.6), MD -1 (95% CI -2.7 to 0.7), P = 0.2, NS **STALD (receptive language skills):** 0.3 (SD 2.1) deterioration vs 0.5 point (SD 1.7) deterioration, MD-0.2, (95% CI -1.1 to 0.6), P = 0.6, NS **STALD (expressive language skills):** 0.2 (SD 2.5) improvement vs 0.6 point (SD 1.8) deterioration, MD -1.0, (95% CI -2.0 to 0.04), P = 0.06, NS. Devanand 2011: Cognition (MMSE) did not differ - No data were provided. Devanand 2012:

				No evidence of a difference (MMSE, ADAS-cog, and Physical Self-Maintenance Scale) - Supporting data were not reported. Findlay 1989: No difference (CAS). Outcomes were reported as means with a range and number of observations. However, the difference between the discontinuation and continuation groups at baseline could have influenced the result. van Reekum 2002: No difference (MMSE and MDRS)-Data were not reported.
		N = 1 n= 36 Bridges-Parlet 1997	Use of physical restraint	No difference - No supporting data provided.
		N = 2 n= 275 (Ballard 2008, Devanand 2012)	Mortality	Ballard 2008: **Probability of survival:** first 12 months : 77% (95%CI 64%to 85%) vs 70% (95% CI 58% to 80%) 24 months : 71% vs 46% 36 months: 59% vs 30 % **reported as SS in favour of discontinuation-**not details reported Devanand 2012: 16 and 32 weeks, **number of death**: 1 vs 2
		Ruths 2008 N=1 n=30 (Subgroup analysis)	Time, in days, until prescription of any psychotropic agent except antipsychotics	Unchanged for all participants- no supporting data.
		N=4 n=329 (Ballard 2008, Devanand 2011,	Global functioning	Ballard 2008: **BADLS:** improvement of 0.2 (SD 7.2) vs improvement of 1.8 (SD 8.9) MD 1.7, (95% CI -1.2 to 4.6), P = 0.2, NS Devanand 2011:

		Devanand 2012, van Reekum 2002)		No evidence of a difference in BFAS - Supporting data were not reported Devanand 2012: No evidence of a difference in MMSE, ADAS-cog, and Physical Self-Maintenance Scale - Supporting data were not reported van Reekum 2002: No difference- Supporting data were not provided
		N=2 n= 66 (Bridges-Parlet 1997, Ruths 2008)	Sleep	Ruths 2008 : **Sleep efficiency :** 75% (i.e. 54 minutes less sleep) vs 86%, p = 0.29, NS Bridges-Parlet 1997 : No difference in time sleeping-No data were provided
		N=3 n=311 (Ballard 2008, Devanand 2012, Findlay 1989)	Clinical global impression	Ballard 2008: No evidence of differences (CGI-C) (P = 0.9) Findlay 1989 no difference: **SCAGS**: Authors' conclusions were not supported with extractable data. Devanand 2012: Assessment was not reported, no conclusions were made.

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as judged by Cochrane)
Ballard 2004(57) Doubled-blind	n=100	Care facility residents aged > 65 years, probable or possible Alzheimer's disease and no severe behavioural symptoms, taking neuroleptics for more than 3 months.	3 months	Abrupt discontinuation of antipsychotics. vs Continuing antipsychotics. No dose reduction of tapering.	-Random sequence generation (selection bias): unclear risk. Method of sequence generation is not reported - Allocation concealment (selection bias): unclear risk. Method of allocation concealment

		Discontinuation: Mean age 83.1 years (SD 7.1), M 11, F 35 Continuing: Mean age 83.6 years (SD 9.3), M 7 F 47			is not described. - Blinding (performance bias and detection bias) – All outcomes: Low risk. - Incomplete outcome data (attrition bias) – All outcomes: low risk. ITT - Selective reporting: low risk. - Other bias: low risk - Funding: Research into Aging and Age Concern.
Ballard 2008 (58) Randomized, double-blinded	n=165	Patient lived in a nursing or residential home, that fulfilled the NINCDS/ADRDA criteria for possible or probable Alzheimer's Disease, and having either a MMSE score > 6 or a Severe Battery Impairment score > 30. Patients were taking at least 10mg chlorpromazine equivalents of a typical neuroleptic or at least 0.5 mg daily of risperidone. Exclusion: person with any physical condition that would have made participation in the trial distressing, patient currently taking thioridazine and showing a prolonged QTc on electrocardiogram. Discontinuation : 84.9 years (SD 6.1), M 20, F 62 Continuation : 84.4 years (SD 7.0), M 19, F 64	12 months	Abrupt discontinuation of neuroleptics. vs Continuation of neuroleptics.	- Random sequence generation (selection bias): low risk. - Allocation concealment (selection bias): low risk. - Blinding (performance bias and detection bias)– All outcomes: low risk. - Incomplete outcome data (attrition bias) – All outcomes: low risk. ITT - Selective reporting: low risk. - Other bias: low risk. -Funding: possibly by the Alzheimer's Research Trust, Cambridge, UK.

Bergh 2011(59) Randomized, doubled blinded	n=19	Patient from nursing homes with clinical dementia rating 1, 2, or 3 (vascular or Alzheimer dementia, or mixed Alzheimer's disease/vascular Dementia) and given risperidone for 3 months or more. Discontinuation : 81.7 years, M 6, F 3 Continuation: 82.6 years, M 3, F7	25 weeks	Discontinuation of risperidone vs Continuation of risperidone For discontinuation risperidone was titrated out over one week. All kinds of concomitant therapy were allowed before, during and after the study.	- Random sequence generation (selection bias): low risk. - Allocation concealment (selection bias): low risk. - Blinding (performance bias and detection bias)– All outcomes: low risk. - Incomplete outcome data (attrition bias) – All outcomes: high risk. All randomised participants are described in the flowchart. Very high dropout and withdrawal in the discontinuation group (7/9) suggests high risk of bias. Dropouts were more frequent in the ApDG (7/9, 77.8%) than in the ApCG (0/10, 0.0%) (P = 0.001). The analysis was based on modified ITT. - Selective reporting: high risk. Protocol was registered in ClinicalTrials.gov, outcome measurements were not all reported as per protocol paper. Study is unpublished, no peer reviewing to valid results suggests high risk of bias - Other bias: low risk. Sponsor: InnlandetHospital Trust Unpublished study
Bridges-Parlet 1997(60)	n=36	Patient in long term care facilities with diagnosis of possible or	4 weeks	withdrawal of neuroleptics vs	- Random sequence generation (selection bias): low risk.

Doubled blinded		probable Alzheimer's dementia and receiving a stable dose of neuroleptic for 3 months. Discontinuation : 22 Continuation : 14 Exclusion: primary psychiatric diagnoses, mental retardation and terminal illness or other recent acute, changes in health status.		no withdrawal of neuroleptics Abrupt withdrawal or tapering of a neuroleptic when baseline dose exceeded the equivalent of 50 mg of chlorpromazine. The tapering was done by dropping the baseline neuroleptic dose by half during week 1 and then discontinuing the neuroleptic completely at the beginning of week 2.	- Allocation concealment (selection bias): unclear risk. Method of allocation concealment is not described, and may not have been blinded. Participant groups were well matched for age, chlorpromazine-equivalent neuroleptic dose and physically aggressive behaviour at baseline. - Blinding (performance bias and detection bias)– All outcomes: low risk. - Incomplete outcome data (attrition bias) – All outcomes: low risk. ITT - Selective reporting: low risk. - Other bias: low risk. -Funding: Research grant from the Alzheimer's Association
Devanand 2011(61) Randomized, doubled blinded discontinuation trial (phase B) following 20 weeks response to haloperidol open treatment (phase A)	n= 44, 20 in phase B	Patients aged 50 to 95 years with clinical diagnosis of dementia and probable Alzheimer's disease by NNCDS-ADRA criteria, having current symptoms of psychosis, agitation or aggression. Exclusion: acute unstable medical condition, delirium, alcohol or substance	6 months, 24 weeks discontinuation trial	Phase A: flexible doses of haloperidol 0.5 to 5mg daily were individually titrated to maximize therapeutic response. For responders, phase B: haloperidol continuation vs	- Random sequence generation (selection bias): unclear risk. Not described in the study. - Allocation concealment (selection bias): unclear risk. No description of the blinding of random allocation. - Blinding (performance bias and detection bias)– All outcomes: unclear risk. Blinding of outcome raters is

		abuse or dependence during the prior year, clinical evidence of stroke, other dementias including vascular or Lewy body or frontotemporal dementia, multiple sclerosis, Parkinson's disease, Huntington's disease, tardive dyskinesia, diagnosis of a psychotic disorder predating the onset of dementia, antipsychotic medication usage during the 4 weeks before study entry, and contra-indication to the use of haloperidol. Discontinuation: n=10 Continuation: n=10 Gender distribution : M 33% Mean age: 75 years (SD 8.0)		Placebo (i.e. discontinuation). There was a 2-week double-blind sequential placebo substitution.	not described.. - Incomplete outcome data (attrition bias) – All outcomes: low risk. ITT - Selective reporting: unclear risk. Several outcomes were measured at baseline of the open haloperidol treatment and at time of the discontinuation period, but no results were reported at later times of assessment. - Other bias: low risk. -Funding: study supported by NIH grant, authors had financial links with several pharmaceutical companies.
Devanand 2012(62) Randomized, double-blinded discontinuation trial (phase B) following response to 16 weeks risperidone open treatment (phase A)	n=180, 110 in phase B	outpatients or residents of nursing homes, aged 50 to 95 years that met the criteria for dementia and the criteria for probable Alzheimer's disease, a score on the Neuropsychiatric Inventory (NPI) of 4 or more at both psychosis score or agitation score. Exclusion: history of stroke, transient ischaemic attack, or uncontrolled atrial Fibrillation. Gender distribution : M 41 %	48 weeks, at least 6 months for discontinuation	Phase A: open-label treatment with flexible dose risperidone Phase B: for risperidone responders: continue risperidone vs continue risperidone for 16 weeks and then placebo vs discontinuation of antipsychotics	- Random sequence generation (selection bias): low risk - Allocation concealment (selection bias): low risk - Blinding (performance bias and detection bias)– All outcomes: low risk - Incomplete outcome data (attrition bias) – All outcomes: low risk - Selective reporting: unclear risk The results for the CGI-C were not reported in the study, the total NPI scores and the NPI core score were measured at baseline

		Mean age: 79.6 years (SD 7.6).		Concomitant treatment: stable doses of selective serotonin-reuptake inhibitors, low-dose trazodone or sedatives or hypnotic agents were permitted. Lorazepam, at a dose of 1 mg or less per day, was permitted if needed. Cholinesterase inhibitors and memantine at stable dose were permitted.	(phase A) and at time of randomisation (phase B), but no results were reported at later times of assessment. - Other bias: low risk -Funding: "...Johnson & Johnson, donated the risperidone tablets and matching placebo but had no role in the conduct of the study or the analysis or reporting of the data..."; Supported by NIH and the Department of Veterans Affairs. The first author received grants from several pharmaceutical companies.
Findlay 1989(63) Randomized, Double-blinded	n=36	Patient with senile dementia, Alzheimer type, receiving a stable dose of between 10 mg and 100 mg of thioridazine per day for at least 2 months. Exclusion: male, multi-infarct dementia and antipsychotic agents other than thioridazine. Gender distribution: 100% women Mean age: 65 years or older	4 weeks	Withdrawal of thioridazine vs Continuation of thioridazine	- Random sequence generation (selection bias): unclear risk Methods of sequence generation were not described. - Allocation concealment (selection bias): unclear risk. The randomisation process was not completely successful. - Blinding (performance bias and detection bias)– All outcomes: unclear risk. Study is described as double blinded, blinding of the outcome assessors

					is not described. Assessment was done by clinicians and nurses with psychiatric training. - Incomplete outcome data (attrition bias) – All outcomes: unclear risk. Information of dropouts is not reported in the study. - Selective reporting: unclear risk. Primary outcome is not described, it is unclear if a selection of measured outcomes was reported. - Other bias: unclear risk. The randomisation procedure unfortunately resulted in a baseline imbalance in 1 of the 3 cognitive/behavioural rating scales. The author noted: ”Difference represents an artefact of the randomisation process.“ It is unclear if this has had an impact on outcomes. -Funding: not reported
Ruths 2008(65) Randomized, Double-blinded	n=55	Patients aged 65 years and over, with diagnosed dementia, resident in nursing home for at least 3 months and taking antipsychotic for nonpsychotic symptoms for at least 3 months.	4 weeks	Abrupt discontinuation of antipsychotic. vs No discontinuation of antipsychotic medication.	- Random sequence generation (selection bias): low risk. - Allocation concealment (selection bias): unclear risk. Allocation concealment was provided central, no further details were reported.

		Exclusion: participants with antipsychotic use for a primary diagnosis of major psychotic disorder, mental retardation, terminal illness with life expectancy judged to be shorter than 3 months and recent major changes in health status. Discontinuation: mean age 83.6 years (SD 8.1), M 7, F 20 Continuation: mean age 84.6 years (SD 5.9), M 5, F 23			- Blinding (performance bias and detection bias)– All outcomes: unclear risk. Study is described as double blinded. Blinding of the assessment interviewers is not described. - Incomplete outcome data (attrition bias) – All outcomes: unclear risk. All 55 participants completed at least the week one evaluation were included in study analysis. No statistical difference in dropout between intervention and reference group. - Selective reporting: low risk. - Other bias: unclear risk. The selection of participants may have been biased. It is not clear if the participating nursing homes participants are different from non-participating nursing home patients. - Funding: not reported
van Reekum 2002(64) Randomized, Double-blinded	n=34	Patient residents of nursing home, having any form of dementia, receiving antipsychotics for 6 months or longer, stable behavior. Exclusion: history of antipsychotic discontinuation having failed within	26 weeks	Discontinuation antipsychotics vs Continuing antipsychotic 2 week dose reduction period by tapering	- Random sequence generation (selection bias): low risk. - Allocation concealment (selection bias): unclear risk. No reference made to the method in which allocation concealment was ensured.

		the past 6 months, a history of schizophrenia, antipsychotic use for nausea, diagnosis of delirium, a global rating scale of 3 on the BEHAVE-AD rating scale at the time of the screening, 1 week prior to the start of the study or within the 2 weeks of the pre-trial period. Discontinuation: mean age 84.4 years (SD 4;6), M 8, F 9. Continuation: mean age 82.9 years (SD 6.9) M 9, F 8.			- Blinding (performance bias and detection bias)– All outcomes: unclear risk. Blinding of the research team is not described. - Incomplete outcome data (attrition bias) – All outcomes: low risk. ITT - Selective reporting: high risk. Some data of the continuation and the discontinuation group for several outcomes is not completely given in numerical results but only in descriptive figures. NPS assessed by NPI, aggression assessed by the ROAS, extrapyramidal signs assessed by the ESRS, cognitive functioning assessed by MMSE and functional outcome assessed by the BDS were not reported in the paper. - Other bias: low risk. - Funding: not reported

Remarks
- 10 RCTs with 632 participants were included. Nine studies were parallel-group RCTs. Data from one crossover RCT (Cohen-Mansfield 1999)(66) could not be used since outcome data were not reported separately for the different medications discontinued (benzodiazepine as well as antipsychotics). - For most of the outcomes authors were unable to pool data due to the clinical heterogeneity of the studies, and considerable discrepancies in the ways outcomes were measured. Pooling was only possible for behavioural outcomes assessed by neuropsychiatric inventory score (NPI). - The included studies used different antipsychotics at different dosages. Antipsychotics used were thioridazine, chlorpromazine, haloperidol, trifluoperazine, risperidone or olanzapine. Trifluoperazine, chlorpromazine and thioridazine are not or not anymore available in Belgium. They are associated to FGAs and we decided to not exclude them from studies. Baseline dosage regimen were classified as according to the dosage table proposed by Ballard 2008 (e.g. risperidone: 0.5mg 1x/d is very low, 0.5mg 2x/d is low, and 1mg 2x/dis high; haloperidol 0.75 mg 1x/d is very low, 0.75 mg 2x/d is low, and 1.5 mg 2x/d is high; chlorpromazine 12.5 mg 1x/d is very low, 12.5 mg 2x/d is low and 25 mg 2x /d is high). - At baseline, participants in most of the studies were described as having moderate to severe dementia, measured with a variety of methods and a variety of methods were used to measure baseline cognitive severity. Studies used either abrupt, tapered or mixed withdrawal schedules. The duration of follow-up in trials also varied considerably in different studies from 1 (Ballard 2008) to 36 months (Ballard 2011). - Participants' average age was 80 years or over in most studies and Findlay 1989 recruited only female participants. - Success of withdrawal was defined as the ability to complete the study (i.e. no dropout due to worsening of neuropsychiatric symptoms (NPS) or no relapse to antipsychotic drugs use during the trial). This was not reported in any of the included studies. Therefore authors used the difference between groups in the number of non-completers of the study as a proxy for our primary outcome. Behavioural and psychological symptoms was measured with NPI and NPI-Q score or with other scales such as the primary endpoint changes in Cornell Scale for Depression in Dementia (CSDD), physically aggressive behaviour scale, Brief Psychiatric Rating Scale or BEHAVE-AD (Behavioural Pathology in Alzheimer's disease Rating Scale). - Subgroup analyses of Ballard 2004 and Ballard 2008 on behavioural and psychological symptoms suggested that the effect of antipsychotic discontinuation may differ depending on the severity of NPS at baseline. It was suggested that some participants with less severe NPS (NPI score ≤ 14) may benefit from discontinuation of antipsychotics in terms of agitation while some participants with more severe NPS (total NPI > 14) may benefit from continuing antipsychotic treatment. - Total adverse events likely to be related to antipsychotic use were not systematically reported in the included studies. Different adverse effects were evaluated in different studies. Studies reported only a selection of adverse events such as parkinsonism, movement disorders, falls, mobility, balance,

extrapyramidal symptoms, heart rate and blood pressure. In Devanand 2012 all adverse events were individually reported (expanded version of this table was provided in supplemental table below).

- Authors also intended to investigate presence or absence of withdrawal symptoms/syndrome in the first four weeks. However, none of the studies assessed these specific outcomes.

Author's conclusions

- "There is low-quality evidence that antipsychotics may be successfully discontinued in older people with dementia and NPS who have been taking antipsychotics for at least three months, and that discontinuation may have little or no important effect on behavioural and psychological symptoms. There may be benefits especially for those with milder NPS. There may be people with more severe symptoms who benefit from continuing treatment, but more research in people with both milder and more severe NPS is needed to be sure about this."

- "Discontinuation may have little or no effect on overall cognitive function."; "Discontinuation may make no difference to adverse events and quality of life. "

- "Based on the trials in this review, we are uncertain whether discontinuation of antipsychotics leads to a decrease in mortality."

- "More studies focusing on different methods of withdrawal are needed to provide the evidence base for clinical recommendations. "

Table S2. Adverse events in the total sample, responders and non-responders in Phase A, and sub-groups in Phase B.

Adverse Events number (%)	Phase A: 0-16 weeks			Phase B: 16-48 weeks				
	Total (n=180)	Resp (n=112)	Nonresp (n=68)	R wk 16-32 (n=70)	P wk 16-32 (n=40)	R-R wk 32-48 (n=13)	R-P wk 32-48 (n=27)	P-P wk 32-48 (n=13)
†Serious Adverse Events								
Deaths	3 (2)	0 (0)	3 (4)	1 (1)	1 (3)	1 (8)	0 (0)	0 (0)
Cardiovascular	5 (3)	2 (2)	3 (4)	1 (1)	1 (3)	1 (8)	0 (0)	0 (0)
Neurological	5 (3)	3 (3)	2 (3)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
Agitation/aggression	2 (1)	1 (1)	1 (1)	0 (0)	2 (5)	0 (0)	0 (0)	0 (0)
Pulmonary	2 (1)	1 (1)	1 (1)	1 (1)	1 (3)	0 (0)	0 (0)	0 (0)
Falls, fractures	3 (2)	1 (1)	2 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	5 (3)	1 (1)	4 (6)	2 (3)	2 (5)	0 (0)	0 (0)	0 (0)
*Adverse Events								
Extrapyramidal signs	30 (17)	20 (18)	10 (15)	13 (19)	4 (10)	4 (31)	4 (15)	2 (15)
Akathisia/restlessness	12 (7)	9 (8)	3 (4)	4 (6)	6 (15)	1 (8)	3 (11)	1 (8)
Sedation	20 (11)	14 (13)	6 (9)	7 (10)	5 (13)	1 (8)	1 (4)	1 (8)
Insomnia	4 (2)	5 (5)	5 (7)	3 (4)	1 (3)	0 (0)	1 (4)	0 (0)
Dizziness	4 (2)	2 (2)	2 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Headache	2 (1)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Confusion	11 (6)	5 (5)	6 (9)	4 (7)	4 (10)	1 (8)	3 (11)	1 (8)
Agitation/aggression	8 (4)	4 (4)	4 (6)	1 (1)	1 (3)	0 (0)	1 (4)	1 (8)
Fatigue/weakness	3 (2)	1 (1)	2 (3)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Falls	10 (6)	5 (5)	5 (7)	2 (3)	1 (3)	0 (0)	0 (0)	0 (0)
Chest pain/vascular	4 (2)	2 (2)	2 (3)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Respiratory	2 (1)	1 (1)	1 (1)	2 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Urinary tract infection	2 (1)	1 (1)	1 (1)	3 (4)	1 (3)	0 (0)	0 (0)	0 (0)
Urinary incontinence	2 (1)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Infection of extremity	1 (0.5)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Nausea/vomiting	11 (6)	8 (8)	3 (4)	2 (3)	2 (5)	2 (15)	0 (0)	1 (8)
Constipation	3 (2)	2 (2)	1 (1)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
Weight gain	2 (1)	1 (1)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Dermatitis	1 (1)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Other	11 (6)	8 (8)	3 (4)	3 (4)	1 (3)	0 (0)	1 (4)	1 (8)

Column headings: Resp: responder, Nonresp: Nonresponder, R: risperidone, P: placebo, R-R: risperidone followed by risperidone cell with data on risperidone weeks 32-48, R-P: risperidone followed by placebo cell with data on placebo weeks 32-48, P-P placebo followed by placebo cell with data on placebo weeks 32-48. The number in parentheses is the percent (nearest integer) for that group.

† A serious adverse event was any adverse drug-related event that resulted in any of the following outcomes: death, a life-threatening condition, hospital admission or prolongation of a hospital stay, an unexpected event leading to clinically significant disability or incapacity. The classification of an adverse event as severe was based on the judgment of the investigator and study medical monitor.

*An adverse event was either (1) report of a clinically significant new adverse event, or (2) worsening from baseline in a symptom to a moderate or severe level rating on the Treatment Emergent Symptoms Scale (TESS). On the Simpson-Angus Extrapyramidal Signs Scale, extrapyramidal signs were rated as an adverse event if there was an average increase of 1 or more (mild symptoms, range 0-4) on the scale compared to baseline, and akathisia/restlessness was rated as an adverse event if there was an increase of 1 or more (range 0-4) on the akathisia/restlessness item on the Simpson-Angus Scale compared to baseline.

12 Appendix. Evidence tables: BPSD - CVA

12.1 SGA versus placebo for BPSD: CVA

Meta-analysis:
The efficacy and safety of atypical antipsychotics for the treatment of dementia: a meta-analysis of randomized placebo-controlled trials
Inclusion criteria:
"Only studies on humans were included. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. As single dose or short term trials (less than 6 weeks in length) are common for several of the new uses, we decided, at the TEP's suggestion, not to limit inclusion by study duration."
Search strategy:
"Our search included MEDLINE, PsychINFO, and the Cochrane Central Register of ControlledTrials. Primary search terms were "dementia", "psychological, psychiatric, or behavioral symptoms", "double-blind","placebo", "random", together with one of the following terms: "atypical antipsychotic", "quetiapine",
"aripiprazole", "risperidone", "olanzapine", "amisulpride", or "ziprasidone". Moreover, the references of the included studies as well as previously-published reviews and meta-analytic papers satisfying our selection criteria (see below) were checked manually for additional relevant articles. All the articles have been published as of June 2013, and written in English. The trials presented at meetings but not published were not included. At the same time, trials, in which drugs were administrated by intramuscular injection and effect evaluations were immediate (several hours post-treatment), were also excluded."
Assessment of quality of included trials: yes
Other methodological remarks: /

Ref	Comparison	N/n	Outcomes	Result
Ma 2014 ref* Design: MA	Aripiprazole Vs Placebo	N= 3 n= 951 (De Deyn 2005,Mintzer 2007, Streim 2008)	CVA	8/603 vs 2/348 OR 1.58 (95%CI: 0.38, 6.55) I^2= 0% NS
	Olanzapine	N= 2	CVA	7/304 vs 1/236

Search date: (Jun-2013)	Vs Placebo	n= 540 (Deberdt 2005, Schneider 2006)		OR 3.93 (95%CI: 0.62, 25.10) I^2= 0% NS
	Quetiapine Vs Placebo	N= 3 n= 759 (Schneider 2006 (Tariot 2006, Zhong 2007)	CVA	4/426 vs 5/333 OR 0.65 (95%CI: 0.16, 2.58) I^2= 0% NS
	Risperidone Vs Placebo	N= 4 n= 1327 (Brodaty 2003, Deberdt 2005, Mintzer 2006, Schneider 2006)	CVA	24/683 vs 5/644 OR 4.53 (95%CI: 1.75, 11.72) I^2=0% **SS in favour of risperidone**
	SGA (aripiprazole, olanzapine, quetiapine, risperidone) Vs placebo	N= 9 n= 3577 (Brodaty 2003, De Deyn 2005, Deberdt 2005, Mintzer 2007, Schneider 2006, Tariot 2006, Mintzer 2006, Zhong 2007, Streim 2008)	CVA	43/2016 vs 13/1561 OR 2.50 (95%CI: 1.36, 4.60) I^2= 0% **SS in favour of SGA**

Remarks:

-Ma 2014 contained more detailed information in their meta-analyses for adverse events than AHRQ 2011 and was therefore used in this evaluation.

-All included studies in the analysis for adverse events were included in AHRQ 2011. For the characteristics of the here mentioned studies, see the tables for efficacy analyses from AHRQ 2011.

Author's conclusions:

"The higher risks for AEs and mortality may offset the efficacy of atypical antipsychotics for treatment of dementia. Efficacy, safety, and tolerability thus should be carefully considered against clinical need."

"In total, 2.1%of patients in the pooled drug group experienced CVAEs compared to 0.8%(0.9%after duplicate correction) in the pooled control group. There was no evidence of overall heterogeneity across these 12 available comparisons from 9 studies ($\chi 2 = 8.33$, $p = 0.68$, $I2 = 0\%$). Meta-analysis demonstrated a significantly higher risk of CVAEs in the pooled antipsychotic group (OR= 2.50, 95% CI: 1.36–4.60, $p = 0.003$) and in the risperidone subgroup ($p = 0.002$)."

12.2 SGA versus haloperidol for BPSD: CVA

Meta-analysis:
AHRQ 2011: Maglione M, Ruelaz Maher A, Hu J, et al. Off-Label Use of Atypical Antipsychotics: An Update. Comparative Effectiveness Review No. 43.
Inclusion criteria:
"Only studies on humans were included. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. As single dose or short term trials (less than 6 weeks in length) are common for several of the new uses, we decided, at the TEP's suggestion, not to limit inclusion by study duration."
Search strategy:
"We conducted an initial update search on June 1, 2008, as part of a project to determine if Comparative Effectiveness Reviews (CERs) funded by AHRQ needed updating; this search included only the drugs aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Regular update searches continued through May 2011. The search for off-label use of the newly approved atypicals (iloperidone, paliperidone and asenapine) included all years available in the electronic databases through May 2011."

"Databases searched include: DARE (Database of Abstracts of Reviews of Effects), Cochrane Database of Systematic Reviews, CENTRAL (Cochrane Central Register of Controlled Trials), PubMed (National Library of Medicine, includes MEDLINE), Embase (biomedical and pharmacological bibliographic database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), and PsycINFO."
"Other sources of literature include clinicaltrials.gov, references of included studies, references of relevant reviews, and personal files from related topic projects. In addition, the AHRQ Effective Health Care Program Scientific Resource Center (SRC) at Oregon Health Sciences University requested unpublished studies from pharmaceutical manufacturers and searched the FDA and Health Canada databases."
Assessment of quality of included trials: yes
Other methodological remarks: "For reporting the data on adverse events, we treated each atypical antipsychotic separately and (in general) did not group them together as a class. However, we did summarize the findings of other published analyses that treated these drugs as a class."

Remarks: the AHRQ 2011 found no studies comparing SGA with FGA for the risk of CVA in patients with dementia.

12.3 SGA versus SGA for BPSD: CVA

Meta-analysis:
AHRQ 2011 AHRQ 2011(6) - Maglione M, Ruelaz Maher A, Hu J, et al. Off-Label Use of Atypical Antipsychotics: An Update. Comparative Effectiveness Review No. 43.
Inclusion criteria:
"Only studies on humans were included. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. As single dose or short term trials (less than 6 weeks in length) are common for several of the new uses, we decided, at the TEP's suggestion, not to limit inclusion by study duration."
Search strategy:
"We conducted an initial update search on June 1, 2008, as part of a project to determine if Comparative Effectiveness Reviews (CERs) funded by AHRQ needed updating; this search included only the drugs aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Regular update searches continued through May 2011. The search for off-label use of the newly approved atypicals (iloperidone, paliperidone and asenapine) included all years available in the electronic databases through May 2011."

"Databases searched include: DARE (Database of Abstracts of Reviews of Effects), Cochrane Database of Systematic Reviews, CENTRAL (Cochrane Central Register of Controlled Trials), PubMed (National Library of Medicine, includes MEDLINE), Embase (biomedical and pharmacological bibliographic database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), and PsycINFO."
"Other sources of literature include clinicaltrials.gov, references of included studies, references of relevant reviews, and personal files from related topic projects. In addition, the AHRQ Effective Health Care Program Scientific Resource Center (SRC) at Oregon Health Sciences University requested unpublished studies from pharmaceutical manufacturers and searched the FDA and Health Canada databases."
Assessment of quality of included trials: yes
Other methodological remarks: "For reporting the data on adverse events, we treated each atypical antipsychotic separately and (in general) did not group them together as a class. However, we did summarize the findings of other published analyses that treated these drugs as a class."

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2011 AHRQ 2011(6) Design: MA Search date: (May -2011)	Risperidone Vs Olanzapine	N= 2 n= 224 (Deberdt 2005, Schneider 2006/Sultzer 2008)	CVA	2/104 vs 4/120 OR 1.75 (95%CI: 0.05, 10.48) NS
	Risperidone Vs Quetiapine	N= 2 n= 251 (Rainer 2007, Schneider 2006/Sultzer 2008)	CVA	2/119 vs 2/132 OR 0.90 (95%CI: 0.06, 12.71) NS

Remarks:

-Characteristics of the included studies and risk of bias assessment can be found in the sections evaluating efficacy of SGA versus SGA.

13 Appendix. Evidence tables: BPSD - mortality

13.1 SGA versus placebo for BPSD: mortality

Meta-analysis:
Yeh TC 2019(54)
Mortality Risk of Atypical Antipsychotics for Behavioral and Psychological Symptoms of Dementia: A Meta-Analysis, Meta-Regression, and Trial Sequential Analysis of Randomized Controlled Trials.
Inclusion criteria:
"(1) dementia diagnosis, (2) AAP use, (3) placebo-controlled RCT, and (4) data sets not overlapping with those of other studies. When patients from two articles overlapped, we included only the article with the larger sample size."
Search strategy:
"Two authors searched for RCTs in electronic databases, namely PubMed, Embase, MEDLINE, the Cochrane Library, PsycINFO, ClinicalTrials.gov, and the World Health Organization's International Clinical Trials Registry Platform, from database inception to May 31, 2018. ClinicalTrials. gov was searched specifically to identify unpublished and ongoing studies."
Assessment of quality of included trials: yes
Other methodological remarks: /

Ref	Comparison	N/n	Outcomes	Result
Yeh TC 2019(54) Design: MA of RCT's Search date:	Aripiprazole Vs Placebo	N= 3 n= 921 (De Deyn 2005, Mintzer 2007, Streim 2008)	Mortality	OR 1.649 (0.644, 4.225); p=0.297 NS
	Olanzapine Vs Placebo	N= 3 n= 1096 (Satterlee 1995, Street 2000, De Deyn 2004)	Mortality	OR 1.919 (0.660, 5.582); p=0.232 NS

(May 31-2018)	Quetiapine Vs Placebo	N= 3 n= 710 (Ballard 2005, Tariot 2006, Zhong 2007)	Mortality	OR 1.663 (0.674, 4.102); p=0.270 NS
	Risperidone Vs Placebo	N= 6 n= 1721 (De Deyn 1999, Katz 1999, Brodaty 2003, Mintzer 2006, RIS-BEL-14, RIS-INT-83)	Mortality	OR 1.354 (0.757, 2.422); p=0.307 NS
	SGA (aripiprazole, olanzapine, quetiapine, risperidone) Vs Placebo	N= 15 n= 4448 (De Deyn 2005, Mintzer 2007, Streim 2008, Satterlee 1995, street 2000, De Deyn 2004, Ballard 2005, Tariot 2006, Zhong 2007, De Deyn 1999, Katz 1999, Brodaty 2003, Mintzer 2006, RIS-BEL-14, RIS-INT-83)	Mortality	OR 1.536 (1.028, 2.296); p=0.036 **SS in favour of SGA**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (Risk of Bias Assessment as judged by Yeh 2019)
De Deyn 2005(31) Double blind, randomized	208	AD with BPSD Setting: Outpatient	10 weeks	Aripiprazole = 106 vs Placebo = 102	-Random sequence generation (selection bias): unclear risk -Allocation concealment (selection bias): unclear risk -Blinding of participants and personnel: (performance bias): unclear risk -Blinding of outcome data (detection bias): low risk -Incomplete outcome data (attrition bias): unclear risk -Selective outcome reporting (reporting bias): low risk -Other bias: low risk -Overall ROB: Unclear risk
Mintzer 2007(30) Double blind, randomized	457	AD with BPSD Setting: Nursing home	10 weeks	Aripiprazole = 336 vs Placebo = 121	-Random sequence generation (selection bias): unclear risk -Allocation concealment (selection bias): unclear risk -Blinding of participants and personnel: (performance bias): unclear risk -Blinding of outcome data (detection bias): low risk -Incomplete outcome data (attrition bias): low risk

					-Selective outcome reporting (reporting bias): low risk -Other bias: low risk -Overall ROB: Unclear risk
Streim 2008(33) Double blind, randomized	256	AD with BPSD Setting: Nursing home	10 weeks	Aripiprazole = 131 vs Placebo = 125	-Random sequence generation (selection bias): unclear risk -Allocation concealment (selection bias): unclear risk -Blinding of participants and personnel: (performance bias): unclear risk -Blinding of outcome data (detection bias): low risk -Incomplete outcome data (attrition bias): high risk -Selective outcome reporting (reporting bias): low risk -Other bias: low risk -Overall ROB: High risk
Satterlee 1995(55) Double blind, randomized	238	AD with BPSD Setting: Outpatient	8 weeks	Olanzapine = 120 vs Placebo = 118	-Random sequence generation (selection bias): unclear risk -Allocation concealment (selection bias): unclear risk -Blinding of participants and personnel: (performance bias): unclear risk -Blinding of outcome data (detection bias): unclear risk -Incomplete outcome data (attrition bias): unclear risk -Selective outcome reporting (reporting bias): unclear risk -Other bias: unclear risk

					-Overall ROB: unclear risk
Street 2000(39) Double blind, randomized	206	AD with BPSD Setting: Nursing home	6 weeks	Olanzapine = 159 vs Placebo = 47	-Random sequence generation (selection bias): low risk -Allocation concealment (selection bias): unclear risk -Blinding of participants and personnel: (performance bias): low risk -Blinding of outcome data (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Other bias: low risk -Overall ROB: High risk
De Deyn 2004(34) Double blind, randomized	652	AD with BPSD Setting: Nursing home	10 weeks	Olanzapine = 523 vs Placebo = 129	-Random sequence generation (selection bias): unclear risk -Allocation concealment (selection bias): unclear risk -Blinding of participants and personnel: (performance bias): unclear risk -Blinding of outcome data (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Other bias: unclear risk -Overall ROB: High risk
Ballard 2005(40)	93	AD with agitation	26 weeks	Quetiapine = 31 vs	-Random sequence generation (selection bias): low risk

Double blind, randomized		Setting: Nursing home		Rivastigmine = 31 vs Placebo = 31	-Allocation concealment (selection bias): low risk -Blinding of participants and personnel: (performance bias): unclear risk -Blinding of outcome data (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Other bias: low risk -Overall ROB: Unclear risk
Tariot 2006(42) Double blind, randomized	284	Mixed dementia with BPSD (AD or VD) Setting: Nursing home	10 weeks	Haloperidol = 94 vs Quetiapine = 91 vs Placebo = 99	-Random sequence generation (selection bias): unclear risk -Allocation concealment (selection bias): unclear risk -Blinding of participants and personnel: (performance bias): low risk -Blinding of outcome data (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Other bias: low risk -Overall ROB: Unclear risk
Kurlan 2007(19) Double blind, randomized	40	DLB, PD with dementia, AD with parkinsonian features Setting: At home or nursing home	10 weeks	Quetiapine = 20 vs Placebo = 20	This study, not meeting our inclusion criterion for population (exclusion: parkinsonian features), reported zero mortality and was excluded from the meta-analysis.

Zhong 2007(44) Double blind, randomized	333	Mixed dementia with BPSD and Aggression (AD or VD) Setting: Nursing home	10 weeks	Quetiapine = 241 vs Placebo = 92	-Random sequence generation (selection bias): low risk -Allocation concealment (selection bias): low risk -Blinding of participants and personnel: (performance bias): low risk -Blinding of outcome data (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Other bias: low risk -Overall ROB: low risk
Paleacu 2008 Paleacu 2008(41) Double blind, Randomized	40	AD with BPSD Setting: not available	6 weeks	Quetiapine = 20 vs Placebo = 20	This study reported zero mortality and was excluded from the meta-analysis.
De Deyn 1999(47) Double blind, randomized	229	Mixed dementia, with BPSD and Aggression (AD or VD) Setting: Nursing home	12 weeks	Risperidone = 115 vs Placebo = 114	-Random sequence generation (selection bias): unclear risk -Allocation concealment (selection bias): unclear risk -Blinding of participants and personnel: (performance bias): unclear risk -Blinding of outcome data (detection bias): low risk -Incomplete outcome data (attrition bias): low risk

					-Selective outcome reporting (reporting bias): low risk -Other bias: low risk -Overall ROB: Unclear risk
Katz 1999(48) Double blind, randomized	625	Mixed dementia, with BPSD and Aggression (AD or VD) Setting: Nursing home	12 weels	Risperidone = 462 vs Placebo = 163	-Random sequence generation (selection bias): unclear risk -Allocation concealment (selection bias): unclear risk -Blinding of participants and personnel: (performance bias): low risk -Blinding of outcome data (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Other bias: low risk -Overall ROB: Unclear risk
Brodaty 2003(45) Double blind, randomized	337	Mixed dementia, with BPSD and Aggression (AD or VD) Setting: Nursing home	12 weeks	Risperidone = 167 vs Placebo = 170	-Random sequence generation (selection bias): unclear risk -Allocation concealment (selection bias): unclear risk -Blinding of participants and personnel: (performance bias): unclear risk -Blinding of outcome data (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Other bias: low risk

					-Overall ROB: Unclear risk
Mintzer 2006(49) Double blind, randomized	473	AD with BPSD Setting: Nursing home	8 weeks	Risperidone = 235 vs Placebo = 238	-Random sequence generation (selection bias): unclear risk -Allocation concealment (selection bias): low risk -Blinding of participants and personnel: (performance bias): low risk -Blinding of outcome data (detection bias): low risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): low risk -Other bias: low risk -Overall ROB: Unclear risk
RIS-BEL-14 (1993) (Unpublished) Double blind, randomized	39	AD with BPSD Setting: not available	4 weeks	Risperidone = 20 vs Placebo = 19	-Random sequence generation (selection bias): unclear risk -Allocation concealment (selection bias): unclear risk -Blinding of participants and personnel: (performance bias): unclear risk -Blinding of outcome data (detection bias): unclear risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): unclear risk -Other bias: unclear risk -Overall ROB: Unclear risk
RIS-INT-83 (2001) (Unpublished)	18	AD with BPSD	8 weeks	Risperidone = 10 vs	-Random sequence generation (selection bias): unclear risk

Double blind, randomized		Setting: not available		Placebo = 8	-Allocation concealment (selection bias): unclear risk -Blinding of participants and personnel: (performance bias): unclear risk -Blinding of outcome data (detection bias): unclear risk -Incomplete outcome data (attrition bias): low risk -Selective outcome reporting (reporting bias): unclear risk -Other bias: unclear risk -Overall ROB: Unclear risk

Remarks:

"Two studies (Kurlan 2007, Paleacu 2008) reported zero mortality in both arms and thus were excluded to prevent underestimation of harmful effects (Peto's method)."

Author's conclusions:

"Atypical antipsychotics are associated with increased short-term mortality risk, although a disease-drug interaction may contribute to such risk in people with dementia. Patients with dementia may still benefit by AAPs after appropriate assessment of the disease severity as well as the dosage of AAPs, treatment duration, and monitoring of AAPs."

13.2 SGA versus haloperidol for BPSD: mortality

Meta-analysis:
AHRQ 2011(6) - Maglione M, Ruelaz Maher A, Hu J, et al. Off-Label Use of Atypical Antipsychotics: An Update. Comparative Effectiveness Review No. 43.
Inclusion criteria:
"Only studies on humans were included. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. As single dose or short term trials (less than 6 weeks in length) are common for several of the new uses, we decided, at the TEP's suggestion, not to limit inclusion by study duration."
Search strategy:
"We conducted an initial update search on June 1, 2008, as part of a project to determine if Comparative Effectiveness Reviews (CERs) funded by AHRQ needed updating; this search included only the drugs aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Regular update searches continued through May 2011. The search for off-label use of the newly approved atypicals (iloperidone, paliperidone and asenapine) included all years available in the electronic databases through May 2011."

"Databases searched include: DARE (Database of Abstracts of Reviews of Effects), Cochrane Database of Systematic Reviews, CENTRAL (Cochrane Central Register of Controlled Trials), PubMed (National Library of Medicine, includes MEDLINE), Embase (biomedical and pharmacological bibliographic database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), and PsycINFO."
"Other sources of literature include clinicaltrials.gov, references of included studies, references of relevant reviews, and personal files from related topic projects. In addition, the AHRQ Effective Health Care Program Scientific Resource Center (SRC) at Oregon Health Sciences University requested unpublished studies from pharmaceutical manufacturers and searched the FDA and Health Canada databases."
Assessment of quality of included trials: yes
Other methodological remarks: "For reporting the data on adverse events, we treated each atypical antipsychotic separately and (in general) did not group them together as a class. However, we did summarize the findings of other published analyses that treated these drugs as a class."

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2011(6) Design: MA	FGA Vs Olanzapine	N= 1 n= 346 (Moretti 2005)	Mortality	6/173 vs 4/173 OR 0.66 (95%CI: 0.13, 2.84) NS

Search date: (May -2011)				

Remarks:

-Characteristics of the included studies and risk of bias assessment can be found in the sections evaluating efficacy of SGA versus haloperidol.

-The included study of Moretti 2005 did not meet our inclusion criterion for study type (open label). We decided to retain the results of this study for the outcome mortality. The studied FGA in the study of Moretti 2005(50) comprised of haloperidol or promazine.

-We observed slightly different absolute values in Moretti 2005(50) than in the analysis by the AHRQ 2011(6) analysis.

13.3 SGA versus SGA for BPSD: mortality

Meta-analysis:
AHRQ 2011(6) - Maglione M, Ruelaz Maher A, Hu J, et al. Off-Label Use of Atypical Antipsychotics: An Update. Comparative Effectiveness Review No. 43.
Inclusion criteria:
"Only studies on humans were included. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. As single dose or short term trials (less than 6 weeks in length) are common for several of the new uses, we decided, at the TEP's suggestion, not to limit inclusion by study duration."
Search strategy:
"We conducted an initial update search on June 1, 2008, as part of a project to determine if Comparative Effectiveness Reviews (CERs) funded by AHRQ needed updating; this search included only the drugs aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Regular update searches continued through May 2011. The search for off-label use of the newly approved atypicals (iloperidone, paliperidone and asenapine) included all years available in the electronic databases through May 2011."

"Databases searched include: DARE (Database of Abstracts of Reviews of Effects), Cochrane Database of Systematic Reviews, CENTRAL (Cochrane Central Register of Controlled Trials), PubMed (National Library of Medicine, includes MEDLINE), Embase (biomedical and pharmacological bibliographic database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), and PsycINFO."

"Other sources of literature include clinicaltrials.gov, references of included studies, references of relevant reviews, and personal files from related topic projects. In addition, the AHRQ Effective Health Care Program Scientific Resource Center (SRC) at Oregon Health Sciences University requested unpublished studies from pharmaceutical manufacturers and searched the FDA and Health Canada databases."
Assessment of quality of included trials: yes
Other methodological remarks: "For reporting the data on adverse events, we treated each atypical antipsychotic separately and (in general) did not group them together as a class. However, we did summarize the findings of other published analyses that treated these drugs as a class."

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2011(6) Design: MA Search date: (May - 2011)	Risperidone Vs Olanzapine	N= 1 n= 185 (Schneider 2006)	Mortality	1/85 vs 1/100 OR 0.85 (95%CI: 0.01, 67.39) NS
	Risperidone Vs Quetiapine	N= 2 n= 251 (Rainer 2007, Schneider 2006)	Mortality	1/119 vs 3/132 OR 2.75 (95%CI: 0.22, 147.08) NS

Remarks:

-Characteristics of the included studies and risk of bias assessment can be found in the sections evaluating efficacy of SGA versus placebo.

14 Appendix. Evidence tables: BPSD - EPS

14.1 SGA versus placebo for BPSD: extrapyramidal symptoms

Meta-analysis:
Ma 2014(23) - The efficacy and safety of atypical antipsychotics for the treatment of dementia: a meta-analysis of randomized placebo-controlled trials
Inclusion criteria:
"Only studies on humans were included. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. As single dose or short term trials (less than 6 weeks in length) are common for several of the new uses, we decided, at the TEP's suggestion, not to limit inclusion by study duration."
Search strategy:
"Our search included MEDLINE, PsychINFO, and the Cochrane Central Register of ControlledTrials. Primary search terms were "dementia", "psychological, psychiatric, or behavioral symptoms", "double-blind", "placebo", "random", together with one of the following terms: "atypical antipsychotic", "quetiapine",
"aripiprazole", "risperidone", "olanzapine", "amisulpride", or "ziprasidone". Moreover, the references of the included studies as well as previously-published reviews and meta-analytic papers satisfying our selection criteria (see below) were checked manually for additional relevant articles. All the articles have been published as of June 2013, and written in English. The trials presented at meetings but not published were not included. At the same time, trials, in which drugs were administrated by intramuscular injection and effect evaluations were immediate (several hours post-treatment), were also excluded."
Assessment of quality of included trials: yes
Other methodological remarks: /

Ref	Comparison	N/n	Outcomes	Result
Ma 2014(23) Design: MA	Aripiprazole Vs Placebo	N= 3 n= 951 (De Deyn 2005, Mintzer 2007, Streim 2008)	Extrapyramidal symptoms	39/603 vs 16/348 OR 1.29 (95%CI: 0.70, 2.40) I^2=0% NS
	Olanzapine Vs	N= 2 n= 540	Extrapyramidal symptoms	85/304 vs 29/236 OR 1.83 (95%CI: 1.13, 2.97)

Search date: (Jun -2013)	Placebo	(Deberdt 2005, Schneider 2006/Sultzer 2008)		I^2=85% **SS in favour of olanzapine**
	Quetiapine Vs Placebo	N= 4 n=799 (Paleacu 2008, Schneider 2006/Sultzer 2008, Tariot 2006, Zhong 2004/Zhong 2007)	Extrapyramidal symptoms	26/446 vs 23/353 OR 0.82 (95%CI: 0.45, 1.51) I^2=13% NS
	Risperidone Vs Placebo	N= 5 n= 2181 (Brodaty 2003/Brodaty 2005, Deberdt 2005, De Deyn 1999, Katz 1999, Mintzer 2006)	Extrapyramidal symptoms	247/1260 vs 89/921 OR 2.10 (95%CI: 1.59, 2.76) I^2=27% **SS in favour of risperidone**
	SGA (aripiprazole, olanzapine, quetiapine, risperidone) Vs placebo	N= 12 n= 4471 (De Deyn 2005, Mintzer 2007, Streim 2008, Deberdt 2005, Schneider 2006/Sultzer 2008, Paleacu	Extrapyramidal symptoms	397/2613 vs 157/1858 OR 1.74 (95%CI: 1.41, 2.14) I^2=40% **SS in favour of SGA**

		2008, Tariot 2006, Zhong 2004/Zhong 2007, Brodaty 2003/Brodaty 2005, De Deyn 1999, Katz 1999, Mintzer 2006,)		

Remarks:

Ma 2014 contained more detailed information in their meta-analyses for adverse events than AHRQ 2011 and was therefore used in this evaluation. All included studies in the analysis for adverse events were included in AHRQ 2011. For the characteristics of the here mentioned studies, see the tables for efficacy analyses from AHRQ 2011.

Author's conclusions:

"The higher risks for AEs and mortality may offset the efficacy of atypical antipsychotics for treatment of dementia. Efficacy, safety, and tolerability thus should be carefully considered against clinical need."

"Meta-analysis demonstrated that patients receiving SGAs showed a significantly higher risk for EPs compared to those receiving placebo (OR= 1.74, 95% CI: 1.41–2.14, $p < 0.00001$). Risk of EPs was significantly higher for olanzapine ($p = 0.01$) and risperidone ($p < 0.00001$) subgroups."

14.2 SGA versus haloperidol for BPSD: extrapyramidal symptoms

Meta-analysis:
AHRQ 2011(6) - Maglione M, Ruelaz Maher A, Hu J, et al. Off-Label Use of Atypical Antipsychotics: An Update. Comparative Effectiveness Review No. 43.
Inclusion criteria:
"Only studies on humans were included. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. As single dose or short term trials (less than 6 weeks in length) are common for several of the new uses, we decided, at the TEP's suggestion, not to limit inclusion by study duration."
Search strategy:
"We conducted an initial update search on June 1, 2008, as part of a project to determine if Comparative Effectiveness Reviews (CERs) funded by AHRQ needed updating; this search included only the drugs aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Regular update searches continued through May 2011. The search for off-label use of the newly approved atypicals (iloperidone, paliperidone and asenapine) included all years available in the electronic databases through May 2011."

"Databases searched include: DARE (Database of Abstracts of Reviews of Effects), Cochrane Database of Systematic Reviews, CENTRAL (Cochrane Central Register of Controlled Trials), PubMed (National Library of Medicine, includes MEDLINE), Embase (biomedical and pharmacological bibliographic database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), and PsycINFO."
"Other sources of literature include clinicaltrials.gov, references of included studies, references of relevant reviews, and personal files from related topic projects. In addition, the AHRQ Effective Health Care Program Scientific Resource Center (SRC) at Oregon Health Sciences University requested unpublished studies from pharmaceutical manufacturers and searched the FDA and Health Canada databases."
Assessment of quality of included trials: yes
Other methodological remarks: "For reporting the data on adverse events, we treated each atypical antipsychotic separately and (in general) did not group them together as a class. However, we did summarize the findings of other published analyses that treated these drugs as a class."

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2011(6) Design: MA	Olanzapine Vs FGA	N= 2 n= 98 (?Moretti 2005?, ?Verhey 2006?)	Extrapyramidal symptoms	24/48 vs 17/50 OR 0.37 (95%CI: 0.12, 1.10) NS
	Quetiapine	N= 1	Extrapyramidal symptoms	0/11 vs 2/11

Search date: (May -2011)	Vs Haloperidol	n= 22 (Savaskan 2006)		OR 0.00 (95%CI: 0.00, 5.24) NS
	Risperidone Vs FGA	N= 1 n= 40 (?De Deyn 1999?)	Extrapyramidal symptoms	4/20 vs 2/20 OR 0.23 (95%CI: 0.00, 2.65) NS

Remarks:

-Characteristics of the included studies and risk of bias assessment can be found in the sections evaluating efficacy of SGA versus haloperidol.

-References are not added in the AHRQ 2011 adverse events analysis. Therefore we could not always determine the link between the results of meta-analyses and all studies on which they were based on.

14.3 SGA versus SGA for BPSD: extrapyramidal symptoms

Meta-analysis:
AHRQ 2011(6) - Maglione M, Ruelaz Maher A, Hu J, et al. Off-Label Use of Atypical Antipsychotics: An Update. Comparative Effectiveness Review No. 43.
Inclusion criteria:
"Only studies on humans were included. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. As single dose or short term trials (less than 6 weeks in length) are common for several of the new uses, we decided, at the TEP's suggestion, not to limit inclusion by study duration."
Search strategy:
"We conducted an initial update search on June 1, 2008, as part of a project to determine if Comparative Effectiveness Reviews (CERs) funded by AHRQ needed updating; this search included only the drugs aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Regular update searches continued through May 2011. The search for off-label use of the newly approved atypicals (iloperidone, paliperidone and asenapine) included all years available in the electronic databases through May 2011."

"Databases searched include: DARE (Database of Abstracts of Reviews of Effects), Cochrane Database of Systematic Reviews, CENTRAL (Cochrane Central Register of Controlled Trials), PubMed (National Library of Medicine, includes MEDLINE), Embase (biomedical and pharmacological bibliographic database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), and PsycINFO."

"Other sources of literature include clinicaltrials.gov, references of included studies, references of relevant reviews, and personal files from related topic projects. In addition, the AHRQ Effective Health Care Program Scientific Resource Center (SRC) at Oregon Health Sciences University requested unpublished studies from pharmaceutical manufacturers and searched the FDA and Health Canada databases."
Assessment of quality of included trials: yes
Other methodological remarks: "For reporting the data on adverse events, we treated each atypical antipsychotic separately and (in general) did not group them together as a class. However, we did summarize the findings of other published analyses that treated these drugs as a class."

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2011(6) Design: MA Search date: (May - 2011)	Risperidone Vs Olanzapine	N= 3 n= 264 (?,?,?)	Extrapyramidal symptoms	19/124 vs 18/140 OR 0.84 (95%CI: 0.38, 1.82) NS
	Risperidone Vs Quetiapine	N= 2 n= 251 (?Rainer 2007?, Schneider 2006)	Extrapyramidal symptoms	20/119 vs 3/132 OR 0.12 (95%CI: 0.02, 0.41) **SS in favour of risperidone**

Remarks:

-References are not added in the AHRQ 2011 adverse events analysis. Therefore we could not always determine the link between the results of meta-analyses and all studies on which they were based on.

-Characteristics of the included studies and risk of bias assessment can be found in the sections evaluating efficacy of SGA versus SGA.

15 Appendix. Evidence tables: BPSD - Falls

15.1 SGA versus placebo for BPSD: Falls

Meta-analysis:
Ma 2014(23) The efficacy and safety of atypical antipsychotics for the treatment of dementia: a meta-analysis of randomized placebo-controlled trials
Inclusion criteria:
"Only studies on humans were included. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. As single dose or short term trials (less than 6 weeks in length) are common for several of the new uses, we decided, at the TEP's suggestion, not to limit inclusion by study duration."
Search strategy:
"Our search included MEDLINE, PsychINFO, and the Cochrane Central Register of ControlledTrials. Primary search terms were "dementia", "psychological, psychiatric, or behavioral symptoms", "double-blind", "placebo", "random", together with one of the following terms: "atypical antipsychotic", "quetiapine",
"aripiprazole", "risperidone", "olanzapine", "amisulpride", or "ziprasidone". Moreover, the references of the included studies as well as previously-published reviews and meta-analytic papers satisfying our selection criteria (see below) were checked manually for additional relevant articles. All the articles have been published as of June 2013, and written in English. The trials presented at meetings but not published were not included. At the same time, trials, in which drugs were administrated by intramuscular injection and effect evaluations were immediate (several hours post-treatment), were also excluded."
Assessment of quality of included trials: yes
Other methodological remarks: /

Ref	Comparison	N/n	Outcomes	Result
MA 2014(23) Design: MA Search date:	Olanzapine Vs Placebo	N= 1 n= 297 (Deberdt 2005)	Falls	4/203 vs 2/94 OR 0.92 (95%CI: 0.17, 5.14) NS
	Quetiapine Vs Placebo	N= 3 n= 563	Falls	89/352 vs 54/211 OR 0.96 (95%CI: 0.64, 1.45) I^2=0% NS

(Jun -2013)		(Paleacu 2008, Tariot 2006, Zhong 2007)		
	Risperidone Vs Placebo	N= 4 n= 1725 (Brodaty 2003, Deberdt 2005, Katz 1999, Mintzer 2006)	Falls	152/1060 vs 111/665 OR 0.86 (95%CI: 0.65, 1.14) I^2=0% NS
	SGA (olanzapine, quetiapine, risperidone) Vs placebo	N= 7 n= 2585 (Brodaty 2003, Deberdt 2005, Katz 1999, Mintzer 2006, Paleacu 2008, Tariot 2006, Zhong 2007)	Falls	245/1615 vs 167/970 OR 0.89 (95%CI: 0.71, 1.12) I^2=0% NS

Remarks:

MA 2014 contained more detailed information in their meta-analyses for adverse events than AHRQ 2011 and was therefore used in this evaluation. All included studies in the analysis for adverse events were included in AHRQ 2011. For the characteristics of the here mentioned studies, see the tables for efficacy analyses from AHRQ 2011.

Author's conclusions:

"The higher risks for AEs and mortality may offset the efficacy of atypical antipsychotics for treatment of dementia. Efficacy, safety, and tolerability thus should be carefully considered against clinical need."

"Patients receiving SGAs showed significantly higher risks for edema (OR= 1.80, 95% CI: 1.29–2.49, p = 0.0005) and urinary tract infection (OR= 1.35, 95% CI: 1.07–1.71, p = 0.01), but showed no significantly higher risk for falls (OR= 0.89, 95% CI: 0.71–1.12, p = 0.32), insomnia (OR= 0.94, 95% CI: 0.61–1.46, p = 0.78), or vomiting (OR= 1.49, 95% CI: 0.99–2.26, p = 0.06)"

15.2 SGA versus haloperidol for BPSD: Falls

Meta-analysis:
AHRQ 2011(6): Maglione M, Ruelaz Maher A, Hu J, et al. Off-Label Use of Atypical Antipsychotics: An Update. Comparative Effectiveness Review No. 43.
Inclusion criteria:
"Only studies on humans were included. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. As single dose or short term trials (less than 6 weeks in length) are common for several of the new uses, we decided, at the TEP's suggestion, not to limit inclusion by study duration."
Search strategy:
"We conducted an initial update search on June 1, 2008, as part of a project to determine if Comparative Effectiveness Reviews (CERs) funded by AHRQ needed updating; this search included only the drugs aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Regular update searches continued through May 2011. The search for off-label use of the newly approved atypicals (iloperidone, paliperidone and asenapine) included all years available in the electronic databases through May 2011."

"Databases searched include: DARE (Database of Abstracts of Reviews of Effects), Cochrane Database of Systematic Reviews, CENTRAL (Cochrane Central Register of Controlled Trials), PubMed (National Library of Medicine, includes MEDLINE), Embase (biomedical and pharmacological bibliographic database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), and PsycINFO."
"Other sources of literature include clinicaltrials.gov, references of included studies, references of relevant reviews, and personal files from related topic projects. In addition, the AHRQ Effective Health Care Program Scientific Resource Center (SRC) at Oregon Health Sciences University requested unpublished studies from pharmaceutical manufacturers and searched the FDA and Health Canada databases."
Assessment of quality of included trials: yes
Other methodological remarks: "For reporting the data on adverse events, we treated each atypical antipsychotic separately and (in general) did not group them together as a class. However, we did summarize the findings of other published analyses that treated these drugs as a class."

Ref	Comparison	N/n	Outcomes	Result

AHRQ 2011(6) Design: MA Search date: (May -2011)	Olanzapine Vs FGA (Haloperidol, promazine chloridrate)	N= 1 n= 346 (Moretti 2005)	Falls	1 (0.57%) vs 13 (7.51%) No statistical test performed
	Quetiapine Vs Haloperidol	N= 1 n= 284 (Tariot 2006)	Falls	26/91 (28.6%) vs 27/94 (28.7%) NS

Remarks:

-The AHRQ 2011 does not report results for falls. We therefore checked each included study comparing SGA with haloperidol in the AHRQ 2011 review for the outcome falls.(50),(51),(52),(42),(47)

-Characteristics of the included studies and risk of bias assessment can be found in the sections evaluating efficacy of SGA versus haloperidol.

15.3 SGA versus SGA for BPSD: Falls

Meta-analysis:
AHRQ 2011(6): Maglione M, Ruelaz Maher A, Hu J, et al. Off-Label Use of Atypical Antipsychotics: An Update. Comparative Effectiveness Review No. 43.
Inclusion criteria:
"Only studies on humans were included. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. As single dose or short term trials (less than 6 weeks in length) are common for several of the new uses, we decided, at the TEP's suggestion, not to limit inclusion by study duration."
Search strategy:
"We conducted an initial update search on June 1, 2008, as part of a project to determine if Comparative Effectiveness Reviews (CERs) funded by AHRQ needed updating; this search included only the drugs aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Regular update searches continued through May 2011. The search for off-label use of the newly approved atypicals (iloperidone, paliperidone and asenapine) included all years available in the electronic databases through May 2011."

"Databases searched include: DARE (Database of Abstracts of Reviews of Effects), Cochrane Database of Systematic Reviews, CENTRAL (Cochrane Central Register of Controlled Trials), PubMed (National Library of Medicine, includes MEDLINE), Embase (biomedical and pharmacological bibliographic database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), and PsycINFO."
"Other sources of literature include clinicaltrials.gov, references of included studies, references of relevant reviews, and personal files from related topic projects. In addition, the AHRQ Effective Health Care Program Scientific Resource Center (SRC) at Oregon Health Sciences University requested unpublished studies from pharmaceutical manufacturers and searched the FDA and Health Canada databases."
Assessment of quality of included trials: yes
Other methodological remarks: "For reporting the data on adverse events, we treated each atypical antipsychotic separately and (in general) did not group them together as a class. However, we did summarize the findings of other published analyses that treated these drugs as a class."

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2011(6) Design: MA Search date: (May-2011)	Risperidone Vs Quetiapine	N= 1 n= 72 (Rainer 2007)	Falls	Rainer 2007 reported "falls with contusion". 0/34 vs 1/38
	Olanzapine vs Quetiapine Vs Risperidone Vs placebo	N= 1 n= 421 (Schneider 2006)	Falls	Schneider 2006 reported the outcome "falls, fractures, or injuries". Overall, there was no significant difference between the 4 groups: three SGA and placebo. No separate results for falls were reported.

	Olanzapine Vs Risperidone Vs placebo	N= 1 n= 494 (Deberdt 2005)	Falls	11.3% vs 9.2% vs 6.4% NS

Remarks:

-The AHRQ 2011 does not report results for falls. We therefore checked all included studies that compared SGA with SGA in the AHRQ 2011 review individually for the outcome falls. (35),Schneider, 2006 #26},(38),(53)

-Characteristics of the included studies and risk of bias assessment can be found in the sections evaluating efficacy of SGA versus SGA.

16 Appendix. Evidence tables: BPSD - endocrine adverse effects

16.1 SGA versus placebo for BPSD: endocrine adverse effects

Meta-analysis:
AHRQ 2011(6) - Maglione M, Ruelaz Maher A, Hu J, et al. Off-Label Use of Atypical Antipsychotics: An Update. Comparative Effectiveness Review No. 43.
Inclusion criteria:
"Only studies on humans were included. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. As single dose or short term trials (less than 6 weeks in length) are common for several of the new uses, we decided, at the TEP's suggestion, not to limit inclusion by study duration."
Search strategy:
"We conducted an initial update search on June 1, 2008, as part of a project to determine if Comparative Effectiveness Reviews (CERs) funded by AHRQ needed updating; this search included only the drugs aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Regular update searches continued through May 2011. The search for off-label use of the newly approved atypicals (iloperidone, paliperidone and asenapine) included all years available in the electronic databases through May 2011."

"Databases searched include: DARE (Database of Abstracts of Reviews of Effects), Cochrane Database of Systematic Reviews, CENTRAL (Cochrane Central Register of Controlled Trials), PubMed (National Library of Medicine, includes MEDLINE), Embase (biomedical and pharmacological bibliographic database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), and PsycINFO."
"Other sources of literature include clinicaltrials.gov, references of included studies, references of relevant reviews, and personal files from related topic projects. In addition, the AHRQ Effective Health Care Program Scientific Resource Center (SRC) at Oregon Health Sciences University requested unpublished studies from pharmaceutical manufacturers and searched the FDA and Health Canada databases."
Assessment of quality of included trials: yes
Other methodological remarks: "For reporting the data on adverse events, we treated each atypical antipsychotic separately and (in general) did not group them together as a class. However, we did summarize the findings of other published analyses that treated these drugs as a class."

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2011(6)	Risperidone Vs Placebo	N= 1 n= 473 (Mintzer 2006)	diabetes	1.7% (4/235) vs 2.1% (5/238) OR 0.81 (95%CI: 0.16, 3.80) NS
			Prolactin	0/235 vs 0/238

Design: MA Search date: (May - 2011)				Not estimable

Remarks: /

Author's conclusions:

"Our expert panel reported cases of diabetes onset in elderly patients taking atypicals; thus, we were encouraged to conduct an analysis on endocrine outcomes. Only one trial, of risperidone, reported this category of adverse events; there was no difference between patients taking the drug and those taking placebo, although the confidence intervals are wide."

16.2 SGA versus haloperidol for BPSD: endocrine adverse effects

Meta-analysis:
AHRQ 2011(6) - Maglione M, Ruelaz Maher A, Hu J, et al. Off-Label Use of Atypical Antipsychotics: An Update. Comparative Effectiveness Review No. 43.
Inclusion criteria:
"Only studies on humans were included. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. As single dose or short term trials (less than 6 weeks in length) are common for several of the new uses, we decided, at the TEP's suggestion, not to limit inclusion by study duration."
Search strategy:
"We conducted an initial update search on June 1, 2008, as part of a project to determine if Comparative Effectiveness Reviews (CERs) funded by AHRQ needed updating; this search included only the drugs aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Regular update searches continued through May 2011. The search for off-label use of the newly approved atypicals (iloperidone, paliperidone and asenapine) included all years available in the electronic databases through May 2011."

"Databases searched include: DARE (Database of Abstracts of Reviews of Effects), Cochrane Database of Systematic Reviews, CENTRAL (Cochrane Central Register of Controlled Trials), PubMed (National Library of Medicine, includes MEDLINE), Embase (biomedical and pharmacological bibliographic database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), and PsycINFO."
"Other sources of literature include clinicaltrials.gov, references of included studies, references of relevant reviews, and personal files from related topic projects. In addition, the AHRQ Effective Health Care Program Scientific Resource Center (SRC) at Oregon Health Sciences University requested unpublished studies from pharmaceutical manufacturers and searched the FDA and Health Canada databases."
Assessment of quality of included trials: yes
Other methodological remarks: "For reporting the data on adverse events, we treated each atypical antipsychotic separately and (in general) did not group them together as a class. However, we did summarize the findings of other published analyses that treated these drugs as a class."

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2011(6) Design: MA Search date: (May-2011)	FGA Vs olanzapine	N= 2 n=386 (Moretti 2005, ?Verhey 2006?)	Diabetes	2/193 vs 3/193 OR 1.50 (95%CI: 0.17, 18.14) NS
	FGA Vs risperidone	N= 1 n= 344 (?De Deyn 1999?)	Diabetes	0/20 vs 0/20 Not estimable

Remarks:

-Characteristics of the included studies and risk of bias assessment can be found in the sections evaluating efficacy of SGA versus haloperidol.

-References are not added in the AHRQ 2011 adverse events analysis. Therefore we could not always determine the link between the results of meta-analyses and all studies on which they were based on.

16.3 SGA versus SGA for BPSD: endocrine adverse events

Meta-analysis:
AHRQ 2011(6) - Maglione M, Ruelaz Maher A, Hu J, et al. Off-Label Use of Atypical Antipsychotics: An Update. Comparative Effectiveness Review No. 43.
Inclusion criteria:
"Only studies on humans were included. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. As single dose or short term trials (less than 6 weeks in length) are common for several of the new uses, we decided, at the TEP's suggestion, not to limit inclusion by study duration."
Search strategy:
"We conducted an initial update search on June 1, 2008, as part of a project to determine if Comparative Effectiveness Reviews (CERs) funded by AHRQ needed updating; this search included only the drugs aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Regular update searches continued through May 2011. The search for off-label use of the newly approved atypicals (iloperidone, paliperidone and asenapine) included all years available in the electronic databases through May 2011."

"Databases searched include: DARE (Database of Abstracts of Reviews of Effects), Cochrane Database of Systematic Reviews, CENTRAL (Cochrane Central Register of Controlled Trials), PubMed (National Library of Medicine, includes MEDLINE), Embase (biomedical and pharmacological bibliographic database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), and PsycINFO."
"Other sources of literature include clinicaltrials.gov, references of included studies, references of relevant reviews, and personal files from related topic projects. In addition, the AHRQ Effective Health Care Program Scientific Resource Center (SRC) at Oregon Health Sciences University requested unpublished studies from pharmaceutical manufacturers and searched the FDA and Health Canada databases."
Assessment of quality of included trials: yes
Other methodological remarks: "For reporting the data on adverse events, we treated each atypical antipsychotic separately and (in general) did not group them together as a class. However, we did summarize the findings of other published analyses that treated these drugs as a class."

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2011(6) Design: MA	Risperidone Vs Olanzapine	N= 1 n= 40 (?)	diabetes	0/20 vs 0/20 Not estimable

Search date: (May -2011)				

Remarks:

-References are not added in the AHRQ 2011 adverse events analysis. Therefore we could not always determine the link between the results of meta-analyses and all studies on which they were based on. The AHRQ 2011 review included two studies (Deberdt 2005(35), Schneider 2006(37)/Sultzer 2008(38)) comparing risperidone with olanzapine. We could not verify which one was used by AHRQ 2011 for their diabetes results.

-Characteristics of the included studies and risk of bias assessment can be found in the sections evaluating efficacy of SGA versus SGA.

17 Appendix. Evidence tables: BPSD - urinary tract infections

17.1 SGA versus placebo for BPSD: urinary tract infections

Meta-analysis:
Ma 2014(23) - The efficacy and safety of atypical antipsychotics for the treatment of dementia: a meta-analysis of randomized placebo-controlled trials
Inclusion criteria:
"Only studies on humans were included. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. As single dose or short term trials (less than 6 weeks in length) are common for several of the new uses, we decided, at the TEP's suggestion, not to limit inclusion by study duration."
Search strategy:
"Our search included MEDLINE, PsychINFO, and the Cochrane Central Register of ControlledTrials. Primary search terms were "dementia", "psychological, psychiatric, or behavioral symptoms", "double-blind", "placebo", "random", together with one of the following terms: "atypical antipsychotic", "quetiapine",
"aripiprazole", "risperidone", "olanzapine", "amisulpride", or "ziprasidone". Moreover, the references of the included studies as well as previously-published reviews and meta-analytic papers satisfying our selection criteria (see below) were checked manually for additional relevant articles. All the articles have been published as of June 2013, and written in English. The trials presented at meetings but not published were not included. At the same time, trials, in which drugs were administrated by intramuscular injection and effect evaluations were immediate (several hours post-treatment), were also excluded."
Assessment of quality of included trials: yes
Other methodological remarks: /

Ref	Comparison	N/n	Outcomes	Result
Ma 2014(23) Design: MA Search date: (Jun -2013)	Aripiprazole Vs Placebo	N= 3 n= 951 (De Deyn 2005, Mintzer 2007, Streim 2008)	Urinary tract infection	89/603 vs 39/348 OR 1.18 (95%CI: 0.77, 1.79) I^2=18% NS
	Quetiapine Vs	N= 2 n= 523	Urinary tract infection	40/332 vs 12/191 OR 1.96 (95%CI: 0.99, 3.87)

	Placebo	(Tariot 2006, Zhong 2007)		I^2=0% NS
	Risperidone Vs Placebo	N= 3 n= 1435 (Brodaty 2003, Katz 1999, Mintzer 2006)	Urinary tract infection	139/864 vs 70/571 OR 1.34 (95%CI: 0.97, 1.84) I^2= 17% NS
	SGA (aripiprazole, quetiapine, risperidone) Vs placebo	N= 8 n= 2909 (De Deyn 2005, Mintzer 2007, Streim 2008, Tariot 2006, Zhong 2007, Brodaty 2003, Katz 1999, Mintzer 2006)	Urinary tract infection	268/1799 vs 121/1110 OR 1.35 (95%CI: 1.07, 1.71) I^2=0% **SS in favour of SGA**

Remarks:

The systematic review by Ma 2014(23) contained more detailed information in their meta-analyses for adverse events than the AHRQ 2011 review(6) and was therefore used in this evaluation. Furthermore, AHRQ 2011 combined results for urinary incontinence and urinary tract infections. All included studies in the analysis for adverse events were included in AHRQ 2011. For the characteristics of the here mentioned studies, see the tables for efficacy analyses from AHRQ 2011.

Author's conclusions:

"The higher risks for AEs and mortality may offset the efficacy of atypical antipsychotics for treatment of dementia. Efficacy, safety, and tolerability thus should be carefully considered against clinical need."

"Patients receiving SGAs showed significantly higher risks for edema (OR= 1.80, 95% CI: 1.29–2.49, p = 0.0005) and urinary tract infection (OR= 1.35, 95% CI: 1.07–1.71, p = 0.01), but showed no significantly higher risk for falls (OR= 0.89, 95% CI: 0.71–1.12, p = 0.32), insomnia (OR= 0.94, 95% CI: 0.61–1.46, p = 0.78), or vomiting (OR= 1.49, 95% CI: 0.99–2.26, p = 0.06)"

17.2 SGA versus haloperidol for BPSD: urinary tract infections

Meta-analysis:
AHRQ 2011(6): Maglione M, Ruelaz Maher A, Hu J, et al. Off-Label Use of Atypical Antipsychotics: An Update. Comparative Effectiveness Review No. 43.
Inclusion criteria:
"Only studies on humans were included. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. As single dose or short term trials (less than 6 weeks in length) are common for several of the new uses, we decided, at the TEP's suggestion, not to limit inclusion by study duration."
Search strategy:
"We conducted an initial update search on June 1, 2008, as part of a project to determine if Comparative Effectiveness Reviews (CERs) funded by AHRQ needed updating; this search included only the drugs aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Regular update searches continued through May 2011. The search for off-label use of the newly approved atypicals (iloperidone, paliperidone and asenapine) included all years available in the electronic databases through May 2011."

"Databases searched include: DARE (Database of Abstracts of Reviews of Effects), Cochrane Database of Systematic Reviews, CENTRAL (Cochrane Central Register of Controlled Trials), PubMed (National Library of Medicine, includes MEDLINE), Embase (biomedical and pharmacological bibliographic database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), and PsycINFO."
"Other sources of literature include clinicaltrials.gov, references of included studies, references of relevant reviews, and personal files from related topic projects. In addition, the AHRQ Effective Health Care Program Scientific Resource Center (SRC) at Oregon Health Sciences University requested unpublished studies from pharmaceutical manufacturers and searched the FDA and Health Canada databases."
Assessment of quality of included trials: yes
Other methodological remarks: "For reporting the data on adverse events, we treated each atypical antipsychotic separately and (in general) did not group them together as a class. However, we did summarize the findings of other published analyses that treated these drugs as a class."

Ref	Comparison	N/n	Outcomes	Result

AHRQ 2011(6) Design: MA Search date: (May -2011)	Quetiapine Vs Haloperidol	N= 1 n= 284 (Tariot 2006)	Urinary tract infections	11/91 (12.1%) vs 10/94 (10.6%) NS

Remarks:

The AHRQ 2011 review(6) reports results for urinary symptoms for the comparison olanzapine versus FGA and risperidone versus FGA. Results were based on data from 2 studies and 1 study respectively. Since we focused on the outcome urinary tract infection and since the AHRQ 2011 review seems to group urinary symptoms together (urinary incontinence and urinary tract infection) we could not use these data. Furthermore, references are not added in the AHRQ 2011 adverse events analysis. We therefore checked all included studies that compared SGA with FGA in the AHRQ 2011 review individually for urinary tract infections.(50),(51),(52),(42),(47) Only Tariot 2006(42) reported urinary tract infections and this for the comparison quetiapine versus haloperidol.

17.3 SGA versus SGA for BPSD: urinary tract infections

Meta-analysis:
AHRQ 2011(6): Maglione M, Ruelaz Maher A, Hu J, et al. Off-Label Use of Atypical Antipsychotics: An Update. Comparative Effectiveness Review No. 43.
Inclusion criteria:
"Only studies on humans were included. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. As single dose or short term trials (less than 6 weeks in length) are common for several of the new uses, we decided, at the TEP's suggestion, not to limit inclusion by study duration."
Search strategy:

"We conducted an initial update search on June 1, 2008, as part of a project to determine if Comparative Effectiveness Reviews (CERs) funded by AHRQ needed updating; this search included only the drugs aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Regular update searches continued through May 2011. The search for off-label use of the newly approved atypicals (iloperidone, paliperidone and asenapine) included all years available in the electronic databases through May 2011."

"Databases searched include: DARE (Database of Abstracts of Reviews of Effects), Cochrane Database of Systematic Reviews, CENTRAL (Cochrane Central Register of Controlled Trials), PubMed (National Library of Medicine, includes MEDLINE), Embase (biomedical and pharmacological bibliographic database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), and PsycINFO."
"Other sources of literature include clinicaltrials.gov, references of included studies, references of relevant reviews, and personal files from related topic projects. In addition, the AHRQ Effective Health Care Program Scientific Resource Center (SRC) at Oregon Health Sciences University requested unpublished studies from pharmaceutical manufacturers and searched the FDA and Health Canada databases."
Assessment of quality of included trials: yes
Other methodological remarks: "For reporting the data on adverse events, we treated each atypical antipsychotic separately and (in general) did not group them together as a class. However, we did summarize the findings of other published analyses that treated these drugs as a class."

Remarks:

The AHRQ 2011 reports results for urinary symptoms for the comparison risperidone versus olanzapine or quetiapine. Results were based on 1 study for each comparison.(35),(53) Since we focused on the outcome urinary tract infection and since the AHRQ 2011 review seems to group urinary symptoms together (urinary incontinence and urinary tract infection) we could not use these data. We therefore checked both studies individually for urinary tract infections. However both mentioned studies only report urinary incontinence.

18 Appendix. Evidence tables: delirium

18.1 Antipsychotics versus placebo or non-antipsychotic drugs for delirium

Meta-analysis:
Burry 2018, Cochrane review. Antipsychotics for treatment of delirium in hospitalised non-ICU patients.(25)

Inclusion criteria: Randomised or quasi-randomised trials in which antipsychotics, non-antipsychotics (e.g. alternative drug class such as benzodiazepines), or placebo was administered to adults (> 16 years of age) diagnosed with delirium and treated in an acute care setting (excluding critically ill populations).

Excluded: trials with a primary aim of treating delirium secondary to substance/alcohol-induced withdrawal, recruiting participants solely in outpatient, psychiatric, or long-term care settings, or in an intensive care unit.

Search strategy: MEDLINE, Embase, Cochrane EBM Reviews, CINAHL, Thomson Reuters Web of Science and the Latin American and Caribbean Health Sciences Literature (LILACS) were searched from their respective inception dates until July 2017. The Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database, Web of Science ISI Proceedings, were also searched. The reference lists of all retrieved studies was hand searched for additional relevant studies. Unpublished studies and ongoing trials were sought by using the Google search engine, on the following web sites: 1.www.clinicaltrials.gov/; and 2. www.who.int/trialsearch, and by contacting corresponding authors of eligible trials and experts in the field.

Assessment of quality of included trials: yes (GRADE)
ITT analysis: Agar 2016, Breitbart 1996 and Tahir 2010 used ITT analysis. The Hu 2004 study made no mention of how attrition was factored into the statistical analysis

Other methodological remarks:/

Ref	Comparison	N/n	Outcomes	Result
Burry 2018(25)	antipsychotics vs	/	Total duration of delirium (days)	This outcome was not reported in any trial.
		N= 4 n= 494	Delirium severity	SMD -1.08 (95% CI -2.55 to 0.39) I^2= 97%

Design: MA Search date: July-2017	placebo or non-antipsychotic drugs	(Agar 2016, Breitbar 1996, Hu 2004, Tahir 2010)		NS
		N= 3 n= 247 (Breitbart 1996, Hu 2004, Tahir 2010)	Delirium resolution	66/191 vs 15/56 RR 0.95 (95% CI 0.30 to 2.98) I^2= 83% NS
		N= 3 n= 319 (Agar 2016, Breitbart 1996, Tahir 2010)	Mortality	36/208 vs 14/111 RR 1.29 (95% CI 0.73 to 2.27) NS
		/	Hospital length of stay (days)	No trials reported
		/	Hospital discharge disposition (e.g. rehabilitation, chronic care facility, home)	No trials reported
		/	Health-related quality of life	No trials reported
		N=3 n=247 (Breitbart 1996, Hu 2004, Tahir 2010)	Adverse events : Extrapyramidal symptoms	26/191 vs 3/56 RR 1.70 (95% CI 0.04 to 65.57) I^2= 77% NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as judged by Cochrane)
Agar 2016(26) Double-blind, randomised	247	Adult patients receiving hospice or palliative care with advanced, progressive disease that was no longer curable who required inpatient care by a specialist palliative care team with delirium diagnosis. Exclusion: delirium due to substance withdrawal, history of neuroleptic malignant syndrome or previous adverse reaction to an antipsychotic drug, regular use of antipsychotic drugs within 48 hours of the study, extrapyramidal disorders, prolonged QT interval, clinician-predicted survival of 7 days or fewer, cerebrovascular accident or seizure in the prior 30 days, and pregnancy or breastfeeding Risperidone: mean age 74.5 ± 10.6 years, M 57, F 25 Haloperidol: mean age 76.5 ± 8.2 years, M 48, F 33 Placebo: mean age 73.8 ± 10.7 years, M 57, F 27	72 h Last assessment done 12 h after the last dose	Risperidone vs Haloperidol vs Placebo -First dose of 0.5 mg, then 0.5 mg maintenance doses every 12 hours. -Doses could be titrated by 0.25 mg on day 1 and by 0.5 mg thereafter to a maximum dose of 4 mg/d. -For participants > 65 years, the doses of the study drug were halved. All participants received individualized treatment plans, including treatment of reversible precipitants, where clinically indicated, and nonpharmacologic measures, as appropriate. Rescue : S.c. midazolam 2.5 mg every 2 hours PRN was available when participants were deemed to require immediate intervention for safety or	-Random sequence generation (selection bias): low risk - Allocation concealment (selection bias): low risk - Blinding (performance bias and detection bias) – All outcomes: low risk - Incomplete outcome data (attrition bias) – All outcomes: low risk - Selective reporting: low risk - Other bias: low risk Funding: government

				distress. I.v. benztropine mesylate (1 to 2 mg) could be administered for serious extrapyramidal adverse effects	
Breitbart 1996(70) Double-blind, randomised	n=30	Medically hospitalised adults for AIDS (AcquiredImmunodeficiencySyndrome) or AIDS-related medical problems and diagnosed with delirium. Exclusion: AIDS-related dementia where participants could not give informed consent, patients expected to die within 24 hours, known hypersensitivity to study drugs, history of neuroleptic malignant syndrome, concurrent need for treatment with neuroleptic drugs, seizure disorder, current systemic chemotherapy for Kaposi's sarcoma, withdrawal syndrome, current/past diagnosis for schizophrenia, schizoaffective disorder, or bipolar disorder. Mean age 39.2 ± 8.8 years, M 23, F7	6 days	Haloperidol vs Chlorpromazine vs Lorazepam administered either orally or intramuscularly and according to an a priori established increasing titration schedule. Start dosages: Haloperidol: 0.25 mg oral/0.125 mg i.m. Chlorpromazine: 10 mg oral/5 mg i.m. Lorazepam: 0.5 mg oral/0.20 mg i.m. After stabilisation, a maintenance dose equal to one-half of the first 24-hour dose requirement was begun, given in a twice-daily regimen from day 2.	- Random sequence generation (selection bias): low risk - Allocation concealment (selection bias): low risk - Blinding (performance bias and detection bias) – All outcomes: low risk - Incomplete outcome data (attrition bias) – All outcomes: unclear risk Lorazepam arm discontinued early due to adverse events, but data used in analysis - Selective reporting: unclear risk Outcomes in methods matched those reported in results. But protocol not published to confirm all outcomes were reported as planned. - Other bias: Unclear risk No rescue drugs permitted (additional details provided by author).

				Rescue: No rescue drugs permitted.	Sample size/power calculation not reported in the manuscript. Funding: government
Hu 2004(71) Randomised	n=175	Adults aged > 65 years diagnosed with delirium Exclusion: Patients with a severe mental disease, those who had taken any antipsychotic drug, patients with angle-closure glaucoma, paralytic ileus, or material abuse. Olanzapine: mean age 74 ± 8 years, M 45, F 29 Haloperidol: mean age 74 ± 7 years, M 48, F 24 Placebo: mean age 73 ± 7 years, M 18, F 11	7 days	Olanzapine vs Haloperidol vs Placebo Olanzapine 1.25 to 2.5 mg PO, increased to a maximum daily dose of 20 mg. Haloperidol daily dose range of 2.5 to 10 mg, i.m. Rescue: No permitted, except in the instance of the development of extrapyramidal symptoms, for which banzhexol was administered with a maximum dose of 6mg.	- Random sequence generation (selection bias): unclear risk No mention of method of randomization. Stating participants were randomised in a 5:5:2 ratio for olanzapine, haloperidol, and placebo groups, respectively. - Allocation concealment (selection bias): unclear risk No details provided. - Blinding (performance bias and detection bias) – All outcomes: high risk Haloperidol could be given subcutaneously and olanzapine orally. No description of how treatments were concealed. No mention of blinding process. Not likely done. - Incomplete outcome data (attrition bias) – All outcomes: high risk

					No mention of how attrition was factored into statistical analysis (not described as ITT analysis) - Selective reporting: low risk - Other bias: unclear risk Sample size not reported. Unclear methodology regarding dosing protocol.
Tahir 2010(72) Randomised	n= 42	Adults from medical, surgical, and orthopedic units diagnosed with delirium. Exclusion: major pre-existing cognitive deficits (major not defined), alcohol withdrawal, pre-existing psychosis, substance dependence, inability to comply with the constraints of the trial, on medication that interacted with quetiapine. Quetiapine, mean age 84.1 ± 9.45 years, M 6, F 15 Placebo, mean age 84.3 ± 7.16 years, M 6, F 15	10 days	Quetiapine vs Placebo Start dosage at 25 mg daily, with a dose titration of 25 mg/day to a maximum of 175 mg/day, in divided doses. If symptoms improved, dose was reduced in a reverse pattern from initial titration. Rescue drugs: Not specified in the methods. Results reported use of lorazepam.	- Random sequence generation (selection bias): low risk - Allocation concealment (selection bias): low risk - Blinding (performance bias and detection bias) – All outcomes: low risk - Incomplete outcome data (attrition bias) – All outcomes: low risk -Selective reporting: low risk - Other bias: unclear risk Sample size calculation reported. The trial was stopped early at the request of the manufacturer due to the FDA's concern on the use of antipsychotic medication in the

					elderly. The study is, therefore, underpowered. Lorazepam was administered to 4 participants in the quetiapine group versus none in the placebo group. The quetiapine had faster resolution; unclear if this might have influenced the resolution of symptoms. Investigator-initiated study sponsored by AstraZeneca UK. Funding provided for recruitment of a research assistant and trial medication. AstraZeneca UK also provided the randomisation codes.

Remarks
- As no drug has been consistently shown to be more effective than placebo, trials that had a non-antipsychotics group as comparator were included. Therefore, a non-antipsychotic group was thought of as a placebo. Non-antipsychotic agents might include: alpha-2 agonists, antidepressants, benzodiazepines, cholinesterase inhibitors, melatonin or melatonin agonists, or opioids. One study using lorazepam as placebo (Breitbart 1996) was included in the MA. - Adverse events may include prolongation of the QTc interval, sudden cardiac death, cerebral vascular events, seizures, extrapyramidal effects, use of physical restraints, long-term cognitive impairment. However no trials reported the use of physical restraints, long-term cognitive measures, or incidence of seizures, cerebrovascular events, sudden cardiac death or QTc abnormalities. Only extrapyramidal symptoms (EPS) were reported.

- One additional study (Agar 2016) reported significantly greater mean extrapyramidal effects in risperidone versus placebo-treated participants using mixed effects modelling, without specifying the actual summary measure used (0.73, 95% CI 0.09 to 1.37, P = 0.03) and haloperidol versus placebo-treated (0.79, 95% CI 0.17 to 1.41, P = 0.01) participants on each study day. Raw data were not available, thus, authors were unable to pool these data with the other trials.

- The intention of the authors was to investigate clinically relevant outcomes for patients however, It is important to note many of these outcomes were not reported in the studies.

- One study (Breitbart 1996) compared haloperidol or chlorpromazine which is not available in Belgium to the benzodiazepine lorazepam. However we decided to not exclude this study from our analysis.

- The mean reported age of participants across trials reported in this review ranged from 39 (Breitbart 1996) to 84 (Tahir 2010) years. Furthermore, 23% (Breitbart 1996) to 71% (Tahir 2010) of participants were females.

-All studies used titrated study drug according to symptom response.

Author's conclusions

"There were no reported data to determine whether antipsychotics altered the duration of delirium, length of hospital stay, discharge disposition, or health-related quality of life as studies did not report on these outcomes. From the poor quality data available, we found antipsychotics did not reduce delirium severity, resolve symptoms, or alter mortality. Adverse effects were poorly or rarely reported in the trials. Extrapyramidal symptoms were not more frequent with antipsychotics compared to non-antipsychotic drug regimens."
"The majority of recent studies have focused on critically ill participants, still leaving us with insufficient poor quality data for hospitalised, non-critically ill participant."

For clinician:
"Survey data indicates pharmacological interventions, such as antipsychotics, are often used to manage delirium symptoms in clinical practice. After updating this review, we caution clinicians to the fact that there is still insufficient evidence overall on this subject."

18.2 FGA versus SGA for delirium

Meta-analysis:
Burry 2018, Cochrane review. Antipsychotics for treatment of delirium in hospitalised non-ICU patients.(25)

Inclusion criteria: Randomised or quasi-randomised trials in which antipsychotics, non-antipsychotics (e.g. alternative drug class such as benzodiazepines), or placebo was administered to adults (> 16 years of age) diagnosed with delirium and treated in an acute care setting (excluding critically ill populations).

Excluded: trials with a primary aim of treating delirium secondary to substance/alcohol-induced withdrawal, recruiting participants solely in outpatient, psychiatric, or long-term care settings, or in an intensive care unit.

Search strategy: MEDLINE, Embase, Cochrane EBM Reviews, CINAHL, Thomson Reuters Web of Science and the Latin American and Caribbean Health Sciences Literature (LILACS) were searched from their respective inception dates until July 2017. The Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database, Web of Science ISI Proceedings, were also searched. The reference lists of all retrieved studies was hand searched for additional relevant studies. Unpublished studies and ongoing trials were sought by using the Google search engine, on the following web sites: 1.www.clinicaltrials.gov/; and 2. www.who.int/trialsearch, and by contacting corresponding authors of eligible trials and experts in the field.

Assessment of quality of included trials: yes (GRADE)
ITT analysis: Agar 2016 and Maneeton 2013 used ITT analisys. In the Han 2004 study, four participants did not complete the study, three due to medical; these participants were not included in the analysis. The Hu 2004 study made no mention of how attrition was factored into the statistical analysis. Lin 2008 did not report the total number of participants enrolled or lost to follow-up.

Other methodological remarks:/

Ref	Comparison	N/n	Outcomes	Result
Burry 2018(25) Design: MA Search date:	Typical antipsychotics versus atypical antipsychotics	/	Total duration of delirium (days)	This outcome was not reported in any trial.
		N=7 n=542	Delirium severity	SMD -0.17 (95% CI -0.37 to 0.02) NS

(July-2017)		(Agar 2016; Grover 2011; Grover 2016; Han 2004; Hu 2004; Lin 2008; Maneeton 2013)		
		N=5 n=349 (Grover 2011; Grover 2016; Han 2004; Hu 2004; Maneeton 2013)	Delirium resolution	62/185 vs 50/164 RR 1.10 (95%CI 0.79 to 1.52) NS
		N=4 n=342 (Agar 2016; Grover 2011; Grover 2016; Maneeton 2013)	Mortality	17/181 vs 10/161 RR 1.71 (95% CI 0.82 to 3.53) NS
		/	Hospital length of stay (days)	No trials reported
		/	Hospital discharge disposition (e.g. rehabilitation, chronic care facility, home)	No trials reported
		/	Health-related quality of life	No trials reported
		N=2 n=198 (Hu2004; Maneeton 2013)	Adverse events: extrapyramidal symptoms	24/100 vs 0/98 RR 12.16 (95% CI 0.55 to 269.52) $I^2 = 54\%$ NS

* Characteristics of included studies: see below

Ref + design		Population	Duration	Comparison	Methodology (as judged by Cochrane)
Agar 2016(26) Double-blind, randomised	n=247	Adult patients receiving hospice or palliative care with advanced, progressive disease that was no longer curable who required inpatient care by a specialist palliative care team with delirium diagnosis. Exclusion: delirium due to substance withdrawal, history of neuroleptic malignant syndrome or previous adverse reaction to an antipsychotic drug, regular use of antipsychotic drugs within 48 hours of the study, extrapyramidal disorders, prolonged QT interval, clinician-predicted survival of 7 days or fewer, cerebrovascular accident or seizure in the prior 30 days, and pregnancy or breastfeeding Risperidone: mean age 74.5 ± 10.6 years, M 57, F 25 Haloperidol: mean age 76.5 ± 8.2 years, M 48, F 33 Placebo: mean age 73.8 ± 10.7 years, M 57, F 27	72 h Last assessment done 12 h after the last dose	Risperidone vs Haloperidol vs Placebo -First dose of 0.5 mg, then 0.5 mg maintenance doses every 12 hours. -Doses could be titrated by 0.25 mg on day 1 and by 0.5 mg thereafter to a maximum dose of 4 mg/d. -For participants > 65 years, the doses of the study drug were halved. All participants received individualized treatment plans, including treatment of reversible precipitants, where clinically indicated, and nonpharmacologic measures, as appropriate. Rescue : S.c. midazolam 2.5 mg every 2 hours PRN was available when participants were deemed	-Random sequence generation (selection bias): low risk - Allocation concealment (selection bias): low risk - Blinding (performance bias and detection bias) – All outcomes: low risk - Incomplete outcome data (attrition bias) – All outcomes: low risk - Selective reporting: low risk - Other bias: low risk Funding: government

				to require immediate intervention for safety or distress. I.v. benztropine mesylate (1 to 2 mg) could be administered for serious extrapyramidal adverse effects	
Grover 2011(73) Single-blind, Randomised	n= 64	Medical and surgical patients aged > 18 years having a confirmed diagnosis of delirium Exclusion: delirium secondary to alcohol or benzodiazepine withdrawal, adults with dementia, those unresponsive to verbal or physical stimulus, those suffering terminal illness, and those with a comorbid psychotic/mood disorder, profound hearing or visual loss, aphasia, Parkinson's disease, history of neuroleptic malignant syndrome, prolonged QTc interval, past history of hypersensitivity to any of the study drugs. Haloperidol: mean age 44.09 ± 16.84 years, M 12, F 8 Risperidone: mean age 45.39 ± 19.18 years, M 12, F 9 N = 23 Olanzapine: mean age 46.5 ± 14.51 years, M 21, F2	6 days	Haloperidol flexible dose (0.25 to 10 mg/day) vs Risperidone flexible (0.25 to 4 mg/day) vs Olanzapine flexible dose (1.25 to 20 mg/day) Rescue: Haloperidol and olanzapine groups: whenever rescue medication was required, the same drug was used in the injectable form. For the risperidone group: injectable lorazepam or haloperidol was used as risperidone is not available in injectable form.	- Random sequence generation (selection bias): unclear risk No details provided. It is likely that it was done - Allocation concealment (selection bias): low risk - Blinding (performance bias and detection bias) – All outcomes: low risk - Incomplete outcome data (attrition bias) – All outcomes: high risk Six participants could not be assessed at least once during the study (due to worsened clinical status) and four left hospital against medical advice. - Selective reporting: unclear risk Trial protocol not published so unable to confirm all outcomes were reported as planned

					- Other bias: unclear risk One group (i.e. risperidone) received lorazepam or haloperidol as injectable risperidone was not available. However, haloperidol and olanzapine groups received the same drug they were assigned to for rescue. Referral bias: participants who were referred to the consultation-liaison psychiatry team were eligible for the study. It is unknown if all participants with suspected delirium are routinely referred to psychiatry in this hospital. Note: Sample size/power calculation not reported. Study funded by Institute Research Fund.
Grover 2016(74) Single-blind RCT	n= 63	Medical and surgical patients aged > 18 years having a confirmed diagnosis of delirium Exclusion: delirium secondary to alcohol or benzodiazepine withdrawal, adults with dementia, those unresponsive to verbal or physical stimulus, those suffering terminal illness, and those with a comorbid psychotic/mood disorder, profound	6 days	Quetiapine flexible dose (12.5 to 75 mg/day) vs Haloperidol flexible dose (0.25 to 10 mg/day) For all subjects, caregivers advised to provide optimal level of environmental stimulation, avoid sensory	- Random sequence generation (selection bias): low risk - Allocation concealment (selection bias): unclear risk Not reported. - Blinding (performance bias and detection bias) – All outcomes: low risk

		hearing or visual loss, aphasia, Parkinson's disease, history of neuroleptic malignant syndrome, prolonged QTc interval, past history of hypersensitivity to any of the study drugs. Quetiapine: mean age 48.51 ± 19.75 years, M 21, F 10 Haloperidol: mean age 44.4 ± 16.76 years, M 28, F 4		impairments of the participant, and make the environment familiar to the participant by ensuring proper environmental cues that could facilitate orientation. Rescue: Benzodiazepines were not permitted. Other drugs for severe agitation: not reported.	- Incomplete outcome data (attrition bias) – All outcomes: high risk Seven participants not included in the analysis. Two participants in each group were not available for assessment after the first 1 to 2 study days because they left against medical advice. One participant in the quetiapine group received injectable haloperidol for symptom management on study day 2, and was excluded. One participant from each group could not be started on the assigned medication due to medical deterioration -Selective reporting: unclear risk Trial protocol not published so unable to confirm all outcomes were reported as planned. - Other bias: unclear risk Mansucript source reported as 'invited manuscript.' Referral bias: participants who were referred to the consultation-liaison psychiatry team were eligible for the study. It is unknown if all participants with suspected

					delirium are routinely referred to psychiatry in this hospital Note: Sample size/power calculation not reported.
Han 2004(75) Double-blind, randomised trial	n=24	Patients from medical, intensive care, or oncology wards, presenting with altered mental status and diagnosed with delirium. Exclusion: any type of dementia or other psychiatric diagnosis, patients already administered an antipsychotic prior to screening for disturbing behavioural problems. Haloperidol: mean age 66.5 ± 15.9 years, M 7, F 5 Risperidone: mean age 65.6 ± 8.3 years, M 6, F 6	7 days	Risperidone flexible dose, initial dose of 0.5 mg, 2x/d. vs Haloperidol flexible dose, initial dose of 0.75 mg 2x/d. Rescue: none reported.	- Random sequence generation (selection bias): unclear risk A consulting psychiatrist (not a member of the investigative team) randomly assigned participants without any knowledge of their care. Method of sequence generation not provided - Allocation concealment (selection bias): unclear risk Stated as a double-blind study. However, authors stated it was not possible to obtain identical looking tablets but the 'patients and caretakers did not know the name or effects of their drug'. Likely blinded - Blinding (performance bias and detection bias) – All outcomes: low risk - Incomplete outcome data (attrition bias) – All outcomes: high risk Intially, N = 28 and final sample of N = 24. Two participants in the haloperidol group dropped out:

					one because of medical deterioration on the second study day, and one because of severe sedation on the third study day. Two participants in the risperidone group dropped out: one because of spousal refusal to participate on the second study day, and one because of a tracheotomy operation on the fourth study day. Attrition not reported in the analysis -Selective reporting: unclear risk Trial protocol not found. - Other bias: low risk Funding: government
Hu 2004(71) Randomised	n=175	Adults aged > 65 years diagnosed with delirium Exclusion: Patients with a severe mental disease, those who had taken any antipsychotic drug, patients with angle-closure glaucoma, paralytic ileus, or material abuse. Olanzapine: mean age 74 ± 8 years, M 45, F 29 Haloperidol: mean age 74 ± 7 years, M 48, F 24	7 days	Olanzapine vs Haloperidol vs Placebo Olanzapine 1.25 to 2.5 mg PO, increased to a maximum daily dose of 20 mg Haloperidol daily dose range of 2.5 to 10 mg, i.m.	- Random sequence generation (selection bias): unclear risk No mention of method of randomization. Stating participants were randomised in a 5:5:2 ratio for olanzapine, haloperidol, and placebo groups, respectively. - Allocation concealment (selection bias): unclear risk No details provided.

		Placebo: mean age 73 ± 7 years, M 18, F 11		Rescue: No permitted, except in the instance of the development of extrapyramidal symptoms, for which banzhexol was administered with a maximum dose of 6mg.	- Blinding (performance bias and detection bias) – All outcomes: high risk Haloperidol could be given subcutaneously and olanzapine orally. No description of how treatments were concealed. No mention of blinding process. Not likely done. - Incomplete outcome data (attrition bias) – All outcomes: high risk No mention of how attrition was factored into statistical analysis (not described as ITT analysis) - Selective reporting: low risk - Other bias: unclear risk Sample size not reported. Unclear methodology regarding dosing protocol.
Lin 2008(76) Single-blind, Randomised	n=30	Patients from the hospice and palliative care center with advanced cancer diagnosed for delirium. Olanzapine: mean age 61.13 ± 16.5 years, M 9, F 7 Haloperidol: mean age 68 ± 12.14 years, M 4, F 10	7 days	Olanzapine 5 mg PO daily, permitted, daily maximum dose 15 mg vs Haloperidol 5mg PO daily, permitted, daily maximum dose 15 mg Rescue:	- Random sequence generation (selection bias): unclear risk Stated as a prospective randomised controlled clinical trial. Likely randomised. Methods of randomisation not stated - Allocation concealment (selection bias): unclear risk

				If adjunctive therapy required for acute symptoms, midazolam i.m. was used.	Insufficient details to assess. Stated that if participant needed an antipsychotic, they were 'separated randomly to an olanzapine group or a haldol group'. - Blinding (performance bias and detection bias) – All outcomes: low risk - Incomplete outcome data (attrition bias) – All outcomes: high risk Total number of participants enrolled and/or lost to follow-up not reported -Selective reporting: unclear risk Trial protocol not published so unable to confirm all outcomes were reported as planned. - Other bias: unclear risk Referral bias: A psychiatric specialist determined whether it was necessary for the participant to receive antipsychotic drug treatment based on clinical grounds. If an antipsychotic was deemed needed (criteria for use not provided), the participants were consented and randomized.

					Note: Sample size calculation not reported.
Maneeton 2013(77) Double-blind, randomised trial	n=52	medically ill adult diagnosed with delirium Exclusion: substance-induced delirium, known allergy or intolerance to study drugs, pregnancy or breast feeding, already receiving an antipsychotic drug, renal or hepatic failure. Quetiapine: mean age 56.6 ± 12 years, M 15, F 9 Haloperidol: mean age 57 ± 11.9 years, M 20, F 8	7 days	Quetiapine fexible dose (25 to 100mg/day) vs haloperidol flexible dose (0.5 to 2 mg/day) -Drug given at bed time with additional doses if required, daily maximum of four doses. -Dose was adjusted based on clinical safety, sleepiness, and calmness. Environmental manipulations emphasised, such as noise control, light intensity, reassurance, and stimulus modification. Rescue drugs: Other psychotropic drugs,	- Random sequence generation (selection bias): low risk - Allocation concealment (selection bias): low risk - Blinding (performance bias and detection bias) – All outcomes: low risk - Incomplete outcome data (attrition bias) – All outcomes: high risk Stated 13/24 quetiapine- and 22/ 28 haloperidol-treated participants completed the study. They used intention-to treat analysis if a participant received at least one dose of the study drug -Selective reporting: low risk - Other bias: unclear risk

				including benzodiazepines, were prohibited.	Trial was registered with clinicaltrials.gov (CNT00954603). Referral bias: All inpatients presumed to have delirium and needing consultation-liaison services from the psychiatric department were evaluated for Inclusion. Study funded by the Faculty ofMedicine, ChiangMai University, ChiangMai, Thailand.

Remarks
- Adverse events may include prolongation of the QTc interval, sudden cardiac death, cerebral vascular events, seizures, extrapyramidal effects, use of physical restraints, long-term cognitive impairment. However no trials reported the use of physical restraints, long-term cognitive measures, cerebrovascular events, sudden cardiac death or QTc abnormalities. One trial (Maneeton 2013) reported on seizures with one seizure in the quetiapine group and no seizures in the haloperidol group. This trial also reported arrhythmias with one AV block episode in the haloperidol group and no events in the quetiapine group. Note that Grover 2011 and Grover 2016 excluded patient with basal prolonged QTc interval - The intention of the authors was to investigate clinically relevant outcomes for patients however, It is important to note many of these outcomes were not reported in the studies. - Of note: 9 % (Grover 2011) to 71% (Lin 2008) of participants were females. - Mortality was very low and no deaths were reported in two studies (Grover 2011; Grover 2016). - All studies used titrated study drug according to symptom response.

Author's conclusions
"We found low-quality evidence indicating there is no difference between typical and atypical antipsychotics." "Adverse effects were poorly or rarely reported in the trials. Extrapyramidal symptoms were no different for typical compared to atypical antipsychotics." "The majority of recent studies have focused on critically ill participants, still leaving us with insufficient poor quality data for hospitalised, non-critically ill participant." For clinician: "Survey data indicates pharmacological interventions, such as antipsychotics, are often used to manage delirium symptoms in clinical practice. After updating this review, we caution clinicians to the fact that there is still insufficient evidence overall on this subject."

18.3 SGA versus SGA for delirium

Meta-analysis:
Neufeld 2019. AHRQ 2019 Antipsychotics for the Prevention and Treatment of Delirium.(27)

Inclusion criteria: RCTs for all outcomes except adverse events; and RCTs, non-RCTs, and prospective cohort studies with and without a comparison group for adverse, in any language, investigating adults who are at risk of delirium or adults with delirium, that evaluated any first-generation or second generation antipsychotic agents

Excluded: studies that did not use a validated instrument to diagnose delirium, studies of children, studies in which the effects of the antipsychotic drugs cannot be isolated, and studies that do not have a comparison group for outcomes other than adverse events.

Search strategy: Authors searched PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL®), and PsycINFO® through March 2019. We also hand-searched the reference lists of included articles, relevant reviews, and delirium-specific bibliographic repositories.

Assessment of quality of included trials: Risk of bias was evaluated: for randomized controlled trials (RCTs), the Cochrane Risk of Bias Tool was used, for observational studies, the Cochrane Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool was used. "We graded the strength of evidence using the grading scheme recommended by the Guide for Conducting Comparative Effectiveness Reviews."

Other methodological remarks: “We conducted meta-analyses when there were sufficient data (i.e., at least three studies) and studies were sufficiently homogenous with respect to key variables (e.g., population characteristics, study duration, treatment, and outcome definition).” “We qualitatively summarized studies that were not amenable to pooling.”

Remarks

- Although the drugs may have different mechanisms of action, authors anticipated that most drugs within a class would have similar clinical effects. Therefore, authors combined studies of unique medications within classes when reporting outcomes.
- The authors found 3 RCTs (Grover D 2011, Kim SW 2010, Lee KU 2005)(73),(78),(79) comparing SGA with SGA that could not be pooled. None of these studies met our inclusion criteria for study type or population size.

Author’s conclusions

“We were unable to draw conclusions for any type of drug-drug comparisons between second-generation antipsychotics or comparisons with any other types of therapies (i.e., other than antipsychotics) due to the absence of studies or insufficient evidence. In all RCTs and observational studies evaluating haloperidol versus placebo, second-generation antipsychotics versus placebo, haloperidol versus second-generation antipsychotics, and second-generation antipsychotics versus second-generation antipsychotics, there were no statistically significant differences in the occurrence of any of types of cardiac effects reported. … the larger body of evidence in all other patient populations, found no statistically significant increase in any neurological effect for any first- or second-generation antipsychotic compared with placebo or in other head-to-head trials.”

For clinician:
Our findings do not support the use of antipsychotics for the routine treatment of delirium. Notably, across a range of cardiac and neurological effects evaluated, there was little evidence of increased serious harms related to antipsychotics compared with placebo or with other antipsychotics (i.e., drug-to-drug comparisons),

19 Appendix. Evidence tables: insomnia

19.1 SGA versus placebo/active comparator

19.1.1 Olanzapine vs placebo/active comparator for insomnia

Meta-analysis: Thompson 2016
Atypical antipsychotics for insomnia: a systematic review(68)
Inclusion criteria:
"We searched for studies involving patients ≥18 years of age who were prescribed atypical antipsychotics for >1 week to treat primary insomnia or insomnia in the setting of another co-morbidity. Studies had to compare atypical antipsychotics to an active comparator or placebo. Eligible studies had to report efficacy or safety outcomes attributable to the intervention. The following study designs were included: randomized controlled trials (RCTs), controlled before– after studies, interrupted time series, case–control studies and prospective and retrospective cohort studies."
"We excluded studies of patients with bipolar disorder or schizophrenia (due to well established efficacy for these indications or where atypical antipsychotics were used as part of drug or alcohol addiction therapy. Studies of atypical antipsychotics for mood or anxiety disorders (and not specifically to treat insomnia) were excluded based on consultation with and consensus of clinical experts in neurologic and psychiatric pharmacotherapy and psychiatry."
Search strategy:
"We searched PubMed, EMBASE (1980 onward), Cochrane Central Register of Controlled Trials (current issue) and PsycINFO (1806 onward) from March 2015. We scanned reference lists of included studies, searched for additional clinical trials on clinicaltrials.gov and the World Health Organization Clinical Trials Registry website, and performed a grey literature search using the Turning Research Into Practice (TRIP) database, the Agency for Healthcare Research and Quality website and UpToDate. We contacted the manufacturers of quetiapine, risperidone and olanzapine for unpublished data. There were no language or publication-type restrictions."
Assessment of quality of included trials: yes
Other methodological remarks: /

Remarks:

The systematic review of Thompson 2016 found no studies comparing olanzapine to placebo/active comparator for insomnia. (68)

Author's conclusions:

“Following a systematic literature search, one RCT was identified regarding the efficacy and harms of quetiapine for primary insomnia. The study reported no significant difference in total sleep time, sleep latency and sleep satisfaction for quetiapine compared with placebo. A GRADE assessment found this study to be very low quality. Atypical antipsychotics are commonly used to manage insomnia. However, the findings of our systematic review suggest that these drugs should be avoided for first-line treatment of primary insomnia.”

19.1.2 Quetiapine vs placebo/active comparator for insomnia

Meta-analysis: Thompson 2016
Atypical antipsychotics for insomnia: a systematic review(68)
Inclusion criteria:
“We searched for studies involving patients ≥18 years of age who were prescribed atypical antipsychotics for >1 week to treat primary insomnia or insomnia in the setting of another co-morbidity. Studies had to compare atypical antipsychotics to an active comparator or placebo. Eligible studies had to report efficacy or safety outcomes attributable to the intervention. The following study designs were included: randomized controlled trials (RCTs), controlled before– after studies, interrupted time series, case–control studies and prospective and retrospective cohort studies.”
“We excluded studies of patients with bipolar disorder or schizophrenia (due to well established efficacy for these indications or where atypical antipsychotics were used as part of drug or alcohol addiction therapy. Studies of atypical antipsychotics for mood or anxiety disorders (and not specifically to treat insomnia) were excluded based on consultation with and consensus of clinical experts in neurologic and psychiatric pharmacotherapy and psychiatry.”
Search strategy:
“We searched PubMed, EMBASE (1980 onward), Cochrane Central Register of Controlled Trials (current issue) and PsycINFO (1806 onward) from March 2015. We scanned reference lists of included studies, searched for additional clinical trials on clinicaltrials.gov and the World Health Organization Clinical Trials Registry website, and performed a grey literature search using the Turning Research Into Practice (TRIP) database, the Agency for Healthcare Research and Quality website and UpToDate. We contacted the manufacturers of quetiapine, risperidone and olanzapine for unpublished data. There were no language or publication-type restrictions.”
Assessment of quality of included trials: yes
Other methodological remarks: /

Remarks:

The systematic review of Thompson 2016(68) found one double-blind RCT comparing quetiapine with placebo for 2 weeks. This study (n= 16) did not meet our inclusion criterion for sample size (n>40 for each arm).(69)

Author's conclusions:

"Following a systematic literature search, one RCT was identified regarding the efficacy and harms of quetiapine for primary insomnia. The study reported no significant difference in total sleep time, sleep latency and sleep satisfaction for quetiapine compared with placebo. A GRADE assessment found this study to be very low quality. Atypical antipsychotics are commonly used to manage insomnia. However, the findings of our systematic review suggest that these drugs should be avoided for first-line treatment of primary insomnia."

19.1.3 risperidone vs placebo/active comparator for insomnia

Meta-analysis: Thompson 2016
Atypical antipsychotics for insomnia: a systematic review(68)
Inclusion criteria:
"We searched for studies involving patients ≥18 years of age who were prescribed atypical antipsychotics for >1 week to treat primary insomnia or insomnia in the setting of another co-morbidity. Studies had to compare atypical antipsychotics to an active comparator or placebo. Eligible studies had to report efficacy or safety outcomes attributable to the intervention. The following study designs were included: randomized controlled trials (RCTs), controlled before– after studies, interrupted time series, case–control studies and prospective and retrospective cohort studies."
"We excluded studies of patients with bipolar disorder or schizophrenia (due to well established efficacy for these indications or where atypical antipsychotics were used as part of drug or alcohol addiction therapy. Studies of atypical antipsychotics for mood or anxiety disorders (and not specifically to treat insomnia) were excluded based on consultation with and consensus of clinical experts in neurologic and psychiatric pharmacotherapy and psychiatry."
Search strategy:
"We searched PubMed, EMBASE (1980 onward), Cochrane Central Register of Controlled Trials (current issue) and PsycINFO (1806 onward) from March 2015. We scanned reference lists of included studies, searched for additional clinical trials on clinicaltrials.gov and the World Health Organization Clinical Trials Registry website, and performed a grey literature search using the Turning Research Into Practice (TRIP) database, the Agency for Healthcare Research and Quality website and UpToDate. We contacted the manufacturers of quetiapine, risperidone and olanzapine for unpublished data. There were no language or publication-type restrictions."

Assessment of quality of included trials: yes
Other methodological remarks: /

Remarks:

The systematic review of Thompson 2016 found no studies comparing risperidone to placebo/active comparator for insomnia.(68)

Author's conclusions:

"Following a systematic literature search, one RCT was identified regarding the efficacy and harms of quetiapine for primary insomnia. The study reported no significant difference in total sleep time, sleep latency and sleep satisfaction for quetiapine compared with placebo. A GRADE assessment found this study to be very low quality. Atypical antipsychotics are commonly used to manage insomnia. However, the findings of our systematic review suggest that these drugs should be avoided for first-line treatment of primary insomnia."

19.1.4 Haloperidol versus placebo/active comparator

Meta-analysis: Schroeck 2016
Review of Safety and Efficacy of Sleep Medicines in Older Adults(67)
Inclusion criteria:
This review included systematic reviews, randomized controlled trials, observational studies, and case series that had an emphasis on insomnia in an older population.
Search strategy:
"The articles included in this review were chosen after a search of the published English-language medical literature. A secondary search was performed via review of the references found from the initial search. Non-English abstracts were included from the secondary search if an abstract was available in English. The search was conducted by using MEDLINE via Ovid (1966–June 2016), PubMed, and EMBASE (1980–June 2016) and included systematic reviews, randomized controlled trials, observational studies, case series, and case reports that involved neurologic effects, specifically sleep initiation and maintenance disorders in the geriatric patient population. Search terms included medications approved by the US Food and Drug Administration for insomnia: benzodiazepines (triazolam, estazolam, temazepam, flurazepam, and quazepam), non-BzRAs (zaleplon, zolpidem, and eszopiclone), the orexin receptor antagonist suvorexant, the melatonin receptor agonist ramelteon, and the antidepressants doxepin and trazodone. Off-label drugs such as other antidepressants, antihistamines, antipsychotics, gabapentin, pramipexole, tiagabine, valerian, and melatonin were also included."
Assessment of quality of included trials: no
Other methodological remarks: /

Remarks:

The review of Schroeck 2016 focusing on an older population did not discuss any study comparing haloperidol or any other FGA with placebo/active comparator for insomnia.(67)

21 Appendix: Safety of antipsychotics in children and young adults

21.1 Mortality

21.1.1 Antipsychotic vs control

Ray 2019(80)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results*** Only high dose vs control was calculated
Design: Retrospecitive cohort Followup: control group: 123005 person-years lower dose group:16159 person-years	n= 247 858 **high-dose:** 30 120 **low-dose:** 28 377 **control:** 189361	5-24 yrs USA No diagnosis of severe somatic illness, schizophrenia or related psychoses, or Tourette or chronic tic disorder	Current, new antipsychotic use (high dose) Vs (Current, new antipsychotic use (low dose) Vs)	Mortality (classified as deaths due to injury, suicide or unexpected deaths)	**RR: 1.80 (95%CI 1.06 to 3.07)** **NNH 2283 (888 to 30097)**
				Unexpected deaths	**RR 3.51 (1.54 to 7.96)** **NNH 2229 (802 to 10288)**
				Death due to injury or suicide	**RR** 1.03 (0.53 to 2.01)

higher dose group: 27345 person-years			Control medications (ADHD medication, antidepressants, mood stabilizers)		
*propensity-score adjusted					

21.1.2 FGA vs SGA

No studies met our inclusion criteria

21.1.3 SGA vs SGA

Ref	Comparison	N/n	Outcomes	Result
(3) AHRQ 2017 SR	Aripiprazole vs paliperidone	N= 1 n= 228 (Savitz 2015)	Mortality	0/115 vs 0/113

For characteristics of included studies: see chapter “Characteristics of included studies in AHRQ 2017 (Pillay 2017)”

21.1.4 FGA vs placebo

No studies met our inclusion criteria

21.1.5 SGA vs placebo

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2017 (3) SR	All SGA Vs Placebo	N= 13 n= 2447 (Findling 2008a, Haas 2009b, Singh 2011, NCT00194012, Findling 2015b, Findling 2013b, Findling 2009, Haas 2009c, Tohen 2007, Findling 2014b, Kent 2013, Marcus 2009, Owen 2009)	Mortality	0/1635 vs 0/812
	Aripiprazole Vs placebo	N= 6 n= 1051 (Findling 2008a, NCT00194012, Findling 2009, Findling 2014b, Marcus 2009, Owen 2009)	Mortality	0/680 vs 0/371
	Asenapine Vs placebo	N= 1 n= 403 (Findling 2015b)	Mortality	0/302 vs 0/101
	Olanzapine Vs	N= 1 n= 161	Mortality	0/107 vs 0/54

	placebo	(Tohen 2007)		
	Paliperidone Vs placebo	N= 1 n= 200 (Singh 2011)	Mortality	0/149 vs 0/51
	Risperidone Vs Placebo	N= 3 n= 395 (Haas 2009b, Haas 2009c, Kent 2013)	Mortality	0/248 vs 0/147

For characteristics of included studies: see chapter “Characteristics of included studies in AHRQ 2017 (Pillay 2017)”

21.2 Cardiac arrhythmias

21.2.1 FGA vs SGA

No studies met our inclusion critera.

21.2.2 SGA vs SGA

No studies of the AHRQ systematic review met our inclusion critera.

We found following studies, published after the AHRQ review:

Alda 2016(93)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: Prospective cohort Follow-up 12 months	n= 216	<18 yrs First prescription of any antipsychotic within 30 days prior to enrollment	Risperidone Vs Quetiapine Vs Olanzapine	QTc interval	Risperidone – olanzapine p=0.578 NS Risperidone – quetiapine p=0.216 NS Olanzapine – quetiapine p=0.528 NS

*adjusted for gender, age, antidepressant use, weight

Study details	n/Population	Comparison	Outcomes		Methodological
Jensen 2018(91) Design: RCT (DB, PG) Duration of follow-up: 12 weeks	n= 113 Mean age: 15.8 yr <u>Inclusion</u> 12-17 yr First episode of psychosis <u>Exclusion</u> Severe chronic somatic illness Pregnancy or lactation Substance dependence Organic or drug-induced psychosis	Quetiapine extended release Vs Aripiprazole	Safety		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: 82.3 % in safety analysis Drop-outs and Exclusions: • Described: no • Balanced across groups: unclear ITT:
			QTc change (ms) (PO) (using Hodges formula)	Quetiapine 6.8 ±20.2 Aripiprazole -3.4 ± 18.9 **Between-group difference p =0.004** **SS**	
			QTc > 450 ms	No patient had a QTcH exceeding 450ms	

					no (only patients with baseline and at least one follow-up ECG, exclusion of patients who had discontinued the trial medication prematurely) SELECTIVE REPORTING: no Sponsor: Non-industry

21.2.3 FGA vs placebo

No studies met our inclusion critera.

21.2.4 SGAs vs placebo

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2017 (3) SR	All SGA vs placebo	N= 14 n= 2425 (Findling 2013a, Findling 2012a, Singh 2011, Findling 2015a, Findling 2015b, Findling 2014a, DelBello 2009, Findling 2009, Pathak 2013, Owen 2009, Shea 2004, Aman 2002, Snyder 2002, Yoo 2013)	Cardiac arrhythmia	19/1490 vs 9/935 *No statistical testing*
	Aripiprazole vs placebo	N=3 n= 453 (Findling 2009, Owen 2009, Yoo 2013)	Cardiac arrhythmia	11/276 vs 8/117 *No statistical testing*
	Asenapine vs placebo	N= 2 n= 631 (Findling 2015a, Findling 2015b)	Cardiac arrhythmia	3/453 vs 0/178 *No statistical testing*
		N= 1 n= 403 (Findling 2015b)	QT prolongation	0/302 vs 0/101 *No statistical testing*
	Paliperidone vs placebo	N= 1 n= 99 (Singh 2011)	Cardiac arrhythmia	0/48 vs 0/51 *No statistical testing*
	Quetiapine vs placebo	N= 4 n= 655	Cardiac arrhythmia	0/375 vs 14/280 *No statistical testing*

		(Findling 2012a, Findling 2014a, DelBello 2009, Pathak 2013)		
	Risperidone vs placebo	N=3 n= 304 (Shea 2004, Aman 2002, Snyder 2002)	Cardiac arrhythmia	1/145 vs 0/159 *No statistical testing*

For characteristics of included studies: see chapter "Characteristics of included studies in AHRQ 2017 (Pillay 2017)"

Burcu 2018(103)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: Retrospective cohort Average follow-up 24.8 months	n= 74700	5-20 year olds who initiated atypical antipsychotic treatment	Current use atypical AP Vs Former use	Cardiovascular events	**RR: 1.55 (95% CI 1.09 to 2.21)**
*adjusted for disease risk score (similar to propensity score) and time from cohort entry (i.e. follow-up month)					

21.3 Metabolic and endocrine adverse events

21.3.1 Cardiometabolic Events

21.3.1.1 FGA vs SGA

Chung 2019(82)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results** **Adjusted HR*** **(95% CI)**

Design: Retrospective cohort Minimum follow-up of 2 years or until the occurrence of endpoint or discontinuation or switching of antipsychotic	n= 29030	Data from Taiwanese National Health Insurance Database 5-18 yrs Diagnosed with a psychiatric disorder (schizophrenia, bipolar disorders, depressive disorders, autism spectrum or other psychiatric disorders) and newly receiving antipsychotics (haloperidol, sulpiride, olanzapine, quetiapine, risperidone, amisulpride, aripiprazole, paliperidone or ziprasidone)	Haloperidol Vs risperidone	**occurrence of cardiometabolic events** type 2 diabetes mellitus, hypertension, dyslipidemia and major adverse cardiovascular events (MACE), including AMI, IHD, ischemic stroke, and cardiac death.	0.98 (0.56 to 1.70) NS

*adjusted for patients' age, sex, mental conditions (e.g., schizophrenic disorders, bipolar, anxiety, major depressive disorder, autism, hyperkinetic syndrome, conduct disorders), and use of mood stabilizers, hypnotics, sedatives, antidepressants, psychostimulants *NA* not applicable due to too few events,

21.3.1.2 SGA vs SGA

Chung 2019(82)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results** **Adjusted HR*** **(95% CI)**
Design: Retrospective cohort	n= 29030	Data from Taiwanese National Health Insurance Database	Aripiprazole Vs Risperidone	**Occurrence of cardiometabolic events**	HR 0.90 (0.54–1.48) NS

Minimum follow-up of 2 years or until the occurrence of endpoint or discontinuation or switching of antipsychotic		5-18 yrs Diagnosed with a psychiatric disorder (schizophrenia, bipolar disorders, depressive disorders, autism spectrum or other psychiatric disorders) and newly receiving antipsychotics (haloperidol, sulpiride, olanzapine, quetiapine, risperidone, amisulpride, aripiprazole, paliperidone or ziprasidone)	Olanzapine Vs risperidone	**Occurrence of cardiometabolic events**	HR 1.85 (0.79–4.32) NS
			Quetiapine Vs risperidone	**Occurrence of cardiometabolic events**	1.00 (0.50–1.96) NS

*adjusted for patients' age, sex, mental conditions (e.g., schizophrenic disorders, bipolar, anxiety, major depressive disorder, autism, hyperkinetic syndrome, conduct disorders), and use of mood stabilizers, hypnotics, sedatives, antidepressants, psychostimulants *NA* not applicable due to too few events,

21.3.2 Development of diabetes

21.3.2.1 FGA vs SGA

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2017 (3)	FGA Vs SGA	N= 1 n= 111 (Cianchetti 2011)	Development of diabetes	FGA Haloperidol: 0/29 pts SGA Clozapine: 1/12 pts developed diabetes at 2 years Risperidone: 0/33 Olanzapine: 0/12 Quetiapine and aripiprazole: too few patients to compare

For characteristics of included studies: see chapter "Characteristics of included studies in AHRQ 2017 (Pillay 2017)"

Chung 2019(82)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results** **Adjusted HR*** **(95% CI)**

Design: Retrospective cohort Minimum follow-up of 2 years or until the occurrence of endpoint or discontinuation or switching of antipsychotic	n= 29030	Data from Taiwanese National Health Insurance Database 5-18 yrs Diagnosed with a psychiatric disorder (schizophrenia, bipolar disorders, depressive disorders, autism spectrum or other psychiatric disorders) and newly receiving antipsychotics (haloperidol, sulpiride, olanzapine, quetiapine, risperidone, amisulpride, aripiprazole, paliperidone or ziprasidone)	Haloperidol Vs risperidone	**Type 2 diabetes melllitus**	0.42 (0.09–2.02) NS

*adjusted for patients' age, sex, mental conditions (e.g., schizophrenic disorders, bipolar, anxiety, major depressive disorder, autism, hyperkinetic syndrome, conduct disorders), and use of mood stabilizers, hypnotics, sedatives, antidepressants, psychostimulants

NA not applicable due to too few events,

21.3.2.2 SGA vs SGA

No studies met our inclusion criteria.

Update:

Chung 2019(82)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results** **Adjusted HR*** **(95% CI)**

Design: Retrospective cohort Minimum follow-up of 2 years or until the occurrence of endpoint or discontinuation or switching of antipsychotic	n= 29030	Data from Taiwanese National Health Insurance Database 5-18 yrs Diagnosed with a psychiatric disorder (schizophrenia, bipolar disorders, depressive disorders, autism spectrum or other psychiatric disorders) and newly receiving antipsychotics (haloperidol, sulpiride, olanzapine, quetiapine, risperidone, amisulpride, aripiprazole, paliperidone or ziprasidone)	Aripiprazole Vs Risperidone	**Type 2 diabetes melllitus**	0.39 (0.10–1.81) NS
			Olanzapine Vs risperidone	**Type 2 diabetes melllitus**	**4.70** **(1.01–21.82)** **SS more diabetes with olanzapine**
			Quetiapine Vs	**Type 2 diabetes melllitus**	0.68 (0.09–5.37)

			risperidone		NS
*adjusted for patients' age, sex, mental conditions (e.g., schizophrenic disorders, bipolar, anxiety, major depressive disorder, autism, hyperkinetic syndrome, conduct disorders), and use of mood stabilizers, hypnotics, sedatives, antidepressants, psychostimulants *NA* not applicable due to too few events,					

21.3.2.3 FGA vs placebo

21.3.2.4 SGA vs placebo

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2017 (3)	SGA vs placebo	N= 3 n= 703 (Findling 2015a, Finding 2014a, Pathak 2013)	Development of type 2 diabetes mellitus	21/436 vs 4/267
	Asenapine vs placebo	N= 1 n= 228 (Findling 2015a)	Development of type 2 diabetes mellitus	14/151 vs 4/77
	Quetiapine vs placebo	N= 2 n= 475 (Finding 2014a, Pathak 2013)	Development of type 2 diabetes mellitus	7/285 vs 0/190
	SGA Vs	N= 1 n= 43287		25.3 vs. 7.8 cases per 10,000 person-years follow-up HR 2.89 (95% CI 1.64 to 5.10) **SS**

	propensity-score matched controls not on antipsychotics	(Bobo 2013)	Development of type 2 diabetes mellitus (>12 months)	
				Risperidone (15,608 person-years): 16.7 cases per 10,000 person-years; HR 2.20, 95% CI 1.14 to 4.26 **SS (p < 0.0001)**
				Olanzapine (7,778 person-years): 20.6 cases per 10,000 person-years; HR 2.17, 95% CI 1.04 to 4.53 NS
				Quetiapine (6,554 person-years): 30.5 cases per 10,000 person-years; HR 2.76, 95% CI 1.37 to 5.56 NS
				Aripiprazole (2,470 person-years): 72.9 cases per 10,000 person-years; HR 7.72, 95% CI 3.70 to 16.12 **SS (p < 0.0001)**

For characteristics of included studies: see chapter "Characteristics of included studies in AHRQ 2017 (Pillay 2017)"

Chen 2016(83)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: Prospective cohort	n= 30550	10-29 yrs	Nonuse of atypical antipsychotics (<30 days cDDD)	Development of type 2 diabetes mellitus	**<u>In <18 years group:</u>** **Short-term user vs nonuser** HR 1.39 (0.94 to 3.02)

Follow-up:2-9 yrs Average follow-up NR		Diagnosis of ASD, and controls matched by age, sex and time of enrollment	Vs Short-term user (30-365 days cDDD) Vs Long-term user (>365 days cDDD)		NS **Long-term user vs nonuser** **HR 2.35 (1.23 to 4.50)** **SS more DM II with long-term users**
*unadjusted					

cDDD= cumulative defined daily dose

Xing 2017(84)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design:	n= 982214	6-24 yrs New users of SGA and non-SGA psychotropic medications (anxiolytics,	SGA use Vs	New diabetes diagnosis	SGA : 33/10000 patient-years Non-SGA : 18/10000 patient-years

Prospective cohort Median follow-up 384 days in non-SGA cohort, 223 days in SGA follow-up	SGA users: 45289 Non-SGA users: 932336	antidepressants, hypnotics, and mood stabilizers)	Non-SGA use		<u>SGA vs non-SGA :</u> **HR 1.71 (95%CI 1.33 to 2.20)** **SS more DM II with SGA use**
*controls were propensity score matched					

Chen 2018(85)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: Prospective cohort Follow-up 2-9yrs Average follow-up NR	n= 107847	10-29 yrs Diagnosis of ADHD, and controls matched by age, sex and time of enrollment	Nonuse of atypical antipsychotics (<30 days cDDD) Vs	Development of type 2 diabetes mellitus	**<u>In <18 years group:</u>** **Short-term user vs nonuser** HR 1.51 (95% CI 0.76 to 2.99) NS **Long-term user vs nonuser**

			Short-term user (30-365 days cDDD) Vs Long-term user (>365 days cDDD)		**HR 2.73 (95%CI 1.50 to 4.99)** **SS more DM II with long-term use**
*unadjusted					

21.3.3 Increased fasting glucose

21.3.3.1 FGA vs SGA

No studies met our inclusion criteria.

21.3.3.2 SGA vs SGA

No studies of the AHRQ systematic review met our inclusion critera.

We found following studies, published after the AHRQ review:

Study details	n/Population	Comparison	Outcomes		Methodological
Jensen 2019(89) Design: RCT (DB, PG) Duration of follow-up: 12 weeks	n= 113 Mean age: 15.7 yr <u>Inclusion</u> 12-17 yr First episode of psychosis <u>Exclusion</u> Severe chronic somatic illness Pregnancy or lactation Substance dependence Organic or drug-induced psychosis	Quetiapine extended release Vs Aripiprazole	Safety		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Drop-outs and Exclusions: • Described: yes • Balanced across groups: unclear ITT: no (all patients who received at least one dose of trial medication)
			Change in body weight (kg) (PO)	Quetiapine **4.88 (3.92 to 5.83)** Aripiprazole **1.97 (0.97 to 2.97)** **Between-group difference** **2.91 (1.54 to 4.29)** **SS more weight gain with quetiapine**	
			Change in BMI	Quetiapine **1.48 (1.16 to 1.81)** Aripiprazole **0.45 (0.11 to 0.80)** **Between-group difference** **1.03 (0.56 to 1.50)** **SS more weight gain with quetiapine**	
			Change in systolic BP	Quetiapine 2.15 (-0.85 to 5.15) Aripiprazole -2.91 (-5.86 to 0.03) **Between-group difference** **5.06 (1.13 to 8.99)**	

				SS more rise in systolic BP with quetiapine	SELECTIVE REPORTING: no Sponsor: Non-industry
			Change in diastolic BP	Quetiapine **2.88 (0.46 to 5.31)** Aripiprazole -3.94 (-6.34 to -1.55) **Between-group difference** **6.83 (3.72 to 9.93)** **SS more rise in diastolic BP with quetiapine**	
			Change in glucose (mmoL/L)	Quetiapine 0.02 (-0.01 to 0.04) Aripiprazole 0.01 (-0.01 to 0.04) **Between-group difference** 0.01 (-0.03 to 0.04) NS	
			Change in total cholesterol (mmoL/L)	Quetiapine **0.10 (0.06 to 0.15)** Aripiprazole -0.02 (-0.06 to 0.02) **Between-group difference** **0.12 (0.07 to 0.18)**	

				SS more rise in total cholesterol with quetiapine	
			Change in triglycerides (mmoL/L)	Quetiapine **0.24 (0.12 to 0.35)** Aripiprazole -0.01 (-0.12 to 0.11) **Between-group difference** **0.24 (0.09 to 0.39)** **SS more rise in triglycerides with quetiapine**	

21.3.3.3 FGA vs placebo

No studies met our inclusion criteria.

21.3.3.4 SGA vs placebo

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2017 (3) SR	All SGA Vs Placebo	N= 7 n= 1204 (Findling 2009, Findling 2008a, Yoo 2013, Pathak 2013, Aman 2014, Delbello 2009, Tohen 2007)	Increased fasting glucose	10/797 vs 5/407 RR 0.85 (95%CrI 0.26-2.76) NS
	Aripiprazole Vs placebo	N= 3 n= 651 (Findling 2009, Findling 2008a, Yoo 2013)	Increased fasting glucose	7/459 vs 3/192 RR 0.90 (95%CrI 0.16-5.44) NS
		N= 1 n= 197 (Findling 2013)	Increased fasting glucose (6to<12 months)	2/140 vs 1/57 RR 0.81 (95%CI: 0.08-8.80) NS
	Quetiapine Vs placebo	N= 1 n= 248 (Pathak 2013)	Increased fasting glucose	2/167 vs 0/81 RR 2.44 (95%CI: 0.12-50.25) NS
	Risperidone Vs Placebo	N= 1 n= 153 (Aman 2014)	Increased fasting glucose	0/73 vs 1/80 RR 0.36 (95%CI: 0.02-8.82) NS

For characteristics of included studies: see chapter “Characteristics of included studies in AHRQ 2017 (Pillay 2017)”

21.3.4 Weight

21.3.4.1 FGA vs SGA

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2017 (3) SR	FGA vs SGA	N= 14 n= 506 (Sikich 2008, Yoo 2011, Sikich 2004, Ratzoni 2002, Malone 2001, Miral 2008, Bruggeman 2001, Gilbert 2004, Ebert 2014, Kumra 1996, Conus 2015)	Weight (kg)	MD -2.67 (95% CrI -4.61 to -0.70) SS less weight gain with FGA
		N= 7 n= 236 (Sikich 2008, Sikich 2004, Gothelf 2002, Ratzoni 2002) NOTE: the AHRQ document only reported 4 of the 7 references	BMI (kg/m^2)	MD -1.57 (95% CrI -2.49 to -0.53) SS less weight gain with FGA

For characteristics of included studies: see chapter “Characteristics of included studies in AHRQ 2017 (Pillay 2017)”

21.3.4.2 SGA vs SGA

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2017 (3) SR	Aripiprazole vs olanzapine	N= 1 n= 99 (Correll 2009)	Weight (kg)	MD -4.12 (95% CI -5.50 to -2.74) SS less weight gain with aripiprazole
		N= 1 n= 86 (Correll 2009)	≥7% increase in weight	24/41 vs 38/45 RR 0.69 (95% CI 0.52 to 0.92) SS fewer patients with ≥7% increase in weight with aripiprazole
		N= 1 n= 99 (Correll 2009)	BMI (kg/m^2)	MD -1.34 (95% CI -1.85 to -0.83) SS Less weight gain with aripiprazole
	Aripiprazole vs paliperidone	N= 1 n= 226 (Savitz 2015)	Weight (kg)	MD -1.28 (95% CI -1.95 to -0.61) SS less weight gain with aripiprazole

		N= 1 n= 226 (Savitz 2015)	BMI (kg/m^2)	MD -0.50 (95% CI -0.74 to -0.26) SS less weight gain with aripiprazole
		N= 1 n= 226 (Savitz 2015)	Weight (6-12 months)	MD -1.90 (95% CI -2.96 to -0.84) SS less weight gain with aripiprazole
		N= 1 n= 226 (Savitz 2015)	BMI (kg/m^2) (6-12 months)	MD -0.70 (95% CI -1.07 to -0.33) SS less weight gain with aripiprazole
		N= 1 n= 226 (Savitz 2015)	≥7% increase in weight	20/114 vs 29/112 RR 0.68 (95% CI 0.41 to 1.12) NS

	Aripiprazole vs quetiapine	N= 1 n= 92 (Correll 2009)	Weight (kg)	MD -1.63 (95% CI -3.01 to -0.25) SS less weight gain with aripiprazole
		N= 1 n= 92 (Correll 2009)	BMI (kg/m^2)	MD -0.45 (95% CI -0.96 to 0.06) NS
	Aripiprazole vs risperidone	N= 1 n= 215 (Correll 2009)	Weight (kg)	MD -0.90 (95% CI -1.81 to 0.01) NS

		N= 1 n= 176 (Correll 2009)	≥7% increase in weight	24/41 vs 87/135 RR 0.91 (95% CI 0.68 to 1.21) NS
		N= 1 n= 215 (Correll 2009)	BMI (kg/m^2)	MD -0.25 (95% CI -0.62 to 0.12)
		N= 1 n= 142 (Wink 2014)	BMI (kg/m^2) (>12 months)	MD -0.31 (95%CI -1.78 to 1.16)

	Clozapine vs olanzapine	N= 5 n= 136 (Shaw 2006, Kumra 2008, Fleischhaker 2006, Hrdlicka 2009, Kumra 1998)	Weight (kg)	MD -1.56 (95% CrI -5.12 to 1.57) NS
		N= 3 n= 87 (Shaw 2006, Kumra 2008, Fleischhaker 2006)	BMI (kg/m^2)	MD -0.66 (95% CrI -2.59 to 1.23) NS
	Olanzapine vs quetiapine	N= 3 n= 232 (Correll 2009, Arango 2014, Fraguas 2008)	Weight (kg)	MD 4.00 (95% CrI -1.67 to 10.79) NS

		N= 3 n= 185 (Arango 2009, Arango 2014, Fraguas 2008)	Weight (kg) (6-12 months)	MD 7.91 (95% CrI 3.65 to 12.29) SS more weigh gain with olanzapine
		N= 3 n= 192 (Correll 2009, Jensen 2008, Arango 2014)	≥7% increase in weight	72/99 vs 47/93 RR 1.41 (95% CrI 0.65 to 2.83) NS
		N= 1 n= 91 (Arango 2014)	≥7% increase in weight (6-12 months)	18/44 vs 22/47 RR 0.87 (95% CI 0.55 to 1.40) NS

		N= 3 n= 232 (Correll 2009, Arango 2014, Fraguas 2008)	BMI (kg/m^2)	MD 1.36 (95% CrI -0.29 to 3.40) NS
		N= 4 n= 203 (Castro-Fornieles 2008, Arango 2009, Arango 2014, Fraguas 2008)	BMI (kg/m^2) (6-12 months)	MD 2.68 (95% CrI 0.96 to 4.27) SS more weight gain with olanzapine
	Olanzapine vs risperidone	N= 13 n= 936 (Sikich 2008, Sikich 2004, Ratzoni 2002, Correll 2009, Fleischhaker 2006, Hrdlicka 2009, Arango 2014, Fraguas 2008, Mozes 2006, Van Bruggen 2003, Biederman 2005, Pogge 2005, Crocq 2007)	Weight (kg)	MD 2.18 (95% CrI 1.13 to 3.25)

		N= 4 n= 295 (Sikich 2008, Arango 2009, Fleischhaker 2006, Fraguas 2008)	Weight (kg) (6-12 months)	MD 4.40 (95% CrI -0.54 to 9.86)
		N= 6 n= 504 (Ratzoni 2002, Correll 2009, Fleischhaker 2006, Jensen 2008, Arango 2014, Van Bruggen 2003)	≥7% increase in weight	107/150 vs 188/354 RR 1.36 (95% CrI 0.93 to 3.42)
		N= 3 n= 264 (Cianchetti 2011, Fleischhaker 2006, Arango 2014)	≥7% increase in weight (6-12 months)	28/64 vs 64/200 RR 1.44 (95% CrI 0.55 to 5.50)

		N= 9 n= 737 (Crocq 2007, Sikich 2008, Sikich 2004, Ratzoni 2002, Arango 2014, Correll 2009, Fleischhaker 2006, Fraguas 2008, Khan 2009)	BMI (kg/m^2)	MD 0.94 (95% CrI 0.64 to 1.30) SS more weight gain with olanzapine
		N= 5 n= 328 (Sikich 2008, Castro-Fornieles 2008, Arango 2014, Fleischhaker 2006, Fraguas 2008)	BMI (kg/m^2) (6-12 months)	MD 1.66 (95% CrI 0.19 to 3.42) SS more weight gain with olanzapine
	Quetiapine vs risperidone	N= 3 n= 436 (Correll 2009, Arango 2014, Fraguas 2008)	Weight (kg)	MD 0.08 (95% CrI -3.77 to 3.14) NS

		N= 3 n= 295 (Arango 2014, Fraguas 2008, Ronsley 2015)	Weight (kg) (6-12 months)	MD -1.48 (95% CI -4.16 to 1.18) NS
		N= 4 n= 417 (Correll 2009, Jensen 2008, Arango 2014, Swadi 2010)	≥7% increase in weight	55/104 vs 176/313 RR 0.91 (95% CrI 0.56 to 1.44) NS
		N= 1 n= 204 (Arango 2014)	≥7% increase in weight (6-12 months)	22/47 vs 56/157 RR 1.31 (95% CI 0.91 to 1.90) NS
		N= 3 n= 436 (Arango 2014, Correll 2009, Fraguas 2008)	BMI (kg/m^2)	MD 0.04 (95% CrI -1.34 to 1.20) NS

		N= 4 n= 328 (Castro-Fornieles 2008, Arango 2014, Fraguas 2008, Ronsley 2015)	BMI (kg/m^2) (6-12 months)	MD -0.32 (95% CrI -1.56 to 1.12) NS

For characteristics of included studies: see chapter "Characteristics of included studies in AHRQ 2017 (Pillay 2017)"

Study details	n/Population	Comparison	Outcomes		Methodological
Jensen 2019(89) Design: RCT (DB, PG)	n= 113 Mean age: 15.7 yr <u>Inclusion</u> 12-17 yr First episode of psychosis	Quetiapine extended release Vs Aripiprazole	Safety		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes
			Change in body weight (kg) (PO)	Quetiapine **4.88 (3.92 to 5.83)** Aripiprazole **1.97 (0.97 to 2.97)** **Between-group difference** **2.91 (1.54 to 4.29)** **SS more weight gain with quetiapine**	
			Change in BMI	Quetiapine **1.48 (1.16 to 1.81)** Aripiprazole **0.45 (0.11 to 0.80)**	

Duration of follow-up: 12 weeks	<u>Exclusion</u> Severe chronic somatic illness Pregnancy or lactation Substance dependence Organic or drug-induced psychosis			**Between-group difference** **1.03 (0.56 to 1.50)** **SS more weight gain with quetiapine**	FOLLOW-UP: Drop-outs and Exclusions: • Described: yes • Balanced across groups: unclear ITT: no (all patients who received at least one dose of trial medication) SELECTIVE REPORTING: no Sponsor: Non-industry
			Change in systolic BP	Quetiapine 2.15 (-0.85 to 5.15) Aripiprazole -2.91 (-5.86 to 0.03) **Between-group difference** **5.06 (1.13 to 8.99)** **SS more rise in systolic BP with quetiapine**	
			Change in diastolic BP	Quetiapine **2.88 (0.46 to 5.31)** Aripiprazole -3.94 (-6.34 to -1.55) **Between-group difference** **6.83 (3.72 to 9.93)** **SS more rise in diastolic BP with quetiapine**	
			Change in glucose (mmoL/L)	Quetiapine 0.02 (-0.01 to 0.04) Aripiprazole 0.01 (-0.01 to 0.04)	

				Between-group difference 0.01 (-0.03 to 0.04) NS	
			Change in total cholesterol (mmoL/L)	Quetiapine **0.10 (0.06 to 0.15)** Aripiprazole -0.02 (-0.06 to 0.02) **Between-group difference** **0.12 (0.07 to 0.18)** **SS more rise in total cholesterol with quetiapine**	
			Change in triglycerides (mmoL/L)	Quetiapine **0.24 (0.12 to 0.35)** Aripiprazole -0.01 (-0.12 to 0.11) **Between-group difference** **0.24 (0.09 to 0.39)** **SS more rise in triglycerides with quetiapine**	

Yoon 2016(87)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: Retrospective cohort Mean follow-up 1.22 years	n= 202	2-20 yrs ASD Treated with one of five SGAs (risperidone, aripiprazole, olanzapine, quetiapine or ziprasidone)	Olanzapine use vs aripiprazole use	BMI z-score change	**0.39 (0.08 to 0.70)** **SS more weight gain with olanzapine**
			Olanzapine use vs quetiapine use	BMI z-score change	**0.62 (0.27 to 0.96)** **SS more weight gain with olanzapine**
			Olanzapine use vs risperidone use	BMI z-score change	**0.43 (0.12 to 0.74)** **SS more weight gain with olanzapine**
			aripiprazole use vs quetiapine use	BMI z-score change	0.22 (-0.01 to 0.46) NS
			Risperidone use vs aripiprazole use	BMI z-score change	-0.04 (-0.23 to 0.15) NS
			Risperidone use vs quetiapine use	BMI z-score change	0.18 (-0.05 to 0.42) NS
*adjusted for weight gain-attenuating medications					

Baeza 2017(104)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: Prospective cohort Follow-up 1 year	n= 117	4-17 yr Any psychiatric disorder except eating disorders Being AP-naïve or quasi-naïve (having begun any first AP treatment up to 30 days before baseline) Starting AP.	Risperidone Vs Olanzapine Vs Quetiapine	Weight	*We do not report the results for this outcome as 67% of participants dropped out and the size of each group was deemed too small.*
				BMI	*We do not report the results for this outcome as 67% of participants dropped out and the size of each group was deemed too small.*

Schoemakers 2019(92)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: Retrospective cohort Follow-up: 12 months	n= 131	≤19 yrs Long-term treatment with risperidone or aripiprazole	Risperidone use Vs Aripiprazole use	BMI z-score change	**Risperidone** 0.37 (0.21 to 0.53) **Aripiprazole** 0.30 (0.07 to 0.53) **Risperidone vs aripiprazole** No significant difference between groups p= 0.973

*unadjusted					

21.3.4.3 FGA vs placebo

No studies met our inclusion criteria.

21.3.4.4 SGA vs placebo

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2017 (3) SR	SGA vs placebo	N= 37 n= 3919 (Findling 2013a, Findling 2012a, Kryzhanovskaya 2009, Woods 2003, Singh 2011, Findling 2014a, Kowatch 2015, DelBello 2009, DelBello 2002, Findling 2013b, Findling 2009, Haas 2009c, Pathak 2013, Tohen 2007, Tramontina	Weight (kg)	MD 1.53 (95% CI 1.11 to 1.98) SS more weight gain with SGA

		2009, Findling 2014b, Hellings 2006, Hollander 2006, Loebel 2016, Marcus 2009, McCracken 2002, Owen 2009, Shea 2004, Aman 2014, Aman 2002, Aman 2009, Armenteros 2007, Buitelaar 2001, Connor 2008, Findling 2000, Snyder 2002, Sallee 2000, Yoo 2013, Van Bellinghen 2001, Bastiaens 2009, Findling 2015a, Findling 2015b)		
		N= 16 n= 2462 (Findling 2008a, Kryzhanovskaya 2009, Findling 2015b, Kowatch 2015, DelBello 2009, Findling 2009, Haas 2009c, Tohen 2007, Loebel 2016, Kent 2013, Marcus 2009, Owen 2009, Armenteros 2007, Reyes 2006, Snyder 2002, Yoo 2013)	BMI (kg/m^2)	MD 0.66 (95% CI 0.44 to 0.91) SS more weight gain with SGA

		N= 17 n= 3057 (Findling 2012a, Findling 2008a, Kryzhanovskaya 2009, Woods 2003, Singh 2011, Findling 2015a, Findling 2015b, Findling 2014a, Findling 2009, Haas 2009c, Pathak 2013, Tohen 2007, Findling 2014b, Hollander 2006, Marcus 2009, Owen 2009, Van Bellinghen 2001)	≥7% increase in weight	337/2023 vs 42/1034 RR 3.53 (95%CrI 2.49 to 5.23)
	Aripiprazole vs placebo	N= 7 n= 1042 (Findling 2008a, Findling 2009, Tramontina 2009, Findling 2014b, Marcus 2009, Owen 2009, Yoo 2013)	Weight (kg)	MD 0.98 (95% CrI 0.54 to 1.48)

		N= 5 n= 991 (Findling 2008a, Findling 2009, Findling 2014b, Marcus 2009, Owen 2009)	≥7% increase in weight	93/647 vs 15/344 RR 3.01 (95% CrI 1.33 to 7.10)
		N= 5 n= 881 (Findling 2008a, Findling 2009, Marcus 2009, Owen 2009, Yoo 2013)	BMI (kg/m^2)	MD 0.33 (95% CI 0.07 to 0.67) SS more weight gain with aripiprazole
	Asenapine vs placebo	N= 2 n= 650 (Findling 2015a, Findling 2015b)	≥7% increase in weight	**Findling 2015b** 26/269 vs 1/89 RR 8.60 (95% CI 1.18 to 62.48) **Findling 2015a** 19/194 vs 3/98 RR 3.20 (95% CI 0.97 to 10.55)

		N= 1 n= 403 (Findling 2015b)	BMI (kg/m^2)	MD 0.52 (95%CI 0.36 to 0.69) SS more weight gain with asenapine
	Olanzapine vs placebo	N= 4 n= 337 (Kryzhanovskaya 2009, Woods 2003, Tohen 2007, Loebel 2016)	Weight (kg)	MD 3.96 (95% CI 2.31 to 6.34)
		N= 1 n= 161 (Tohen 2007)	BMI (kg/m^2)	MD 1.16 (95% CI 0.93 to 1.39)
		N= 4 n= 337 (Kryzhanovskaya 2009, Woods 2003, Tohen 2007, Hollander 2006)	≥7% increase in weight	99/215 vs 8/122 RR 6.08 (95% CrI 1.84 to 27.06)

	Paliperidone vs placebo	N= 1 n= 200 (Singh 2011)	Weight (kg)	MD 0.90 (95% CI 0.34 to 1.46)
		N= 1 n= 200 (Singh 2011)	≥7% increase in weight	15/149 vs 1/51 RR 5.13 (95% CI 0.70 to 37.90)
	Quetiapine vs placebo	N= 6 n= 778 (Findling 2012a, Findling 2014a, DelBello 2009, DelBello 2002, Pathak 2013, Connor 2008)	Weight (kg)	MD 1.44 (95% CI 0.60 to 2.31)
		N= 3 n= 697 (Findling 2012a, Findling 2014a, Pathak 2013)	≥7% increase in weight	70/432 vs 11/265 RR 3.41 (95% CrI 0.95 to 18.37)

	Risperidone vs placebo	N= 14 n= 929 (Kowatch 2015, Haas 2009c, Hellings 2006, Kent 2013, McCracken 2002, Shea 2004, Aman 2014, Aman 2002, Aman 2009, Armenteros 2007, Buitelaar 2001, Findling 2000, Snyder 2002, Van Bellinghen 2001)	Weight (kg)	MD 1.52 (95% CI 0.78 to 2.29)
		N= 4 n= 467 (Luby 2006, Nagaraj 2006, Reyes 2006, Martin 2000)	Weight (kg) (6-12 months)	MD 2.86 (95% CrI -1.22 to 7.42)
		N= 1 n= 169 (Haas 2009c)	≥7% increase in weight	13/111 vs 3/58 RR 2.26 (95% CI 0.67 to 7.63)

		N= 6 n= 730 (Kowatch 2015, Haas 2009c, Kent 2013, Armenteros 2007, Reyes 2006, Snyder 2002)	BMI (kg/m^2)	MD 0.68 (95% CI 0.27 to 1.18) SS more weight gain with risperidone
		N= 1 n= 335 (Reyes 2006)	BMI (kg/m^2) (6-12 months)	MD 0.70 (95% CI 0.49 to 0.91) SS more weight gain with risperidone

For characteristics of included studies: see chapter "Characteristics of included studies in AHRQ 2017 (Pillay 2017)"

Patel 2017(86)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: Retrospective cohort	n= 5391	≤18 yrs New bipolar disorder episode	No treatment Vs	BMI change (kg/m^2)	**0.09 (0.02 to 0.17)** **SS more weight gain with atypical antipsychotic therapy**

Follow-up: 12 months	atypical antipsychotic-treated: 847 untreated: 4544		Atypical antipsychotic therapy		
*adjusted for baseline BMI, sociodemographic factors, comorbidities, and psychotherapy					

21.3.5 Hyperprolactinemia

21.3.5.1 FGA vs SGA

No studies met our inclusion criteria

21.3.5.2 SGA vs SGA

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2017 (3) SR	Aripiprazole vs paliperidone	N= 1 n= 227 (Savitz 2015)	Hyperprolactinemia (6-12 months)	5/114 vs 59/113 **RR 0.04 (95% CI 0.02 to 0.11)** **SS less hyperprolactinemia with aripiprazole**
	Olanzapine vs risperidone	N= 3 n= 128 (Alacqua 2008, Saito 2004, Mozes 2006)	Hyperprolactinemia	7/49 vs 27/79 RR 0.46 (95% CrI 0.11 to 1.70) NS

For characteristics of included studies: see chapter “Characteristics of included studies in AHRQ 2017 (Pillay 2017)”

21.3.5.3 FGA vs placebo

No studies met the inclusion criteria

21.3.5.4 SGA vs placebo

Ref	Comparison	N/n	Outcomes	Result

AHRQ 2017 (3) SR	SGA vs placebo	N= 12 n= 2009 (Owen 2009, Findling 2015a, Tohen 2007, Kryzhanovskaya 2009, Findling 2014a, Findling 2012a, Pathak 2013, Snyder 2002, Sallee 2000, Findling 2013b, Aman 2014, Delbello 2009)	Hyperprolactinemia	231/1261 vs 98/748 RR 2.04 (95% CrI 0.82 to 5.44) NS
	Aripiprazole vs placebo	N= 1 n= 98 (Owen 2009)	Hyperprolactinemia	1/47 vs 3/51 RR 0.36 (95% CI 0.04 to 3.36) NS
	Asenapine vs placebo	N= 1 n= 306 (Findling 2015a)	Hyperprolactinemia	42/204 vs 13/102 RR 1.62 (95% CI 0.91 to 2.87) NS

	Olanzapine vs placebo	N= 1 n= 161 (Tohen 2007)	Hyperprolactinemia	Tohen 2007 50/107 vs 1/54 RR 25.53 (95% CI 3.58 to 177.76) SS more hyperprolactinemia with olanzepine
	Quetiapine vs placebo	N= 3 n= 535 Findling 2014a, Findling 2012a, Pathak 2013	Hyperprolactinemia	33/355 vs 12/180 *No statistical test reported*
	Risperidone vs placebo	N= 2 n= 251 (Snyder 2002, Aman 2014)	Hyperprolactinemia	**Aman 2014** 4/68 vs 4/73 RR 1.07 (95% CI 0.28 to 4.12) NS **Snyder 2002** 6/53 vs 0/57 RR 13.96 (95% CI 0.81 to 241.98) NS

For characteristics of included studies: see chapter “Characteristics of included studies in AHRQ 2017 (Pillay 2017)”

21.3.6 Dyslipidemia

21.3.6.1 FGA vs SGA

Chung 2019(82)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results** **Adjusted HR*** **(95% CI)**
Design: Retrospective cohort Minimum follow-up of 2 years or until the occurrence of endpoint or discontinuation or switching of antipsychotic	n= 29030	Data from Taiwanese National Health Insurance Database 5-18 yrs Diagnosed with a psychiatric disorder (schizophrenia, bipolar disorders, depressive disorders, autism spectrum or other psychiatric disorders) and newly receiving antipsychotics (haloperidol, sulpiride, olanzapine, quetiapine, risperidone, amisulpride, aripiprazole, paliperidone or ziprasidone)	Haloperidol Vs risperidone	**Dyslipidemia**	0.74 (0.25–2.20) NS
*adjusted for patients' age, sex, mental conditions (e.g., schizophrenic disorders, bipolar, anxiety, major depressive disorder, autism, hyperkinetic syndrome, conduct disorders), and use of mood stabilizers, hypnotics, sedatives, antidepressants, psychostimulants					

NA not applicable due to too few events,

21.3.6.2 SGA vs SGA

Chung 2019(82)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results** **Adjusted HR*** **(95% CI)**
Design: Retrospective cohort Minimum follow-up of 2 years or until the occurrence of endpoint or discontinuation or switching of antipsychotic	n= 29030	Data from Taiwanese National Health Insurance Database 5-18 yrs Diagnosed with a psychiatric disorder (schizophrenia, bipolar disorders, depressive	Aripiprazole Vs Risperidone	**Dyslipidemia**	0.67 (0.26–1.69) NS
			Olanzapine Vs risperidone	**Dyslipidemia**	1.18 (0.16–8.92) NS

		disorders, autism spectrum or other psychiatric disorders) and newly receiving antipsychotics (haloperidol, sulpiride, olanzapine, quetiapine, risperidone, amisulpride, aripiprazole, paliperidone or ziprasidone)	Quetiapine Vs risperidone	**Dyslipidemia**	0.33 (0.04–2.44) NS
*adjusted for patients' age, sex, mental conditions (e.g., schizophrenic disorders, bipolar, anxiety, major depressive disorder, autism, hyperkinetic syndrome, conduct disorders), and use of mood stabilizers, hypnotics, sedatives, antidepressants, psychostimulants *NA* not applicable due to too few events,					

21.3.7 Increased total cholesterol

21.3.7.1 FGA vs SGA

No studies met our inclusion criteria

21.3.7.2 SGA vs SGA

Study details	n/Population	Comparison	Outcomes		Methodological
Jensen 2019(89) Design: RCT (DB, PG) Duration of follow-up: 12 weeks	n= 113 Mean age: 15.7 yr <u>Inclusion</u> 12-17 yr First episode of psychosis <u>Exclusion</u> Severe chronic somatic illness Pregnancy or lactation Substance dependence Organic or drug-induced psychosis	Quetiapine extended release Vs Aripiprazole	Safety		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Drop-outs and Exclusions: • Described: yes • Balanced across groups: unclear ITT: no (all patients who received at least one dose of trial medication)
			Change in body weight (kg) (PO)	Quetiapine **4.88 (3.92 to 5.83)** Aripiprazole **1.97 (0.97 to 2.97)** **Between-group difference** **2.91 (1.54 to 4.29)** **SS more weight gain with quetiapine**	
			Change in BMI	Quetiapine **1.48 (1.16 to 1.81)** Aripiprazole **0.45 (0.11 to 0.80)** **Between-group difference** **1.03 (0.56 to 1.50)** **SS more weight gain with quetiapine**	
			Change in systolic BP	Quetiapine 2.15 (-0.85 to 5.15) Aripiprazole -2.91 (-5.86 to 0.03) **Between-group difference**	

				5.06 (1.13 to 8.99) **SS more rise in systolic BP with quetiapine**	SELECTIVE REPORTING: no Sponsor: Non-industry
			Change in diastolic BP	Quetiapine **2.88 (0.46 to 5.31)** Aripiprazole -3.94 (-6.34 to -1.55) **Between-group difference** **6.83 (3.72 to 9.93)** **SS more rise in diastolic BP with quetiapine**	
			Change in glucose (mmoL/L)	Quetiapine 0.02 (-0.01 to 0.04) Aripiprazole 0.01 (-0.01 to 0.04) **Between-group difference** 0.01 (-0.03 to 0.04) NS	
			Change in total cholesterol (mmoL/L)	Quetiapine **0.10 (0.06 to 0.15)** Aripiprazole -0.02 (-0.06 to 0.02) **Between-group difference**	

				0.12 (0.07 to 0.18) **SS more rise in total cholesterol with quetiapine**	
			Change in triglycerides (mmoL/L)	Quetiapine **0.24 (0.12 to 0.35)** Aripiprazole -0.01 (-0.12 to 0.11) **Between-group difference** **0.24 (0.09 to 0.39)** **SS more rise in triglycerides with quetiapine**	

21.3.7.3 FGA vs placebo

No studies met our inclusion criteria

21.3.7.4 SGA vs placebo

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2017 (3) SR	SGA vs placebo	N= 6 n= 643 (DelBello 2009, Findling 2009, Pathak 2013, Tohen 2007, Owen 2009, Bastiaens 2009)	Increased total cholesterol	92/410 vs 13/233 RR 3.17 (95% CI 1.29 to 9.13)
	Aripiprazole vs placebo	N= 2 n= 413 (Marcus 2009, Findling 2009)	Increased total cholesterol	Marcus 2009 0/52 vs 0/166 Not estimable **Findling 2009** 55/130 vs 11/65 RR 2.50 (95% CI 1.41 to 4.44)

		N= 1 n= 198 (Findling 2013)	Increased total cholesterol (6-12 months)	64/141 vs 15/57 RR 1.72 (95% CI 1.08 to 2.76)
	Quetiapine vs placebo	N= 1 n= 153 (Pathak 2013)	Increased total cholesterol	30/109 vs 2/44 RR 6.06 (95% CI 1.51 to 24.26)

For characteristics of included studies: see chapter “Characteristics of included studies in AHRQ 2017 (Pillay 2017)”

21.3.8 Increased triglycerides

21.3.8.1 FGA vs SGA

No studies met our inclusion criteria

21.3.8.2 SGA vs SGA

No studies met our inclusion criteria

Study details	n/Population	Comparison	Outcomes		Methodological
Jensen 2019(89) Design: RCT (DB, PG) Duration of follow-up: 12 weeks	n= 113 Mean age: 15.7 yr <u>Inclusion</u> 12-17 yr First episode of psychosis <u>Exclusion</u> Severe chronic somatic illness Pregnancy or lactation Substance dependence Organic or drug-induced psychosis	Quetiapine extended release Vs Aripiprazole	Safety		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Drop-outs and Exclusions: • Described: yes • Balanced across groups: unclear ITT: no (all patients who received at least one dose of trial medication)
			Change in body weight (kg) (PO)	Quetiapine **4.88 (3.92 to 5.83)** Aripiprazole **1.97 (0.97 to 2.97)** **Between-group difference** **2.91 (1.54 to 4.29)** **SS more weight gain with quetiapine**	
			Change in BMI	Quetiapine **1.48 (1.16 to 1.81)** Aripiprazole **0.45 (0.11 to 0.80)** **Between-group difference** **1.03 (0.56 to 1.50)** **SS more weight gain with quetiapine**	
			Change in systolic BP	Quetiapine 2.15 (-0.85 to 5.15) Aripiprazole -2.91 (-5.86 to 0.03) **Between-group difference**	

				5.06 (1.13 to 8.99) **SS more rise in systolic BP with quetiapine**	SELECTIVE REPORTING: no Sponsor: Non-industry
			Change in diastolic BP	Quetiapine **2.88 (0.46 to 5.31)** Aripiprazole -3.94 (-6.34 to -1.55) **Between-group difference** **6.83 (3.72 to 9.93)** **SS more rise in diastolic BP with quetiapine**	
			Change in glucose (mmoL/L)	Quetiapine 0.02 (-0.01 to 0.04) Aripiprazole 0.01 (-0.01 to 0.04) **Between-group difference** 0.01 (-0.03 to 0.04) NS	
			Change in total cholesterol (mmoL/L)	Quetiapine **0.10 (0.06 to 0.15)** Aripiprazole -0.02 (-0.06 to 0.02) **Between-group difference**	

				0.12 (0.07 to 0.18) **SS more rise in total cholesterol with quetiapine**	
			Change in triglycerides (mmoL/L)	Quetiapine **0.24 (0.12 to 0.35)** Aripiprazole -0.01 (-0.12 to 0.11) **Between-group difference** **0.24 (0.09 to 0.39)** **SS more rise in triglycerides with quetiapine**	

21.3.8.3 FGA vs placebo

No studies met our inclusion criteria

21.3.8.4 SGA vs placebo

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2017 (3) SR	SGA vs placebo	N= 10 n= 1383 (Findling 2012a, Kryzhanovskaya 2009, DelBello 2009, Findling 2009, Pathak 2013, Tohen 2007, Marcus 2009, Owen 2009, Aman 2014, Bastiaens 2009)	Increased triglycerides	130/897 vs 38/486 RR 1.64 (95% CrI 1.09 to 2.63)
	Aripiprazole vs placebo	N= 3 n= 509 (Findling 2009, Marcus 2009, Owen 2009)		64/342 vs 22/167 RR 1.51 (95%CrI 0.53 to 4.65)

		N= 1 n= 197 (Findling 2013)	Increased triglycerides (6 to 12 months)	49/140 vs 21/57 RR 0.95 (95% CI 0.63 to 1.43)
	Quetiapine vs placebo	N= 3 n= 463 (Findling 2012a, Delbello 2009, Pathak 2013)	Increased triglycerides	39/313 vs 9/150 RR 2.11 (95% CrI 0.55 to 12.79)
	Risperidone vs placebo	N= 1 n= 153 (Aman 2014)	Increased triglycerides	1/73 vs 0/80 RR 3.28 (95% Ci 0.14 to 79.36)

For characteristics of included studies: see chapter “Characteristics of included studies in AHRQ 2017 (Pillay 2017)”

21.3.9 Blood pressure

21.3.9.1 FGA vs SGA

Chung 2019(82)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results** **Adjusted HR*** **(95% CI)**

Design: Retrospective cohort Minimum follow-up of 2 years or until the occurrence of endpoint or discontinuation or switching of antipsychotic	n= 29030	Data from Taiwanese National Health Insurance Database 5-18 yrs Diagnosed with a psychiatric disorder (schizophrenia, bipolar disorders, depressive disorders, autism spectrum or other psychiatric disorders) and newly receiving antipsychotics (haloperidol, sulpiride, olanzapine, quetiapine, risperidone, amisulpride, aripiprazole, paliperidone or ziprasidone)	Haloperidol Vs risperidone	**Hypertension**	1.39 (0.66–2.91) NS

*adjusted for patients' age, sex, mental conditions (e.g., schizophrenic disorders, bipolar, anxiety, major depressive disorder, autism, hyperkinetic syndrome, conduct disorders), and use of mood stabilizers, hypnotics, sedatives, antidepressants, psychostimulants

NA not applicable due to too few events,

21.3.9.2 SGA vs SGA

Study details	n/Population	Comparison	Outcomes		Methodological
Jensen 2019(89) Design: RCT (DB, PG) Duration of follow-up:	n= 113 Mean age: 15.7 yr <u>Inclusion</u> 12-17 yr First episode of psychosis <u>Exclusion</u>	Quetiapine extended release Vs Aripiprazole	Safety		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Drop-outs and Exclusions:
			Change in body weight (kg) (PO)	Quetiapine **4.88 (3.92 to 5.83)** Aripiprazole **1.97 (0.97 to 2.97)** **Between-group difference** **2.91 (1.54 to 4.29)** **SS more weight gain with quetiapine**	
			Change in BMI	Quetiapine **1.48 (1.16 to 1.81)** Aripiprazole **0.45 (0.11 to 0.80)** **Between-group difference**	

12 weeks	Severe chronic somatic illness Pregnancy or lactation Substance dependence Organic or drug-induced psychosis			**1.03 (0.56 to 1.50)** **SS more weight gain with quetiapine**	• Described: yes • Balanced across groups: unclear ITT: no (all patients who received at least one dose of trial medication) SELECTIVE REPORTING: no Sponsor: Non-industry
			Change in systolic BP	Quetiapine 2.15 (-0.85 to 5.15) Aripiprazole -2.91 (-5.86 to 0.03) **Between-group difference** **5.06 (1.13 to 8.99)** **SS more rise in systolic BP with quetiapine**	
			Change in diastolic BP	Quetiapine **2.88 (0.46 to 5.31)** Aripiprazole -3.94 (-6.34 to -1.55) **Between-group difference** **6.83 (3.72 to 9.93)** **SS more rise in diastolic BP with quetiapine**	
			Change in glucose (mmoL/L)	Quetiapine 0.02 (-0.01 to 0.04) Aripiprazole 0.01 (-0.01 to 0.04) **Between-group difference**	

				0.01 (-0.03 to 0.04) NS	
			Change in total cholesterol (mmoL/L)	Quetiapine **0.10 (0.06 to 0.15)** Aripiprazole -0.02 (-0.06 to 0.02) **Between-group difference** **0.12 (0.07 to 0.18)** **SS more rise in total cholesterol with quetiapine**	

			Change in triglycerides (mmoL/L)	Quetiapine **0.24 (0.12 to 0.35)** Aripiprazole -0.01 (-0.12 to 0.11) **Between-group difference** **0.24 (0.09 to 0.39)** **SS more rise in triglycerides with quetiapine**	

Chung 2019(82)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results** **Adjusted HR*** **(95% CI)**

Design: Retrospective cohort Minimum follow-up of 2 years or until the occurrence of endpoint or discontinuation or switching of antipsychotic	n= 29030	Data from Taiwanese National Health Insurance Database 5-18 yrs Diagnosed with a psychiatric disorder (schizophrenia, bipolar disorders, depressive disorders, autism spectrum or other psychiatric disorders) and newly receiving antipsychotics (haloperidol, sulpiride, olanzapine, quetiapine, risperidone, amisulpride, aripiprazole, paliperidone or ziprasidone)	Aripiprazole Vs Risperidone	**Hypertension**	1.16 (0.60–2.23) NS
			Olanzapine Vs risperidone	**Hypertension**	1.92 (0.58–6.39) NS

			Quetiapine Vs risperidone	**Hypertension**	1.39 (0.60–3.22) NS
*adjusted for patients' age, sex, mental conditions (e.g., schizophrenic disorders, bipolar, anxiety, major depressive disorder, autism, hyperkinetic syndrome, conduct disorders), and use of mood stabilizers, hypnotics, sedatives, antidepressants, psychostimulants *NA* not applicable due to too few events,					

21.3.10 MACE

21.3.10.1 FGA vs SGA

Chung 2019(82)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results** **Adjusted HR*** **(95% CI)**

Design: Retrospective cohort Minimum follow-up of 2 years or until the occurrence of endpoint or discontinuation or switching of antipsychotic	n= 29030	Data from Taiwanese National Health Insurance Database 5-18 yrs Diagnosed with a psychiatric disorder (schizophrenia, bipolar disorders, depressive disorders, autism spectrum or other psychiatric disorders) and newly receiving antipsychotics (haloperidol, sulpiride, olanzapine, quetiapine, risperidone, amisulpride, aripiprazole, paliperidone or ziprasidone)	Haloperidol Vs risperidone	**MACE**	2.64 (0.16–42.62) NS

*adjusted for patients' age, sex, mental conditions (e.g., schizophrenic disorders, bipolar, anxiety, major depressive disorder, autism, hyperkinetic syndrome, conduct disorders), and use of mood stabilizers, hypnotics, sedatives, antidepressants, psychostimulants *NA* not applicable due to too few events,

21.3.10.2 SGA vs SGA

Chung 2019(82)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results** **Adjusted HR*** **(95% CI)**
Design: Retrospective cohort Minimum follow-up of 2 years or until the occurrence of endpoint or discontinuation or switching of antipsychotic	n= 29030	Data from Taiwanese National Health Insurance Database 5-18 yrs Diagnosed with a psychiatric disorder (schizophrenia, bipolar disorders, depressive	Aripiprazole Vs Risperidone	**MACE**	NA
			Olanzapine Vs risperidone	**MACE**	NA

		disorders, autism spectrum or other psychiatric disorders) and newly receiving antipsychotics (haloperidol, sulpiride, olanzapine, quetiapine, risperidone, amisulpride, aripiprazole, paliperidone or ziprasidone)	Quetiapine Vs risperidone	**MACE**	5.26 (0.32–85.65) NS
*adjusted for patients' age, sex, mental conditions (e.g., schizophrenic disorders, bipolar, anxiety, major depressive disorder, autism, hyperkinetic syndrome, conduct disorders), and use of mood stabilizers, hypnotics, sedatives, antidepressants, psychostimulants *NA* not applicable due to too few events,					

21.4 Extrapyramidal symptoms

21.4.1 Tardive dyskinesia

21.4.1.1 FGA vs SGA

No study met our inclusion criteria

21.4.1.2 SGA v SGA

No study met our inclusion criteria

21.4.1.3 FGA v placebo

No study met our inclusion criteria

21.4.1.4 SGA v placebo

Ref	Comparison	N/n	Outcomes	Result

AHRQ 2017 (3) SR	All SGA vs placebo	N= 5 n= 570 (Haas 2009b, Haas 2009c, Hellings 2006, Shea 2004, Snyder 2002)	Tardive dyskinesia	0/336 vs 2/234 *No statistical testing*
	Risperidone vs placebo	N= 5 n= 570 (Haas 2009b, Haas 2009c, Hellings 2006, Shea 2004, Snyder 2002)	Tardive dyskinesia	0/336 vs 2/234 *No statistical testing*
	SGA vs antipsychotic naive	N= 1 (Wonodi 2007)	Tardive dyskinesia (6-12 months)	5/81 vs 0/80
	Risperidone vs placebo	N=1 n=335 (Reyes 2006)	Tardive dyskinesia (6 months)	No patient developed tardive dyskinesia

For characteristics of included studies: see chapter “Characteristics of included studies in AHRQ 2017 (Pillay 2017)”

21.4.2 Any EPS

21.4.2.1 Antipsychotic vs no antipsychotic

Jeon 2021(81)

(!!disparity between results presented in figure 3 and results in the text – in this table, the results are those presented in the figure)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Retrospective cohort Mean follow-up 2.02 years	n= 10969	Psychiatric patients age 2-18 New prescription of antipsychotic Exclusion: medical history of movement disorder or seizures	Period of antipsychotic exposure Vs Period of no antipsychotic exposure	Movement disorders	**HR 8.17 (95%CI 7.16 – 9.33)** **SS more movement disorders during exposure vs non-exposure to AP**
*adjusted for age, sex, insurance type, psychiatric hospitalization, mental health conditions, and concomitant use of other psychotropic medications					

21.4.2.2 FGA vs SGA

Jeon 2021(81) **(!!disparity between results presented in figure 3 and results in the text – in this table, the results are those presented in the figure)**					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***

Retrospective cohort Mean follow-up 2.02 years	n= 10969	Psychiatric patients age 2-18 New prescription of antipsychotic Exclusion: medical history of movement disorder or seizures	Haloperidol Vs risperidone	Movement disorders	**HR 2.14 (1.57 to 2.91)** **SS more movement disorders with haloperidol vs risperidone**
*adjusted for age, sex, insurance type, psychiatric hospitalization, mental health conditions, and concomitant use of other psychotropic medications					

21.4.2.3 SGA vs SGA

Biscontri 2017(94)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: Prospective cohort Follow-up: 1 year	n= 2427	Age ≤ 19yrs Incident users of quetiapine or risperidone	Quetiapine Vs risperidone	Incidence of EPS	Quetiapine 8.76/100 person-years Risperidone 10.55/100 person-years **Quetiapine vs risperidone**

					HR 0.53 (0.34 to 0.83) **SS fewer EPS with quetiapine**
*adjusted for age, gender, socioeconomic status, comorbid diseases, medication associated with development of movement disorders (i.e. metoclopramide, tetrabenazine, reserpine, methyldopa, amiodarone, valproate, lithium), index year					

Jeon 2021(81) **(!!disparity between results presented in figure 3 and results in the text – in this table, the results are those presented in the figure)**					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Retrospective cohort Mean follow-up 2.02 years	n= 10969	Psychiatric patients age 2-18 New prescription of antipsychotic Exclusion: medical history of	Quetiapine vs Risperidone	Movement disorders	**HR 0.49 (0.34 to 0.71)** **SS fewer movement disorders with quetiapine vs risperidone**
			Olanzapine Vs Risperidone	Movement disorders	HR 0.83 (0.56 to 1.23) NS

		movement disorder or seizures	Aripiprazole vs Risperidone	Movement disorders	HR 0.88 (0.67 to 1.15) NS
*adjusted for age, sex, insurance type, psychiatric hospitalization, mental health conditions, and concomitant use of other psychotropic medications					

21.4.2.4 FGA vs placebo

No studies met our inclusion criteria

21.4.2.5 SGA vs placebo

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2017 (3) SR	All SGA vs placebo	N= 15 n= 2730 (Findling 2013a, Findling 2012a, Findling 2008a, Haas 2009b, McGorry 2013, Findling 2009, Haas 2009c, Pathak 2013, Tramontina 2009, Findling 2014b, Marcus 2009, Shea 2004, Aman 2002, Snyder 2002, Yoo 2013)	Any EPS	233/1757 vs 40/973 RR 2.94 (95%CI 2.02 to 4.27) SS more EPS with SGA
		N= 2 n= 629 (Findling 2013, Reyes 2006)	Any EPS (6 – <12 months)	Findling 2013 62/197 vs 7/97 RR 4.36 (95%CI 2.08 to 9.17) SS more EPS with SGA Reyes 2006 3/172 vs 1/163 RR 2.84 (95%CI 0.30 to 27.06) NS

	Aripiprazole vs placebo	N= 6 n= 1000 (Findling 2008a, Findling 2009, Tramontina 2009, Findling 2014b, Marcus 2009, Yoo 2013)	Any EPS	117/655 vs 17/345 RR 3.10 (95% CrI 1.26 to 7.01) SS more EPS with aripiprazole
	Asenapine vs placebo	N= 1 n= 306 (Findling 2015a)	Any EPS	16/204 vs 4/102 RR 2.00 (95% CI 0.69 to 5.38) NS
	Quetiapine vs placebo	N= 2 n= 505 (Findling 2012a, Pathak 2013)	Any EPS	**Pathak 2013** 7/193 vs 1/90 RR 3.26 (95% CI 0.41 to 26.14) NS **Findling 2012a** 19/147 vs 4/75 RR 2.42 (95% CI 0.86 to 6.87) NS
	Risperidone vs placebo	N= 5 n= 636 (Haas 2009b, Haas 2009c, Shea 2004, Aman 2002, Snyder 2002)	Any EPS	52/365 vs 13/271 RR 2.78 (95% CrI 1.27 to 6.50) SS more EPS with risperidone

		N= 1 n= 335 (Reyes 2006)	Any EPS (6-12 months)	3/172 vs 1/163 RR 2.84 (95% CI 0.30 to 27.06)

For characteristics of included studies: see chapter “Characteristics of included studies in AHRQ 2017 (Pillay 2017)”

21.4.3 Akathisia and Dystonia

21.4.3.1 FGA vs SGA

No studies met our inclusion criteria

21.4.3.2 SGA vs SGA

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2017 (3) SR	Aripiprazole vs olanzapine	N= 1 n= 124 (Correll 2009)	Akathisia	5/66 vs 3/58 RR 1.46 (95%CI 0.37 to 5.86) NS
	Aripiprazole vs paliperidone	N= 1 n= 226 (Savitz 2015)	Akathisia (6-12 months)	6/114 vs 7/112 RR 0.84 (95%CI 0.29 to 2.43)

	Aripiprazole vs quetiapine	N= 1 n= 132 (Correll 2009)	Akathisia	5/66 vs 1/66 RR 5.00 (95% CI 0.60 to 41.65) NS
	Aripiprazole vs risperidone	N= 1 n= 203 (Correll 2009)	Akathisia	5/66 vs 7/137 RR 1.48 (95% CI 0.49 to 4.50) NS
		N= 1 n= 114 (Oh 2013)	Akathisia (6-12 months)	5/62 vs 3/52 RR 1.40 (95%CI 0.35 to 5.57) NS

	Olanzapine vs quetiapine	N= 3 n= 194 (Correll 2009, Arango 2009, Jensen 2008)	Akathisia	13/94 vs 8/100 RR 1.65 (95%CrI 0.42 to 8.06) NS
	Olanzapine vs risperidone	N= 9 n= 507 (Sikich 2008, Sikich 2004, Ratzoni 2002, Correll 2009, Fleischhaker 2006, Jensen 2008, Friedlander 2001, Mozes 2006, Van Bruggen 2003)	Akathisia	20/192 vs 24/315 RR 1.17 (95%CrI 0.59 to 2.40)
		N= 5 n= 270 (Sikich 2008, Sikich 2004, Ratzoni 2002, Alacqua 2008, Fleischhaker 2006, Friedlander 2001)	Dystonia	10/108 vs 13/162 RR 1.65 (95% CrI 0.44 to 6.07)

	Quetiapine vs risperidone	N= 1 n= 203 (Correll 2009)	Akathisia	1/66 vs 7/137 RR 0.30 (95%CI 0.04 to 2.36) NS

For characteristics of included studies: see chapter “Characteristics of included studies in AHRQ 2017 (Pillay 2017)”

Study details	n/Population	Comparison	Outcomes		Methodological
Pagsberg 2017(90) Design: RCT (DB, PG)	n= 113 Mean age: 15.7 to 15.8 yr <u>Inclusion</u>	Quetiapine extended release Vs Aripiprazole	Safety		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes
			Akathasia	Quetiapine 15/47 (32%) Aripiprazole 13/48 (27%) **Between-group difference** **p=0.0023** **SS more akathisia with quetiapine**	

Duration of follow-up: 12 weeks	12-17 yr First episode of psychosis <u>Exclusion</u> Severe chronic somatic illness Pregnancy or lactation Substance dependence Organic or drug-induced psychosis		**Sedation**	Quetiapine 34/47 (72%) Aripiprazole 44/48 (92%) **Between-group difference** **p=0.012** **SS more sedation with aripiprazole**	Assessors: yes FOLLOW-UP: Drop-outs and Exclusions: 16% • Described: yes • Balanced across groups: yes ITT: no (all patients who received at least one dose of trial medication) SELECTIVE REPORTING: no Sponsor: Non-industry

21.4.3.3 FGA vs placebo

No studies met our inclusion criteria

21.4.3.4 SGA vs placebo

Ref	Comparison	N/n	Outcomes	Result

AHRQ 2017 (3) SR	All SGA vs placebo	N= 21 n= 3638 (Findling 2013a, Findling 2008a, Kryzhanovskaya 2009, Haas 2009b, Singh 2011, Findling 2015a, Findling 2015b, Findling 2013b, Findling 2009, Haas 2009c, Tohen 2007, Tramontina 2009, Loebel 2016, Kent 2013, Marcus 2009, Owen 2009, Mankoski 2013, Buitelaar 2001, Connor 2008, Sallee 2000, Yoo 2013)	Akathisia	151/2433 vs 56/1205 RR 1.29 (95%CrI 0.81 to 2.27) NS

		N= 2 n= 629 (Findling 2013, Reyes 2006)	Akathisia (6-12 months)	Findling 2013 20/197 vs 2/97 RR 4.92 (95%CI 1.17 to 20.64) SS more akathisia with SGA Reyes 2006 0/172 vs 0/163 *Not estimable*
		N= 6 n= 1497 (Findling 2009, Findling 2008a, Findling 2015b, Findling 2013, Yoo 2013, Singh 2011)	Dystonia	21/1032 vs 4/465 RR 1.65 (95%CrI 0.44 to 6.07) NS
		N= 2 n= 629 (Findling 2013, Reyes 2006)	Dystonia (6-12 months)	Findling 2013 7/197 vs 2/97 RR 1.72 (95%CI 0.36 to 8.14) NS Reyes 2006 2/172 vs 1/163 RR 1.90 (95%CI 0.17 to 20.70) NS

	Aripiprazole vs placebo	N= 7 n= 1325 (Findling 2008a, Findling 2009, Tramontina 2009, Marcus 2009, Owen 2009, Mankoski 2013, Yoo 2013)	Akathisia	48/873 vs 23/452 RR 0.86 (95% CrI 0.31 to 2.14) NS

		N= 1 n= 294 (Findling 2013)	Akathisia (6-12 months)	20/197 vs 2/97 **RR 4.92 (95% CI 1.17 to 20.64)** **SS more akathisia with aripiprazole**
		N= 3 n= 656 (Findling 2008a, Findling 2009, Yoo 2013)	Dystonia	13/431 vs 4/225 RR 1.42 (95% CrI 0.21 to 8.90) NS
		N= 1 n= 294 (Findling 2013)	Dystonia 6-12 months)	7/197 vs 2/97 RR 1.72 (95% CI 0.36 to 8.14) NS

	Asenapine vs placebo	N= 2 n= 709 (Findling 2015a, Findling 2015b)	Akathisia	**Findling 2015b** 5/302 vs 0/101 RR 3.70 ((95%CI 0.21 to 66.39) NS Findling 2015a 11/204 vs 1/102 RR 5.50 (95% CI 0.72 to 42.01) NS
		N= 1 n= 403 (Findling 2015b)	Dystonia	1/302 vs 0/101 RR 1.01 (95% CI 0.04 to 24.60) NS

	Olanzapine vs placebo	N= 1 n= 152 (Tohen 2007)	Akathisia	3/101 vs 1/51 RR 1.51 (95% CI 0.16 to 14.20) NS
	Paliperidone vs placebo	N= 1 n= 201 (Singh 2011)	Akathisia	14/150 vs 0/51 RR 9.99 (95% CI 0.61 to 164.48) NS
		N= 1 n= 201 (Singh 2011)	Dystonia	6/150 vs 0/51 RR 4.48 (95% CI 0.26 to 78.10) NS

	Risperidone vs placebo	N= 4 n= 428 (Haas 2009b, Haas 2009c, Kent 2013, Buitelaar 2001)	Akathisia	39/264 vs 25/164 RR 1.03 (95% CrI 0.35 to 4.98) NS

		N= 1 n= 335 (Reyes 2006)	Akathisia (6-12 months)	0/172 vs 0/163 Not estimable
		N= 1 n= 115 (Aman 2002)	Dystonia	0/52 vs 0/63 Not estimable
		N= 1 n= 335 (Reyes 2006)	Dystonia (6-12 months)	2/172 vs 1/163 RR 1.90 (95% CI 0.17 to 20.70)

For characteristics of included studies: see chapter “Characteristics of included studies in AHRQ 2017 (Pillay 2017)”

21.5 Sedation

21.5.1 FGA vs SGA

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2017 (3) SR	FGA vs SGA	N= 7 n= 345 (Sikich 2008, Sikich 2004, Ratzoni 2002, Conus 2015) NOTE: the AHRQ document only reported 4 of the 7 references	Sedation	70/160 vs 79/185 RR 1.05 (95%CrI 0.75 to 1.89) NS
		N= 3 n= 160 (Cianchetti 2011) NOTE: the AHRQ document only reported 1 of the 3 references	Sedation (12+ months)	18/87 vs 5/73 RR 2.84 (95% CrI 0.34 to 92.81) NS

For characteristics of included studies: see chapter “Characteristics of included studies in AHRQ 2017 (Pillay 2017)”

None of the individual RCTs met our inclusion criteria

21.5.2 SGA vs SGA

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2017 (3) SR	Aripiprazole vs paliperidone	N= 1 n= 227 (Savitz 2015)	Sedation	3/114 vs 6/113 RR 0.50 (95%CI 0.13 to 1.93) NS
	Aripiprazole vs risperidone	N= 1 n= 114 (Oh 2013)	Sedation (6 -12 months)	1/62 vs 2/52 RR 0.42 (95%CI 0.04 to 4.49) NS
	Olanzapine vs risperidone	N= 7 n= 321 (Sikich 2008, Sikich 2004, Ratzoni 2002, Alacqua 2008, Jensen 2008, Friedlander 2001, Biederman 2005)	Sedation	35/133 vs 36/188 RR 1.19 (95% CrI 0.68 to 2.35) NS

For characteristics of included studies: see chapter “Characteristics of included studies in AHRQ 2017 (Pillay 2017)”

Al-Dhaher 2016(88)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design:	n= 327	4-19 yrs Antipsychotic-naïve, initiating SGAs	Aripiprazole Vs	Drowsiness	No between-group difference

Prospective cohort Follow-up: 3 months	Aripiprazole: 41 Olanzapine: 45 Quetiapine: 36 Risperidone: 135		Olanzapine Vs Quetiapine Vs Risperidone		
*unadjusted					

Study details	n/Population	Comparison	Outcomes		Methodological
Pagsberg 2017(90) Design: RCT (DB, PG)	n= 113 Mean age: 15.7 to 15.8 yr <u>Inclusion</u>	Quetiapine extended release Vs Aripiprazole	Safety		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes
			Akathasia	Quetiapine 15/47 (32%) Aripiprazole 13/48 (27%) **Between-group difference** **p=0.0023** **SS more akathisia with quetiapine**	

Duration of follow-up: 12 weeks	12-17 yr First episode of psychosis <u>Exclusion</u> Severe chronic somatic illness Pregnancy or lactation Substance dependence Organic or drug-induced psychosis		**Sedation**	Quetiapine 34/47 (72%) Aripiprazole 44/48 (92%) **Between-group difference** **p=0.012** **SS more sedation with aripiprazole**	Assessors: yes FOLLOW-UP: Drop-outs and Exclusions: 16% • Described: yes • Balanced across groups: yes ITT: no (all patients who received at least one dose of trial medication) SELECTIVE REPORTING: no Sponsor: Non-industry

21.5.3 FGA vs placebo

No studies met our inclusion criteria

21.5.4 SGA vs placebo

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2017 (3) SR	All SGA vs placebo	N= 21 n= 2710 (Findling 2012a, Kumra 1996, McGorry 2013, Findling 2014a, DelBello 2009, DelBello 2002, Findling 2013b, Findling 2009, Haas 2009c, Pathak 2013, Hollander 2006, Loebel 2016, Kent 2013, Marcus 2009, Owen 2009, Aman 2014, Connor 2008, Findling 2000, Kafantaris 2011, Sallee 2000, Yoo 2013)	Sedation (short term)	288/1696 vs 79/1014 RR 2.19 (95%CrI 1.50 to 3.41) SS more sedation with SGA
	Aripiprazole vs placebo	N= 4 n= 667 (Yoo 2013, Owen 2009	Sedation	50/441 vs 7/226 RR 2.71 (95%CrI 0.77 to 9.78) NS

		Marcus 2009, Findling 2009)		
	Asenapine vs placebo	N= 1 n= 306 (Findling 2015a)	Sedation	16/204 vs 2/102 RR 4.00 (95% CI 0.94 to 17.06) NS
	Olanzapine vs placebo	N= 3 n= 138 (Kafantaris 2011, Hollander 2006, Kryzhanovskaya 2009)	Sedation	16/88 vs 3/50 RR 2.93 (95% CrI 0.62 to 14.41) NS
	Quetiapine vs placebo	N= 6 n= 778 (Findling 2012a, Findling 2014a, DelBello 2009, DelBello 2002, Pathak 2013, Connor 2008)	Sedation	90/473 vs 32/305 RR 1.67 (95% CrI 0.77 to 3.87) NS
	Risperidone vs placebo	N= 4 n= 408 (Aman 2014; Kent 2013, Haas 2009c, Findling 2000)	Sedation	52/225 vs 24/183 RR 2.58 (95%CrI 0.70 to 14.89) NS

For characteristics of included studies: see chapter “Characteristics of included studies in AHRQ 2017 (Pillay 2017)”

21.6 Somnolence

21.6.1 FGA vs SGA

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2017 (3) SR	FGA vs SGA	N= 3 n= 83 (Malone 2001, Bruggeman 2001, Kumra 1996)	Somnolence	15/41 vs 26/42 RR 0.53 (95% CrI 0.14 to 1.75)

For characteristics of included studies: see chapter “Characteristics of included studies in AHRQ 2017 (Pillay 2017)”

None of the individual RCTs met our inclusion criteria

21.6.2 SGA vs SGA

Ref	Comparison	N/n	Outcomes	Result
AHRQ 2017 (3) SR	Aripiprazole vs paliperidone	N= 1 n= 227 (Savitz 2015)	Somnolence	12/114 vs 12/113 RR 0.99 (95%CI 0.47 to 2.11) NS
	Clozapine vs olanzapine	N= 3 n= 96 (Shaw 2006, Kumra 2008, Fleischhaker 2006)	Somnolence	20/46 to 21/50 RR 1.09 (95%CrI 0.41 to 2.75) NS

For characteristics of included studies: see chapter “Characteristics of included studies in AHRQ 2017 (Pillay 2017)”

21.6.3 FGA vs placebo

No studies met our inclusion criteria

21.6.4 SGA vs placebo

Ref	Comparison	N/n	Outcomes	Result

AHRQ 2017 (3) SR	All SGA vs placebo	N= 26 n= 3942 (Findling 2013a, Findling 2012a, Findling 2008a, Kryzhanovskaya 2009, Woods 2003, Haas 2009b, Singh 2011, Findling 2015a, Findling 2014a, Findling 2013b, Findling 2009, Haas 2009c, Pathak 2013, Tramontina 2009, Loebel 2016, Kent 2013, Marcus 2009, McCracken 2002, Owen 2009, Shea 2004, Aman 2002, Armenteros 2007, Buitelaar 2001, Snyder 2002, Sallee 2000, Yoo 2013)	Somnolence	560/2481 vs 119/1461 RR 2.91 (95%CrI 2.27 to 3.86) SS more somnolence with SGA
		N= 2 n= 545 (Reyes 2006, Findling 2013)	Somnolence (6 to 12 months)	Reyes 2006 3/172 vs 2/163 RR 1.42 (95%CI 0.24 to 8.40) Findling 2013 6/146 vs 0/64 RR 5.75 (95% CI 0.33 to 100.53) NS

	Aripiprazole vs placebo	N= 6 n= 1012 (Findling 2008a, Findling 2009, Tramontina 2009, Marcus 2009, Owen 2009, Yoo 2013)	Somnolence	119/661 vs 29/351 RR 2.73 (95% CrI 1.24 to 7.65) SS more somnolence with aripiprazole
		N= 1 n= 210 (Findling 2013)	Somnolence (6-12 months)	6/146 vs 0/64 RR 5.75 (95%CI 0.33 to 100.53) NS
		N= 1 n= 146 (Findling 2013)	Somnolence (12+ months)	6/146 vs 0/64 Not estimable
	Asenapine vs placebo	N= 1 n= 306 (Findling 2015a)	Somnolence	38/204 vs 7/102 RR 2.71 (95% CI 1.26 to 5.86) NS
	Paliperidone vs placebo	N= 1 n= 201 (Singh 2011)	Somnolence	18/150 vs 1/51 RR 6.12 (95% CI 0.84 to 44.70) NS
	Quetiapine vs placebo	N= 3 n= 697 (Findling 2012a, Findling 2014a, , Pathak 2013)	Somnolence	106/432 vs 18/265 RR 2.95 (95% CrI 0.92 to 8.62) NS

	Risperidone vs placebo	N= 9 n= 862 (Kent 2013, McCracken 2002, Aman 2002, Armenteros 2007, Buitelaar 2001, Snyder 2002, Haas 2009b, Haas 2009c, Shea 2004)	Somnolence	163/473 vs 43/389 RR 3.25 (95%CrI 1.96 to 5.94) SS more somnolence with risperidone
		N= 1 n= 335 (Reyes 2006)	Somnolence (6-12 months)	3/172 vs 2/163 RR 1.42 (95%CI 0.24 to 8.40)

For characteristics of included studies: see chapter “Characteristics of included studies in AHRQ 2017 (Pillay 2017)”

21.7 Characteristics of included studies in AHRQ 2017 (Pillay 2017)

Meta-analysis:
AHRQ 2017: Pillay J, Boylan K, Carrey N, et al. First- and Second-Generation Antipsychotics in Children and Young Adults: Systematic Review Update. Comparative Effectiveness Review No. 184. (3)
Inclusion criteria:
-Population: Children and young adults (≤24 years) with one or more of the following conditions/issues: AD, ADHD/DICD, ASD, BD, DD, ED, OCD, PTSD, SUD, SZ, TD, or behavioral issues outside the context of a disorder (e.g., insomnia).
-Interventions:
Any FDA-approved FGA (chlorpromazine, droperidol, fluphenazine, haloperidol, loxapine, molindone, perphenazine, pimozide, prochlorperazine, thiothixene, thioridazine, trifluoperazine)
Any FDA-approved SGA (aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone)
All formulations and doses eligible.
-Comparators:
Placebo/no treatment, any other antipsychotic, or same antipsychotic at different dose. Exclusion of non-antipsychotic medications as comparator.
-Timing: No minimum follow-up duration; Short term: <6 months; Long term: ≥6 months-<12 months; 12 months+
-Any setting
-Clinical trials (RCTs and NRCTs), controlled cohort studies (prospective or retrospective), controlled before-after studies (e.g., open-label extensions with comparator group, pooled analyses of individual patient-level data from one or a combination of similar trials).
Search strategy:
"We comprehensively searched the following electronic databases: Ovid MEDLINE and Ovid MEDLINE® In-Process & Other Non-Indexed Citations (1946 to Present), Cochrane Central Register of Controlled Trials via Wiley Cochrane Library (1991 to Present), EMBASE® via Ovid (1980 to 2016 Week 15), CINAHL Plus with Full Text via EBSCOhost (1937 to Present), PsycINFO® via Ovid (1987 to October Week 1, 2016), ProQuest® Dissertations and Theses Global (1861 to Present), and TOXLINE via The U.S. National Library of Medicine (1840s to Present). The original searches from October 2015 were updated in April 2016. Several other sources were used to obtain studies or additional data, including reference lists of relevant systematic reviews and guidelines, ClinicalTrials.gov, and World Health Organization's International Clinical Trials Registry Platform. Drug manufacturers and other relevant stakeholders were notified of the opportunity to submit scientific information relevant to the interventions of this systematic review. We handsearched the Journal of Child and Adolescent Psychopharmacology, and the Journal of the American Academy of Child and Adolescent Psychiatry (2014-2015). We searched Drugs@FDA for Medical/Clinical and Statistical review documents containing harm data for patients 18 years of age or younger."
Assessment of quality of included trials: yes
Other methodological remarks: for harms outcomes, data were combined from all study designs.

Ref + design	n	Population	Duration	Comparison	Methodology as assessed by authors of AHRQ *(Risk of Bias Assessment for RCTs, Newcastle-Ottawa scale for cohort studies)*
Alacqua 2008(105) Retrospective cohort	73	Mixed conditions (ADHD, ASD, schizophrenia-related, tics) ≤18 yr Received an incident treatment with atypical antipsychotics or SSRIs during the study period	3 months	Clozapine vs Olanzapine vs Quetiapine vs Risperidone	**Funding**: NR **NO scale: 6/8**
Aman 2002(106) RCT	119	ADHD 5-12yr	6 weeks	Risperidone Vs placebo	**Funding**: Industry **RoB: High** **Randomization** Low risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** Low risk **Blinding (outcome assessors)** NA (subj)/Low risk (obj) **Incomplete outcome** High risk **Other sources of bias** Low risk

Aman 2009(107) RCT (crossover)	16	ADHD 4-14 yr	4 weeks	Risperidone Vs Placebo	**Funding**: NR **Risk of Bias: Medium** **Randomization** Low risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** Low risk **Blinding (outcome assessors)** NA **Incomplete outcome** Low risk **Other sources of bias** Low risk
Aman 2014(108) RCT	168	ADHD 6-12yr	6 weeks	Risperidone Vs placebo	**Funding**: Non-industry **Risk of Bias: Medium** **Randomization** Low risk **Allocation concealment** Low risk **Blinding (participants and personnel)** Unclear risk **Blinding (outcome assessors)** Low risk **Incomplete outcome**

					Low risk **Other sources of bias** Low risk
Arango 2009(109) RCT	50	Schizophrenia and related adolescents	6 months	Olanzapine Vs Quetiapine	**Funding**: Industry, Academic **RoB: High** **Randomization** Unclear risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** High risk **Blinding (outcome assessors)** High risk **Incomplete outcome** High risk **Other sources of bias** Low risk
Arango 2014(110) Prospective cochort	303	Mixed conditions 4-7 yr ≤30 days of lifetime exposure to SGAs	6 months	Risperidone Vs Olanzapine Vs Quetiapine	**Funding**: Non-industry **NO scale: 5/8**
Armenteros 2007(111) RCT	25	ADHD 7-12yr	4 weeks	Risperidone Vs placebo	**Funding**: Industry **Risk of Bias: Medium** **Randomization**

					Low risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** Unclear risk **Blinding (outcome assessors)** Unclear risk(subj)/ Low risk(obj) **Incomplete outcome** Low risk **Other sources of bias** Low risk
Bastiaens 2009(112) Retrospective cohort	46	Mixed conditions (BP, Schizophrenia, MDD, ASD) 6-18 yr	8.7 weeks	Aripiprazole Vs Ziprasidone	**Funding**: Internal funding **NO scale: 6/8**
Biederman 2005(113) RCT	31	Bipolar disorder 4-6 yr	8 weeks	Olanzapine Vs Risperidone	**Funding**: Government, Academic **RoB: High** **Randomization** Unclear risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** High risk **Blinding (outcome assessors)** Unclear risk

					Incomplete outcome High risk **Other sources of bias** Low risk
Bobo 2013(114) Retrospective cohort	Total: 43287 Group 1: Antipsychotic users: n= 28858 Group 2: Matched controls : n= 14429	Mixed conditions 6-24 yr	≥1 year	Antipsychotic users Vs Propensity-score matched controls (antipsychotic non-users,)	**Funding**: Nonindustry **NO Scale: 8/8**
Bruggeman 2001(115) RCT	50	Tic disorder 10-65 yr	2.8 month	Pimozide Vs Risperidone	**Funding**: Industry **RoB: NA (subj)/ Medium (obj)** **Randomization** Low risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** NA (subj)/Low risk (obj) **Blinding (outcome assessors)** NA(subj)/ Unclear risk (obj) **Incomplete outcome** Low risk

					Other sources of bias Low risk
Buitelaar 2001(116) RCT	38	ADHD Mean age 13.7 to 14yr	6 weeks	Risperidone Vs placebo	**Funding**: Industry **Risk of Bias: Medium** **Randomization** Low risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** Low risk **Blinding (outcome assessors)** Low risk **Incomplete outcome** Low risk **Other sources of bias** Low risk
Castro-Fornieles 2008(117) Prospective cohort	110	Schizophrenia and related 7-17 yr	24 month	Risperidone Vs Quetiapine Vs Olanzapine	**Funding**: Government **NO Scale: 6/8**
Cianchetti 2011(118) Cohort study	58	Schizophrenia and related Mean age: 15.5	3 to 11 years	Haloperidol vs Risperidone vs Olanzapine vs Clozapine	**Funding**: NR **NO scale: 5/8**

Connor 2008(119) RCT	19	ADHD 12-17 yr	6 weeks	Quetiapine Vs placebo	**Funding**: Industry **Risk of Bias: High** **Randomization** Unclear risk **Allocation concealment** Low risk **Blinding (participants and personnel)** Low risk **Blinding (outcome assessors)** NA (subj)/ Low risk (obj) **Incomplete outcome** High risk **Other sources of bias** Low risk
Conus 2015(120) RCT	98	bipolar disorder 15-28 yr	8 weeks	Chlorpromazine Vs Olanzapine	**Funding**: Industry **RoB High** **Randomization** Low risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** High risk **Blinding (outcome assessors)**

					Low risk (subj)/ Unclear risk (obj) **Incomplete outcome** High risk **Other sources of bias** Low risk
Correll 2009(121) Prospective cohort	312	Mixed conditions (bipolar, ADHD, ASD, schizophrenia-related) 4-19 yr	2.8 months	Aripiprazole Vs Olanzapine Vs Quetiapine Vs Risperidone	**Funding**: Government, Academic **NO Scale:8/8**
Crocq 2007(122) NRCT	52	Adolescents Schizophreniform disorder	2.8 months	Olanzapine (oral disintegrating tablet) Vs Olanzapine (standard tablet) Vs Risperidone	**Funding**: NR **RoB: NA (subj)/High (obj)** **Randomization** High risk **Allocation concealment** High risk **Blinding (participants and personnel)** NA (subj)/Low risk (obj) **Blinding (outcome assessors)** NA (subj)/Low risk (obj) **Incomplete outcome** NA (subj)/ Unclear risk (obj) **Other sources of bias** Unclear risk
Cuerda 2011(123)	61	Mixed conditions	1 yr	Risperidone	**Funding**: Non-industry

Prospective cohort		11-18 yr		Vs Olanzapine Vs Quetiapine	**NO scale: 6/8**
DelBello 2002(124) RCT	30	Bipolar 12-18 yr	6 weeks	Quetiapine Vs placebo	**Funding**: Industry **Risk of Bias: Medium** **Randomization** Low risk **Allocation concealment** Low risk **Blinding (participants and personnel)** Unclear risk **Blinding (outcome assessors)** Unclear risk **Incomplete outcome** Low risk **Other sources of bias** Low risk
DelBello 2009(125) RCT	32	Bipolar disorder 12-18 yr	8 weeks	Quetiapine Vs Placebo	**Funding**: Industry **RoB High** **Randomization** Low risk **Allocation concealment** Low risk **Blinding (participants and personnel)** Unclear risk

					Blinding (outcome assessors) Unclear risk **Incomplete outcome** High risk **Other sources of bias** Low risk
Ebert 2014(126) Retrospective cohort	72	Mixed conditions Mean age 9-10 yr	10-17 weeks	Atypical antipsychotic treatment Vs control	**Funding**: NR **NO scale 5/8**
Findling 2000(127) RCT	20	ADHD 5-15 yr	10 weeks	Risperidone Vs placebo	**Funding**: Industry, Foundation **Risk of Bias: High** **Randomization** Low risk **Allocation concealment** Low risk **Blinding (participants and personnel)** Low risk **Blinding (outcome assessors)** Low risk **Incomplete outcome** High risk **Other sources of bias** Low risk
Findling 2008a(128) RCT	302	Schizophrenia 13-17 yr	6 weeks	Aripiprazole (low dose) Vs Aripiprazole (high dose)	**Funding**: Industry **Risk of Bias: Medium**

				Vs placebo	**Randomization** Low risk **Allocation concealment** Unclear **Blinding (participants and personnel)** Unclear **Blinding (outcome assessors)** Unclear **Incomplete outcome** Low risk **Other sources of bias** Low risk
Findling 2009(129) RCT	296	Bipolar I disorder 10-17 yr	4 weeks	Aripiprazole (low dose) Vs Aripiprazole (high dose) Vs placebo	**Funding**: Industry **Risk of Bias: Medium** **Randomization** Unclear **Allocation concealment** Unclear **Blinding (participants and personnel)** Low risk **Blinding (outcome assessors)** Low risk **Incomplete outcome** Low risk **Other sources of bias** Low risk

Findling 2012a(130) RCT	222	Schizophrenia and related 13-17 yr	6 weeks	Quetiapine (low dose) Vs Quetiapine (high dose) Vs Placebo	**Funding**: Industry **RoB High** **Randomization** Low risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** Low risk **Blinding (outcome assessors)** Low risk **Incomplete outcome** High risk **Other sources of bias** High risk
Findling 2012b(131) RCT	60	Bipolar I, II, NOS or cyclothymia 4-9 yr	72 weeks (after 16 weeks of open label study)	Aripiprazole Vs Placebo	**Funding**: Industry **Risk of bias: High** **Randomization** Unclear **Allocation concealment** Unclear **Blinding (participants and personnel)** Unclear **Blinding (outcome assessors)** Unclear **Incomplete outcome**

					High risk **Other sources of bias** High risk
Findling 2013(132) RCT	210	Bipolar I disorder 10-17 yr	30 weeks	Aripiprazole (low dose) Vs Aripiprazole (high dose) Vs placebo	**Funding**: Industry **Risk of Bias: Medium** **Randomization** Unclear **Allocation concealment** Unclear **Blinding (participants and personnel)** Low risk **Blinding (outcome assessors)** Low risk **Incomplete outcome** Low risk **Other sources of bias** Low risk
Findling 2013a(133) RCT	284	Schizophrenia and related 13-17 yr	6 weeks	Ziprasidone Vs Placebo	**Funding**: Industry **RoB High** **Randomization** Unclear risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** Unclear risk (subj)/Low risk (obj)

					Blinding (outcome assessors) Unclear risk (subj)/Low risk (obj) **Incomplete outcome** High risk **Other sources of bias** Unclear risk
Findling 2013b(134) RCT	238	Bipolar I 10-17 yr	4 weeks	Ziprasidone Vs placebo	**Funding**: Industry, non-industry **Risk of Bias: High** **Randomization** Unclear risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** Unclear risk(subj)/ Low risk (obj) **Blinding (outcome assessors)** Unclear risk(subj)/ Low risk (obj) **Incomplete outcome** High risk **Other sources of bias** Unclear risk
Findling 2014a(135) RCT	193	Bipolar I, II 10-17 yr	8 weeks	Quetiapine Vs Placebo	**Funding**: Industry **RoB High**

					Randomization Low risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** Unclear risk **Blinding (outcome assessors)** Unclear risk **Incomplete outcome** High risk **Other sources of bias** Low risk
Findling 2014b(136) RCT	85	Autism with behavioural problems 6-17 yr	16 weeks	Aripiprazole Vs placebo	**Funding**: Industry **Risk of bias: High** **Randomization** Unclear **Allocation concealment** Low risk **Blinding (participants and personnel)** Unclear **Blinding (outcome assessors)** Unclear **Incomplete outcome** High risk **Other sources of bias** Low risk
Findling 2015a(137)	306	Schizophrenia and related	8 weeks	Asenapine (high dose)	**Funding**: Industry

RCT		12-17 yr		Vs Asenapine (low dose) Vs placebo	**RoB Low** **Randomization** Low risk **Allocation concealment** Low risk **Blinding (participants and personnel)** Low risk **Blinding (outcome assessors)** Low risk **Incomplete outcome** Low risk **Other sources of bias** Low risk
Findling 2015b(138) RCT	404	Bipolar I disorder Mean age 13.7 – 13.9 yr	3 weeks	Asenapine 2.5 mg vs Asenapine 5 mg vs Asenapine 10 mg vs Placebo	**Funding**: Industry **Risk of bias: Low** **Randomization** Low risk **Allocation concealment** Low risk **Blinding (participants and personnel)** Low risk **Blinding (outcome assessors)** Low risk **Incomplete outcome** Low risk

					Other sources of bias Low risk
Fleischhaker 2006(139) Prospective cohort	51	Mixed conditions Mean age 15-17 yr	7.4 weeks (mean)	Clozapine Vs Olanzapine Vs Risperidone	**Funding**: NR **NO scale 3/8**
Fraguas 2008(140) Prospective cohort	92	Mixed conditions Mean age 15-16 yr	6 months	Olanzapine Vs Quetiapine Vs Risperidone	**Funding**: Government, Foundation **NO scale: 6/8**
Friedlander 2001(141) Retrospective cohort	44	Mixed conditions 13-24 yr	6 weeks	Olanzapine Vs Risperidone	**Funding**: NR **NO Scale: 4/8 stars**
Gilbert 2004(142) RCT	19	Tic disorders 7-17 yr	8 weeks	Pimozide Vs Risperidone	**Funding**: Industry, Government **RoB High** **Randomization** Low risk **Allocation concealment** Low risk **Blinding (participants and personnel)** Low risk **Blinding (outcome assessors)** Low risk **Incomplete outcome** High risk

					Other sources of bias Low risk
Gothelf 2002(143) Prospective cohort	20	Schizophrenia Mean age 17 yr	4 weeks	Haloperidol Vs Olanzapine	**Funding**: Government **NO scale 3/8**
Haas 2009b(144) RCT	160	Schizophrenia 13-17 yr	6 weeks	Risperidone (low dose) Vs Risperidone (high dose) Vs placebo	**Funding**: Industry **Risk of bias: High** **Randomization** Low risk **Allocation concealment** Unclear **Blinding (participants and personnel)** Unclear risk(subj)/ N/A (obj) **Blinding (outcome assessors)** Unclear risk (subj)/Low risk (obj) **Incomplete outcome** High risk **Other sources of bias** Low risk
Haas 2009c(145) RCT	170	Bipolar disorder 10-17 yr	3 weeks	Risperidone (low dose) Vs Risperidone (high dose) Vs placebo	**Funding**: Industry **Risk of bias: High** **Randomization** Unclear **Allocation concealment**

					Unclear (subj)/ Low risk (obj) **Blinding (participants and personnel)** Unclear (subj)/ Low risk (obj) **Blinding (outcome assessors)** Low risk **Incomplete outcome** High risk **Other sources of bias** Low risk
Hellings 2006 (146) RCT (crossover)	26	ASD 6-65 yr	5.1 months (6 weeks at each dose)	Risperidone (low dose) Vs Risperidone (high dose) Vs Placebo	**Funding**: Industry, Government **RoB High** **Randomization** Unclear risk **Allocation concealment** Low risk **Blinding (participants and personnel)** Unclear risk (subj)/Low risk (obj) **Blinding (outcome assessors)** Unclear risk (subj)/Low risk (obj) **Incomplete outcome** High risk **Other sources of bias**

					High risk
Hollander 2006(147) RCT	11	ASD 6-17 yr	8 weeks	Olanzapine Vs Placebo	**Funding**: Industry **Risk of Bias: High** **Randomization** Unclear risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** Unclear risk (subj)/ Low risk(obj) **Blinding (outcome assessors)** Unclear risk (subj)/ Low risk(obj) **Incomplete outcome** High risk **Other sources of bias** Low risk
Hrdlicka 2009(148) Retrospective cohort	109	Schizophrenia and related Mean age 15-16 yr	6 weeks	First generation antipsychotics (haloperidol, perphenazide, sulpiride) Vs Second generation antipsychotics (clozapine, olanzapine, risperidone, ziprasidone)	**Funding**: Government, Academic **NO scale 5/8**
Jensen 2008(149)	30	Schizophrenia and related	2.8 months	Olanzapine	**Funding**: NR

RCT		10-18 yr		Vs Quetiapine Vs Risperidone	**RoB High** **Randomization** Low risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** High risk (subj)/Low risk (obj) **Blinding (outcome assessors)** High risk (subj)/Low risk (obj) **Incomplete outcome** High risk **Other sources of bias** Low risk
Kafantaris 2011(150) RCT	20	Eating disorders 12-21 yr	10 weeks	Olanzapine Vs Placebo	**Funding**: Industry **Risk of Bias: Medium** **Randomization** Low risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** Low risk **Blinding (outcome assessors)** Low risk

					Incomplete outcome Low risk **Other sources of bias** Low risk
Kent 2013(151) RCT	96	ASD 5-17 yr	6 weeks	Risperidone (low dose) Vs Risperidone (high dose) Vs placebo	**Funding**: Industry **Risk of bias: Medium** **Randomization** Low risk **Allocation concealment** Unclear **Blinding (participants and personnel)** Low risk **Blinding (outcome assessors)** Low risk **Incomplete outcome** Low risk **Other sources of bias** Low risk
Khan 2009(152) Retrospective cohort	49	Mixed conditions <18 yr	26-27 days	Olanzapine Vs Risperidone	**Funding**: NR **NO scale 6/8**
Kowatch 2015 (153) RCT	25	Bipolar disorder 3-7 yr 11 months	6 weeks	Risperidone Vs placebo	**Funding**: Non-industry **Risk of Bias: Medium** **Randomization** Unclear risk **Allocation concealment** Unclear risk

					Blinding (participants and personnel) Unclear risk **Blinding (outcome assessors)** Unclear risk **Incomplete outcome** Low risk **Other sources of bias** Low risk
Kryzhanovskaya 2009 (154) RCT	107	Schizophrenia and related 13-17 yr	6 weeks	Olanzapine Vs Placebo	**Funding**: Industry **Risk of Bias: High** **Randomization** Unclear risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** Unclear risk(subj)/ Low risk (obj) **Blinding (outcome assessors)** Unclear risk(subj)/ Low risk (obj) **Incomplete outcome** High risk **Other sources of bias** Low risk
Kumra 1996(155) RCT	21	Schizophrenia and related Mean age 13.7 – 14.4 yr	6 weeks	Haloperidol Vs Clozapine	**Funding**: NR **RoB High**

					Randomization Low risk **Allocation concealment** Low risk **Blinding (participants and personnel)** Low risk **Blinding (outcome assessors)** Low risk **Incomplete outcome** High risk **Other sources of bias** Low risk
Kumra 1998(156) Prospective cohort	23	Schizophrenia and related Mean age 13.6- 15.3	6-8 weeks	Clozapine Vs Olanzapine	**Funding**: Industry **NO scale 5/8**
Kumra 2008(157) RCT	40	Schizophrenia and related 10-18 yr	2.8 months	Clozapine Vs Olanzapine	**Funding**: NR **RoB: High** **Randomization** Low risk **Allocation concealment** Low risk **Blinding (participants and personnel)** Unclear risk (subj) Low risk (obj) **Blinding (outcome assessors)**

					Unclear risk (subj) Low risk (obj) **Incomplete outcome** Low risk **Other sources of bias** Low risk
Loebel 2016(158) RCT	150	ASD Mean age 10.5 – 11 yr	6 weeks	Lurasidone Vs Lurasidone Vs Placebo	**Funding**: Industry **RoB Medium** **Randomization** Low risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** Unclear risk **Blinding (outcome assessors)** Unclear risk **Incomplete outcome** Low risk **Other sources of bias** Unclear risk
Luby 2006(159) RCT	24	Autism or PDD-NOS 2.5- 6yr	6 months	Risperidone Vs placebo	**Funding**: Industry **Risk of bias: Medium (subj)/ Low (obj)** **Randomization** Low risk **Allocation concealment** Low risk

					Blinding (participants and personnel) Unclear risk (subj)/ Low risk (obj) **Blinding (outcome assessors)** Unclear risk (subj)/ Low risk (obj) **Incomplete outcome** Low risk **Other sources of bias** Low risk
Malone 2001(160) RCT	12	ASD 5-17 yr	6 weeks	Haloperidol Vs Olanzapine	**Funding**: Industry **RoB High (subj)/ Medium (objective)** **Randomization** Low risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** High risk (subj)/Low risk (obj) **Blinding (outcome assessors)** High risk (subj)/Low risk (obj) **Incomplete outcome** Low risk **Other sources of bias** Low risk

Mankoski 2013 (161) Retrospective cohort	313	ASD Mean age 9.4- 10 yr	8 weeks	Aripiprazole (antipsychotic naïve) Vs Placebo (antipsychotic naïve) Vs Aripiprazole (prior AP exposure) Vs Placebo (prior AP exposure)	**Funding**: Industry **NO scale: 6/8**
Marcus 2009(162) RCT	218	Autism with behavioral problems 6-17 yr	8 weeks	Aripiprazole (low dose) Vs Aripiprazole (medium dose) Vs Aripiprazole (high dose) Vs placebo	**Funding**: Industry **Risk of bias: High** **Randomization** Low risk **Allocation concealment** Low risk **Blinding (participants and personnel)** Unclear risk (subj)/ Low risk (obj) **Blinding (outcome assessors)** Unclear risk (subj)/ Low risk (obj) **Incomplete outcome** High risk **Other sources of bias** Low risk
Martin 2000(163)	70	Mixed conditions	≥6 months	Risperidone	**Funding**: Non-industry

Retrospective cohort		Mean age 12.5 – 13.5 yr		Vs Control	**NO scale: 6/8**
McCracken 2002(164) RCT	101	ASD 5-17 yr	8 weeks	Risperidone Vs placebo	**Funding**: Industry, Government, Foundation **Risk of Bias: Medium** **Randomization** Low risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** Unclear risk (subj)/ Low risk (obj) **Blinding (outcome assessors)** Low risk **Incomplete outcome** Low risk **Other sources of bias** Low risk
McGorry 2013(165) RCT	87	Schizophrenia and related 14-30 yr	52 weeks	Cognitive therapy + risperidone Vs Cognitive therapy + placebo	**Funding**: Industry **Risk of Bias: High** **Randomization** Low risk **Allocation concealment** Low risk

					Blinding (participants and personnel) Low risk **Blinding (outcome assessors)** Low risk **Incomplete outcome** High risk **Other sources of bias** Low risk
Migliardi 2009(166) Retrospective cohort	42	Mixed conditions Mean age 10.7 vs 14.1 yr	12 months	Olanzapine Vs Risperidone	**Funding**: NR **NO scale 7/8**
Miral 2008(167) RCT	30	ASD 8-18 yr	24 weeks	Haloperidol Vs Risperidone	**Funding**: Industry **RoB Medium** **Randomization** Unclear risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** Unclear risk (subj)/Low risk (obj) **Blinding (outcome assessors)** Unclear risk (subj)/Low risk (obj) **Incomplete outcome** Low risk **Other sources of bias**

					Low risk
Mozes 2006(168) RCT	25	Schizophrenia and related Mean age 10.7 – 11.5	2.8 months	Olanzapine Vs Risperidone	**Funding**: No funding **Rob High** **Randomization** Unclear risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** High risk(subj)/ Low risk (obj) **Blinding (outcome assessors)** High risk(subj)/ Low risk (obj) **Incomplete outcome** High risk **Other sources of bias** Low risk
Nagaraj 2006(169) RCT	40	ASD ≤12 yr	6 months	Risperidone Vs Plaebo	**Funding**: Industry, Academic **Risk of Bias: Low** **Randomization** Low risk **Allocation concealment** Low risk **Blinding (participants and personnel)**

					Low risk **Blinding (outcome assessors)** Low risk **Incomplete outcome** Low risk **Other sources of bias** Low risk
NCT00194012(170) RCT	59	Bipolar disorder 5-17 yr	12 weeks, plus 6 weeks open label extension	Aripiprazole Vs placebo	**Funding**: Industry **Risk of bias: High** **Randomization** Unclear **Allocation concealment** Unclear **Blinding (participants and personnel)** Low risk **Blinding (outcome assessors)** Low risk **Incomplete outcome** High risk **Other sources of bias** Low risk
Oh 2013(171) Retrospective cohort	183	Bipolar I, II, NOS 4-18 yr	7-8 months	Aripiprazole Vs Others	**Funding**: NR **NO scale 6/8**
Owen 2009(172) RCT	164	Autism with behavioural problems 6-17 yr	8 weeks	Aripiprazole Vs placebo	**Funding**: Industry **Risk of bias: Medium (subj)/ Low (obj)**

					Randomization Low risk **Allocation concealment** Low risk **Blinding (participants and personnel)** Unclear risk (subj)/ Low risk (obj) **Blinding (outcome assessors)** Unclear risk (subj)/ Low risk (obj) **Incomplete outcome** Low risk **Other sources of bias** Low risk
Pathak 2013(173) RCT	284	Bipolar I 10-17 yr	3 weeks	Quetiapine (low dose) Vs Quetiapine (high dose) Vs Placebo	**Funding**: Industry **RoB High** **Randomization** Low risk **Allocation concealment** Low risk **Blinding (participants and personnel)** Low risk **Blinding (outcome assessors)** Unclear risk **Incomplete outcome** High risk

					Other sources of bias Low risk
Pogge 2005(174) Prospective cohort	86	Mixed conditions Adolescents, mean age 14.9 yr	12 weeks – 18 months	Olanzapine Vs Risperidone	**Funding**: NR **NO scale 6/8**
Ratzoni 2002(175) Prospective cohort	50	Schizophrenia and related Adolescents, mean age 17-17.3 yr	2.8 months	Haloperidol Vs Olanzapine Vs Risperidone	**Funding**: Government, Foundation **NO scale 3/8**
Reyes 2006(176) RCT	335	ADHD 5-17 yr	6 weeks	Risperidone Vs Placebo	**Funding**: Industry **RoB High** **Randomization** Unclear risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** Low risk **Blinding (outcome assessors)** Low risk **Incomplete outcome** High risk **Other sources of bias** Low risk
Ronsley 2015(177) Prospective cohort	130	Mixed conditions 2-18 yrs	12 months	Risperidone Vs Quetiapine	**Funding**: Industry **NO scale 4/8**
Saito 2004(178)	40	Mixed conditions 5-18 yr	11.2 weeks	Olanzapine Vs	**Funding**: Government

Prospective cohort				Quetiapine Vs Risperidone	**NO scale 6/8**
Sallee 1997(179) RCT (crossover)	22	Tic disorders 7-16 yr	6 weeks	Haloperidol Vs Pimozide Vs placebo	**Funding**: Industry, Government **RoB High** **Randomization** Low risk **Allocation concealment** Low risk **Blinding (participants and personnel)** Low risk **Blinding (outcome assessors)** Low risk **Incomplete outcome** Low risk **Other sources of bias** High risk
Sallee 2000(180) RCT	28	Tic disorders 7-17 yr	8 weeks	Ziprasidone Vs Placebo	**Funding**: Industry **Risk of Bias: Medium** **Randomization** Low risk **Allocation concealment** Low risk **Blinding (participants and personnel)** Low risk

					Blinding (outcome assessors) Low risk **Incomplete outcome** Low risk **Other sources of bias** Low risk
Savitz 2015(181) RCT	228	Schizophrenia and related 12-17 yr	8 weeks, 18 weeks maintenance	Paliperidone ER Vs Aripiprazole	**Funding**: Industry **RoB Medium** **Randomization** Low risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** Unclear risk (subj)/Low risk (obj) **Blinding (outcome assessors)** Unclear risk (subj)/Low risk (obj) **Incomplete outcome** Low risk **Other sources of bias** Low risk
Shaw 2006(182) RCT	25	Schizophrenia and related Mean age 11.7 – 12.8 yr	8 weeks	Clozapine Vs Olanzapine	**Funding**: NR **RoB Medium** **Randomization** Low risk

					Allocation concealment Low risk **Blinding (participants and personnel)** Low risk **Blinding (outcome assessors)** Low risk **Incomplete outcome** Low risk **Other sources of bias** Unclear risk
Shea 2004(183) RCT	80	ASD 5-12 yr	8 weeks	Risperidone Vs Placebo	**Funding**: Industry **RoB Medium** **Randomization** Unclear risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** Unclear risk **Blinding (outcome assessors)** Unclear risk **Incomplete outcome** Low risk **Other sources of bias** Low risk
Sikich 2004(184) RCT	50	Schizophrenia and related Mean age 14.6 – 15.4 yr	8 weeks	Haloperidol Vs Olanzapine	**Funding**: Industry, Government, Foundation

				Vs Risperidone	**RoB High** **Randomization** Low risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** Low risk (subj)/ NA (obj) **Blinding (outcome assessors)** Low risk (subj)/ NA (obj) **Incomplete outcome** High risk **Other sources of bias** Low risk
Sikich 2008(185) RCT	116	Schizophrenia and related 8-19 yr	8 weeks (10.1 month extension)	Molindone Vs Olanzapine Vs Risperidone	**Funding**: Government **RoB Low** **Randomization** Low risk **Allocation concealment** Low risk **Blinding (participants and personnel)** Low risk **Blinding (outcome assessors)** Low risk **Incomplete outcome** Low risk **Other sources of bias**

					Low risk
Singh 2011(186) RCT	201	Schizophrenia 12-17 yr	6 weeks	Paliperidone (low dose) Vs Paliperidone (medium dose) Vs Paliperidone (high dose) Vs placebo	**Funding**: Industry **Risk of bias: High (subjective)/ Medium (objective)** **Randomization** Unclear **Allocation concealment** Unclear **Blinding (participants and personnel)** High risk(subj)/ Low risk (obj) **Blinding (outcome assessors)** High risk(subj)/ Low risk (obj) **Incomplete outcome** Low risk **Other sources of bias** Low risk
Snyder 2002(187) RCT	110	ADHD 5-12 yr	6 weeks	Risperidone Vs Placebo	**Funding**: Foundation **RoB High** **Randomization** Low risk **Allocation concealment** Low risk **Blinding (participants and personnel)**

					Low risk **Blinding (outcome assessors)** Low risk **Incomplete outcome** High risk **Other sources of bias** Low risk
Swadi 2010(188) RCT	22	Schizophrenia and related <19 yr	6 weeks	Quetiapine Vs Risperidone	**Funding**: Industry **RoB High** **Randomization** Low risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** High risk (subj)/Low risk (obj) **Blinding (outcome assessors)** High risk (subj)/Low risk (obj) **Incomplete outcome** High risk **Other sources of bias** Low risk
Tohen 2007(189) RCT	161	12-17 yr Manic or mixed bipolar episodes	3 weeks	Olanzapine Vs Placebo	**Funding**: Industry **Risk of bias: Medium** **Randomization**

					Unclear **Allocation concealment** Unclear **Blinding (participants and personnel)** Unclear risk(subj)/ Low risk (obj) **Blinding (outcome assessors)** Unclear risk(subj)/ Low risk (obj) **Incomplete outcome** Low risk **Other sources of bias** Low risk
Tramontina 2009(190) RCT	43	Bipolar disorder 8-17 yr	6 weeks	Aripiprazole Vs Placebo	**Funding**: Industry, Government, Hospital **Risk of Bias: Low** **Randomization** Low risk **Allocation concealment** Low risk **Blinding (participants and personnel)** Low risk **Blinding (outcome assessors)** Low risk **Incomplete outcome** Low risk **Other sources of bias**

					Low risk
Van Bellinghen 2001(191) RCT	13	Behavioral issues 6-18 yr	4 weeks	Risperidone Vs placebo	**Funding**: Industry **Risk of Bias: Medium** **Randomization** Unclear risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** Unclear risk(subj)/ Low risk (obj) **Blinding (outcome assessors)** Unclear risk(subj)/ Low risk (obj) **Incomplete outcome** Low risk **Other sources of bias** Low risk
Van Bruggen 2003(192) RCT	44	Schizophrenia and related 16-28 yr	6.7 - 9.8 weeks	Olanzapine Vs Risperidone	**Funding**: Industry, Government **RoB High** **Randomization** Unclear risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)**

					Unclear risk (subj)/Low risk (obj) **Blinding (outcome assessors)** Unclear risk (subj)/Low risk (obj) **Incomplete outcome** Low risk **Other sources of bias** High risk
Wink 2014(193) Retrospective cohort	142	ASD 2- 20 yr	1.5 – 2.3 yrs	Risperidone Vs Aripiprazole	**Funding**: Industry/ Non-industry **NO scale: 7/8**
Wonodi 2007(194) Retrospective cohort	424	Mixed conditions 5-18 yr	≥6 months	Antipsychotic treatment ≥ 6 months Vs Antipsychotic naïve	**Funding**: Non-Industry **NO scale 8/8**
Woods 2003(195) RCT	60	Schizophrenia and related 12-45 yr	1 year	Olanzapine Vs placebo	**Funding**: Industry, Government **Risk of Bias: High** **Randomization** Low risk **Allocation concealment** Low risk

					Blinding (participants and personnel) Low risk **Blinding (outcome assessors)** Low risk **Incomplete outcome** High risk **Other sources of bias** Low risk
Wudarsky 1999(196) Prospective cohort	47	Schizophrenia and related Mean age 13.7 – 14.7 yr	6 weeks	Haloperidol Vs Clozapine Vs Olanzapine	**Funding**: NR **NO scale 7/8**
Yoo 2013(197) RCT	61	Tic disorders 6-18 yr	10 weeks	Aripiprazole Vs placebo	**Funding**: Industry **Risk of Bias: High** **Randomization** Low risk **Allocation concealment** Unclear risk **Blinding (participants and personnel)** Low risk **Blinding (outcome assessors)** Low risk **Incomplete outcome** High risk **Other sources of bias** Low risk

22 Appendix. Search strategy

22.1 BPSD

("Antipsychotic Agents"[Mesh] OR Antipsychotic*[tiab] OR neuroleptic* [tiab] OR "Aripiprazole"[Mesh] OR Aripiprazole[tiab] OR Asenapine[tiab] OR "Asenapine" [Supplementary Concept] OR "Clozapine"[Mesh] OR Clozapine[tiab] OR "Olanzapine"[Mesh] OR Olanzapine[tiab] OR "Paliperidone Palmitate"[Mesh] OR Paliperidone[tiab] OR "Quetiapine Fumarate"[Mesh] OR Quetiapine [tiab] OR "Risperidone"[Mesh] OR Risperidone [tiab] OR Sertindole[tiab] OR "sertindole" [Supplementary Concept] OR "Haloperidol"[Mesh] OR Haloperidol[tiab])

AND

("Dementia"[Mesh] OR Dementia[tiab] OR “Alzheimer disease”[tiab] OR “Behavioral and Psychological Symptoms”[tiab] OR BPSD[tiab])

AND

(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

AND ("2018/04/31 "[Date - Publication] : "3000"[Date - Publication])

22.2 Withdrawal/discontinuation of antipsychotic drugs for BPSD

("Antipsychotic Agents"[Mesh] OR Antipsychotic*[tiab] OR neuroleptic* [tiab] OR "Aripiprazole"[Mesh] OR Aripiprazole[tiab] OR Asenapine[tiab] OR "Asenapine" [Supplementary Concept] OR "Clozapine"[Mesh] OR Clozapine[tiab] OR "Olanzapine"[Mesh] OR Olanzapine[tiab] OR "Paliperidone Palmitate"[Mesh] OR Paliperidone[tiab] OR "Quetiapine Fumarate"[Mesh] OR Quetiapine [tiab] OR "Risperidone"[Mesh] OR Risperidone [tiab] OR Sertindole[tiab] OR "sertindole" [Supplementary Concept] OR "Haloperidol"[Mesh] OR Haloperidol[tiab])

AND

("Dementia"[Mesh] OR Dementia[tiab] OR “Alzheimer disease”[tiab] OR “Behavioral and Psychological Symptoms”[tiab] OR BPSD[tiab])

AND

(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

AND

("2018/01/01 "[Date - Publication] : "3000"[Date - Publication])

22.3 Insomnia

("Antipsychotic Agents"[Mesh] OR Antipsychotic*[tiab] OR neuroleptic* [tiab] OR "Olanzapine"[Mesh] OR Olanzapine[tiab] OR "Quetiapine Fumarate"[Mesh] OR Quetiapine [tiab] OR "Risperidone"[Mesh] OR Risperidone [tiab] OR "Haloperidol"[Mesh] OR Haloperidol[tiab])

AND

("Sleep Initiation and Maintenance Disorders"[Mesh] OR insomnia*[tiab] OR sleep*[tiab])

AND

(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

22.4 Delirium

("Antipsychotic Agents"[Mesh] OR Antipsychotic*[tiab] OR neuroleptic* [tiab] OR "Aripiprazole"[Mesh] OR Aripiprazole[tiab] OR Asenapine[tiab] OR "Asenapine" [Supplementary Concept] OR "Clozapine"[Mesh] OR Clozapine[tiab] OR "Olanzapine"[Mesh] OR Olanzapine[tiab] OR "Paliperidone Palmitate"[Mesh] OR Paliperidone[tiab] OR "Quetiapine Fumarate"[Mesh] OR Quetiapine [tiab] OR "Risperidone"[Mesh] OR Risperidone [tiab] OR Sertindole[tiab] OR "sertindole" [Supplementary Concept] OR "Haloperidol"[Mesh] OR Haloperidol[tiab])

AND

("Delirium"[Mesh] OR delirium[tiab] OR confusion*[tiab])

AND

(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

AND

("2014/10/01 "[Date - Publication] : "3000"[Date - Publication])

22.5 Safety in children and young adults

("Antipsychotic Agents"[Mesh] OR Antipsychotic*[tiab] OR neuroleptic* [tiab] OR "Aripiprazole"[Mesh] OR Aripiprazole[tiab] OR Asenapine[tiab] OR "Asenapine" [Supplementary Concept] OR "Clozapine"[Mesh] OR Clozapine[tiab] OR "Olanzapine"[Mesh] OR Olanzapine[tiab] OR "Paliperidone Palmitate"[Mesh] OR Paliperidone[tiab] OR "Quetiapine Fumarate"[Mesh] OR Quetiapine [tiab] OR "Risperidone"[Mesh] OR Risperidone [tiab] OR Sertindole[tiab] OR "sertindole" [Supplementary Concept] OR "Haloperidol"[Mesh] OR Haloperidol[tiab])

AND

(“Child”[Mesh] OR Child*[tiab] OR “Infant”[Mesh] OR “Pediatrics”[Mesh] OR Pediatric*[tiab] OR paediatric*[tiab] OR Infant*[tiab] OR “Adolescent”[Mesh] OR Adolescen*[tiab] OR youth*[tiab] OR teen*[tiab] OR young adult[tiab])

AND

(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB] OR “Epidemiologic Studies"[Mesh] OR "Observational Study" [Publication Type] OR "Comparative Study" [Publication Type] OR "Cohort Studies"[Mesh] OR Cohort*[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB] OR observational[TIAB])

22.6 AE diabetes in BPSD

("Dementia"[Mesh] OR Dementia[tiab] OR “Alzheimer disease”[tiab] OR “Behavioral and Psychological Symptoms”[tiab] OR BPSD[tiab])

AND

("Epidemiologic Studies"[Mesh] OR "Observational Study" [Publication Type]) OR "Comparative Study" [Publication Type] OR "Cohort Studies"[Mesh] OR Cohort*[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB] OR observational[TIAB])

AND

("Diabetes Mellitus"[Mesh]) OR "Blood Glucose"[Mesh] OR "Metabolic Syndrome"[Mesh] OR "Metabolic Side Effects of Drugs and Substances"[Mesh] OR diab[tiab] OR glycem[tiab] OR glucose[tiab] OR metabol[tiab])

AND

("Haloperidol"[Mesh] OR Haloperidol[tiab] OR "Aripiprazole"[Mesh] OR Aripiprazole[tiab] OR Asenapine[tiab] OR "Asenapine" [Supplementary Concept] OR "Clozapine"[Mesh] OR Clozapine[tiab] OR "Olanzapine"[Mesh] OR Olanzapine[tiab] OR "Paliperidone Palmitate"[Mesh] OR Paliperidone[tiab] OR "Quetiapine Fumarate"[Mesh] OR Quetiapine [tiab] OR "Risperidone"[Mesh] OR Risperidone [tiab] OR Sertindole[tiab] OR "sertindole" [Supplementary Concept])

22.7 Literature search: update 1

Due to the COVID-19 pandemic and the subsequent postponement of the consensus conference, an additional literature search was performed on the the 15th of January 2021. The search was repeated and the last line in the search syntax was changed to: AND ("2019/12/01"[Date - Publication] : "3000"[Date - Publication])

The first search did not include cariprazine, since it was not available on the Belgian market at that time. A seperate search with cariprazine was added in the update of January 15th.

Due to the COVID-19 pandemic and the second postponement of the consensus conference, an additional literature search was performed on the the 15th of July 2021. The search was repeated for update 2 with search dates from 01/JAN/2021 until 15/JUL/2021.

22.7.1 BPSD and cariprazine

("cariprazine" [Supplementary Concept] OR cariprazine[tiab])

AND

("Dementia"[Mesh] OR Dementia[tiab] OR “Alzheimer disease”[tiab] OR “Behavioral and Psychological Symptoms”[tiab] OR BPSD[tiab])

AND

(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

22.7.2 Withdrawal/discontinuation of antipsychotic drugs for BPSD and cariprazine

("cariprazine" [Supplementary Concept] OR cariprazine[tiab])

AND

("Dementia"[Mesh] OR Dementia[tiab] OR “Alzheimer disease”[tiab] OR “Behavioral and Psychological Symptoms”[tiab] OR BPSD[tiab])

AND

(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

22.7.3 Insomnia and cariprazine

("cariprazine" [Supplementary Concept] OR cariprazine[tiab])

AND

("Sleep Initiation and Maintenance Disorders"[Mesh] OR insomnia*[tiab] OR sleep*[tiab])

AND

(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

22.7.4 Delirium and cariprazine

("cariprazine" [Supplementary Concept] OR cariprazine[tiab])

AND

("Delirium"[Mesh] OR delirium[tiab] OR confusion*[tiab])

AND

(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

22.7.5 Safety in children and young adults and cariprazine

("cariprazine" [Supplementary Concept] OR cariprazine[tiab])

AND

(“Child”[Mesh] OR Child*[tiab] OR “Infant”[Mesh] OR “Pediatrics”[Mesh] OR Pediatric*[tiab] OR paediatric*[tiab] OR Infant*[tiab] OR “Adolescent”[Mesh] OR Adolescen*[tiab] OR youth*[tiab] OR teen*[tiab] OR young adult[tiab])

AND

(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB] OR “Epidemiologic Studies"[Mesh] OR "Observational Study" [Publication Type] OR "Comparative Study" [Publication Type] OR "Cohort Studies"[Mesh] OR Cohort*[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB] OR observational[TIAB])

22.7.6 AE diabetes in BPSD and cariprazine

("Dementia"[Mesh] OR Dementia[tiab] OR “Alzheimer disease”[tiab] OR “Behavioral and Psychological Symptoms”[tiab] OR BPSD[tiab])

AND

("Epidemiologic Studies"[Mesh] OR "Observational Study" [Publication Type] OR "Comparative Study" [Publication Type] OR "Cohort Studies"[Mesh] OR Cohort*[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB] OR observational[TIAB])

AND

("Diabetes Mellitus"[Mesh] OR "Blood Glucose"[Mesh] OR "Metabolic Syndrome"[Mesh] OR "Metabolic Side Effects of Drugs and Substances"[Mesh] OR diab[tiab] OR glycem[tiab] OR glucose[tiab] OR metabol[tiab])

AND

("cariprazine" [Supplementary Concept] OR cariprazine[tiab])

23 Appendix. Excluded articles

23.1 BPSD

Zivkovic S, Koh CH, Kaza N, et al. Antipsychotic drug use and risk of stroke and myocardial infarction: a systematic review and meta-analysis. BMC Psychiatry 2019;19:189.**n, study type**

Yang C, Hao Z, Tian J, et al. Does antipsychotic drug use increase the risk of long term mortality? A systematic review and meta-analysis of observational studies. Oncotarget 2018;9:15101-10.**n, study type**

Van Leeuwen E, Petrovic M, van Driel ML, et al. Discontinuation of Long-Term Antipsychotic Drug Use for Behavioral and Psychological Symptoms in Older Adults Aged 65 Years and Older With Dementia. J Am Med Dir Assoc 2018;19:1009-14.**n, same data as Cochrane publication Van Leeuwen 2018**

Dyer SM, Harrison SL, Laver K, et al. An overview of systematic reviews of pharmacological and non-pharmacological interventions for the treatment of behavioral and psychological symptoms of dementia. Int Psychogeriatr 2018;30:295-309.**n, review of SR; onlyl MA 2014 was mentioned**

Schneider-Thoma J, Efthimiou O, Huhn M, et al. Second-generation antipsychotic drugs and short-term mortality: a systematic review and meta-analysis of placebo-controlled randomised controlled trials. Lancet Psychiatry 2018;5:653-63.**n, only subgroup analysis for BPSD without an analysis per antipsychotic**

Sherman C, Liu CS, Herrmann N, et al. Prevalence, neurobiology, and treatments for apathy in prodromal dementia. Int Psychogeriatr 2018;30:177-84.**n, not a research question**

Randle JM, Heckman G, Oremus M, et al. Intermittent antipsychotic medication and mortality in institutionalized older adults: A scoping review. Int J Geriatr Psychiatry 2019;34:906-20.**n, not a research question**

Ruthirakuhan MT, Herrmann N, Abraham EH, et al. Pharmacological interventions for apathy in Alzheimer's disease. Cochrane Database Syst Rev 2018;5:CD012197.**n, not a research question**

Ahmed M, Malik M, Teselink J, et al. Current Agents in Development for Treating Behavioral and Psychological Symptoms Associated with Dementia. Drugs Aging 2019;36:589-605.**n, no access full article**

Yunusa I, Alsumali A, Garba AE, et al. Assessment of Reported Comparative Effectiveness and Safety of Atypical Antipsychotics in the Treatment of Behavioral and Psychological Symptoms of Dementia: A Network Meta-analysis. JAMA Netw Open 2019;2:e190828.**n, only network meta-analysis**

Kongpakwattana K, Sawangjit R, Tawankanjanachot I, et al. Pharmacological treatments for alleviating agitation in dementia: a systematic review and network meta-analysis. Br J Clin Pharmacol 2018;84:1445-56.**n, all studies included in AHRQ 2011**

23.1.1 Exclusions for update 1

Gedde MH, Husebo BS, Mannseth J, et al. Less Is More: The Impact of Deprescribing Psychotropic Drugs on Behavioral and Psychological Symptoms and Daily Functioning in Nursing Home Patients. Results From the Cluster-Randomized Controlled COSMOS Trial. Am J Geriatr Psychiatry 2020.**n, intervention**

Neville C, Beccaria L, Carey M. Withdrawal versus Continuation of Long-Term Antipsychotic Drug Use for Behavioural and Psychological Symptoms in Older People with Dementia. Issues Ment Health Nurs 2020;41:176-7.**n, discussion of Van Leeuwen 2018**

Gerlach LB, Kales HC. Pharmacological Management of Neuropsychiatric Symptoms of Dementia. Curr Treat Options Psychiatry 2020;7:489-507.**n, studies included in AHRQ 2011 or ineligible**

23.1.2 Exclusions for update 2

Chu CS, Yang FC, Tseng PT, Stubbs B, Dag A, Carvalho AF, et al. Treatment Efficacy and Acceptabilityof Pharmacotherapies for Dementia with Lewy Bodies: A Systematic Review and Network Meta-Analysis. Arch Gerontol Geriatr. 2021;96:104474.**n, no new eligible studies found**

Trinchieri M, Perletti G, Magri V, et al. Urinary side effects of psychotropic drugs: A systematic review and metanalysis. Neurourol Urodyn 2021.**n; outcome not urinary infections**

Vinaşi R, Buciuta A, Coman HG. Atypical antipsychotics in the treatment of psychotic symptoms in Alzheimer's disease: a systematic review. Int Clin Psychopharmacol 2021;36:169-80.**n; no new studies found**

23.2 Insomnia

Anderson SL, Vande Griend JP. Quetiapine for insomnia: A review of the literature. Am J Health Syst Pharm 2014;71:394-402.**n; Thompson 2016 is more recent, none of included studies met our inclusion criteria**

Foral P, Dewan N, Malesker M. Insomnia: a therapeutic review for pharmacists. Consult Pharm 2011;26:332-41.**n, clinical review, no studies found**

Krystal AD, Prather AA, Ashbrook LH. The assessment and management of insomnia: an update. World Psychiatry 2019;18:337-52.**n, no SR. Tassniyom 2010 was mentioned in Thompson and one study (Chakravorty 2014) in 20 pts recovering from alcohol.**

Maher AR, Theodore G. Summary of the comparative effectiveness review on off-label use of atypical antipsychotics. J Manag Care Pharm 2012;18:S1-20.**n, this is a summary of the AHRQ 2011 report; Thompson 2016 is more recent**

Omonuwa TS, Goforth HW, Preud'homme X, et al. The pharmacologic management of insomnia in patients with HIV. J Clin Sleep Med 2009;5:251-62.**n; no RCT's available**

Riemann D, Hajak G. [Insomnias. II. Pharmacological and psychotherapeutic treatment options]. Nervenarzt 2009;80:1327-40.**n, no SR**

Shah C, Sharma TR, Kablinger A. Controversies in the use of second generation antipsychotics as sleep agent. Pharmacol Res 2014;79:1-8.**n, no SR. 1 RCT with olazapine in 9 pts (Sharpley 2000) and 1 RCT with quetiapine in 14 pts (Cohrs 2004) were mentioned. Sample size too small.**

Wine JN, Sanda C, Caballero J. Effects of quetiapine on sleep in nonpsychiatric and psychiatric conditions. Ann Pharmacother 2009;43:707-13.**n, All included studies do not meet our inclusion criteria. Thompson 2016 is more recent**

Maglione M, Maher AR, Hu J, et al. Off-Label Use of Atypical Antipsychotics: An Update. AHRQ Comparative Effectiveness Reviews 2011.**n; The same RCT was found in the more recent Thompson 2016 review.**

23.2.1 Exclusions for update 1

Moon E, Lavin P, Storch KF, et al. Effects of antipsychotics on circadian rhythms in humans: a systematic review and meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry 2020:110162.**n, outcome and population**

23.2.2 Exclusions for update 2

White B, Snyder HS, Patel MVB. Evaluation of Medications Used for Hospitalized Patients With Sleep Disturbances: A Frequency Analysis and Literature Review. J Pharm Pract 2021:8971900211017857.**n; no access to full article**

23.3 Delirium

Campbell NL, Perkins AJ, Khan BA, et al. Deprescribing in the Pharmacologic Management of Delirium: A Randomized Trial in the Intensive Care Unit. J Am Geriatr Soc 2019;67:695-702.**n, not a research question, population**

Cerveira CCT, Pupo CC, Dos Santos SS, et al. Delirium in the elderly: A systematic review of pharmacological and non-pharmacological treatments. Dement Neuropsychol 2017;11:270-5.**n, not a research question**

Forcen FE, Matsoukas K, Alici Y. Antipsychotic-induced akathisia in delirium: A systematic review. Palliat Support Care 2016;14:77-84.**n, no meta-analysis. none of the 10 included studies met our inclusion criteria**

Gonin P, Beysard N, Yersin B, et al. Excited Delirium: A Systematic Review. Acad Emerg Med 2018;25:552-65.**n, not a research question**

Jain R, Arun P, Sidana A, et al. Comparison of efficacy of haloperidol and olanzapine in the treatment of delirium. Indian J Psychiatry 2017;59:451-6.**n; open-label**

Lawley H, Hewison A. An integrative literature review exploring the clinical management of delirium in patients with advanced cancer. J Clin Nurs 2017;26:4172-83.**n; no SR**

Muheim L. Praxis (Bern 1994) 2017;106:328-9.**n, study type. Paper is about Agar 2017**

Oh ES, Fong TG, Hshieh TT, et al. Delirium in Older Persons: Advances in Diagnosis and Treatment. JAMA 2017;318:1161-74.**n; no meta-analysis; references checked**

Schrijver EJ, Verstraaten M, van de Ven PM, et al. Low dose oral haloperidol does not prolong QTc interval in older acutely hospitalised adults: a subanalysis of a randomised double-blind placebo-controlled study. J Geriatr Cardiol 2018;15:401-7.**n, population; study type**

Skelton L, Guo P. Evaluating the effects of the pharmacological and nonpharmacological interventions to manage delirium symptoms in palliative care patients: systematic review. Curr Opin Support Palliat Care 2019;13:384-91.**n, no SR**

van der Vorst M, Neefjes ECW, Boddaert MSA, et al. Olanzapine Versus Haloperidol for Treatment of Delirium in Patients with Advanced Cancer: A Phase III Randomized Clinical Trial. Oncologist 2019.**n, open label**

Wu YC, Tseng PT, Tu YK, et al. Association of Delirium Response and Safety of Pharmacological Interventions for the Management and Prevention of Delirium: A Network Meta-analysis. JAMA Psychiatry 2019;76:526-35.**n; netwerkMA and ICU patients**

Yang C, Hao Z, Tian J, et al. Does antipsychotic drug use increase the risk of long term mortality? A systematic review and meta-analysis of observational studies. Oncotarget 2018;9:15101-10.**n; observational studies only**

Boettger S, Jenewein J. Placebo might be superior to antipsychotics in management of delirium in the palliative care setting. Evid Based Med 2017;22:152-3.**n; paper about Agar 2017**

Hulshof TA, Zuidema SU, Ostelo RW, et al. The Mortality Risk of Conventional Antipsychotics in Elderly Patients: A Systematic Review and Meta-analysis of Randomized Placebo-Controlled Trials. J Am Med Dir Assoc 2015;16:817-24.**n; broader population than our studied population**

Kishi T, Hirota T, Matsunaga S, et al. Antipsychotic medications for the treatment of delirium: a systematic review and meta-analysis of randomised controlled trials. J Neurol Neurosurg Psychiatry 2016;87:767-74.**n, Burry 2018 is more recent**

Neufeld KJ, Yue J, Robinson TN, et al. Antipsychotic Medication for Prevention and Treatment of Delirium in Hospitalized Adults: A Systematic Review and Meta-Analysis. J Am Geriatr Soc 2016;64:705-14.**n; more recent SR available**

Nikooie R, Neufeld KJ, Oh ES, et al. Antipsychotics for Treating Delirium in Hospitalized Adults: A Systematic Review. Ann Intern Med 2019.**n; is part of a larger SR from the AHRQ**

Riviere J, van der Mast RC, Vandenberghe J, et al. Efficacy and Tolerability of Atypical Antipsychotics in the Treatment of Delirium: A Systematic Review of the Literature. Psychosomatics 2019;60:18-26.**n; no meta-analysis; all relevant studies are included in Burry 2018**

Schrijver EJ, de Graaf K, de Vries OJ, et al. Efficacy and safety of haloperidol for in-hospital delirium prevention and treatment: A systematic review of current evidence. Eur J Intern Med 2016;27:14-23.**n, studies that met our inclusion criteria are included in Burry 2018**

Shen YZ, Peng K, Zhang J, et al. Effects of Haloperidol on Delirium in Adult Patients: A Systematic Review and Meta-Analysis. Med Princ Pract 2018;27:250-9.**n, included delirium prophylaxis as well. All relevant studies were included in Burry 2018**

23.3.1 Exclusions for update 1

Simoni-Wastila L, Wei YJ, Lucas JA, et al. Mortality Risk of Antipsychotic Dose and Duration in Nursing Home Residents with Chronic or Acute Indications. J Am Geriatr Soc 2016;64:973-80.**n; study design**

Finucane AM, Jones L, Leurent B, et al. Drug therapy for delirium in terminally ill adults. Cochrane Database Syst Rev 2020;1:Cd004770.**n, studies included in Burry 2018 or ineligible**

Kim MS, Rhim HC, Park A, et al. Comparative efficacy and acceptability of pharmacological interventions for the treatment and prevention of delirium: A systematic review and network meta-analysis. J Psychiatr Res 2020;125:164-76.**n, studies included in Burry 2018 or AHRQ 2019 or ineligible**

Ostuzzi G, Gastaldon C, Papola D, et al. Pharmacological treatment of hyperactive delirium in people with COVID-19: rethinking conventional approaches. Ther Adv Psychopharmacol 2020;10:2045125320942703.**n, data based on Burry 2018**

23.3.2 Exclusions for update 2

Lodewijckx E, Debain A, Lieten S, et al. Pharmacologic Treatment for Hypoactive Delirium in Adult Patients: A Brief Report of the Literature. J Am Med Dir Assoc 2021;22:1313-6.e2.**n; no new eligible studies found**

Kurisu K, Yoshiuchi K. Comparison of Antipsychotics for the Treatment of Patients With Delirium and QTc Interval Prolongation: A Clinical Decision Analysis. Front Psychiatry 2021;12:609678.**n; not a research q**

23.4 Safety in children and youth

Afandiyev I, Azizov V. [Poisoning by Psychopharmacological Drugs in Azerbaijan: The Results of 8-Year Prospective Observation]. Georgian Med News 2017:138-44.**n; language**

Alfageh BH, Wang Z, Mongkhon P, et al. Safety and Tolerability of Antipsychotic Medication in Individuals with Autism Spectrum Disorder: A Systematic Review and Meta-Analysis. Paediatr Drugs 2019;21:153-67.**n; more comprehensive SR selected**

Alonso-Pedrero L, Bes-Rastrollo M, Marti A. Effects of antidepressant and antipsychotic use on weight gain: A systematic review. Obes Rev 2019;20:1680-90.**n; more comprehensive SR selected**

Alphs L, Bossie C, Mao L, et al. Treatment effect with paliperidone palmitate compared with oral antipsychotics in patients with recent-onset versus more chronic schizophrenia and a history of criminal justice system involvement. Early Interv Psychiatry 2018;12:55-65.**n; population**

Alzahrani SH, Alqahtani AH, Farahat FM, et al. Drug poisoning and associated factors in western Saudi Arabia: A five-year retrospective chart review (2011-2016). Pak J Med Sci 2017;33:1188-93.**n; study type**

Arango C, Ng-Mak D, Finn E, et al. Lurasidone compared to other atypical antipsychotic monotherapies for adolescent schizophrenia: a systematic literature review and network meta-analysis. Eur Child Adolesc Psychiatry 2019.**n; intervention**

Araz Altay M, Bozatli L, Demirci Sipka B, et al. Current Pattern of Psychiatric Comorbidity and Psychotropic Drug Prescription in Child and Adolescent Patients. Medicina (Kaunas) 2019;55.**n; not a research question**

Aronow WS, Shamliyan TA. Effects of atypical antipsychotic drugs on QT interval in patients with mental disorders. Ann Transl Med 2018;6:147.**n; more comprehensive SR selected**

Asogwa K, Okudo J, Idowu J. The use and effectiveness of pro re nata psychotropic medications in children and adolescents: A systematic review. Indian J Psychiatry 2017;59:264-74.**n; not a research question**

Atkin T, Nunez N, Gobbi G. Practitioner Review: The effects of atypical antipsychotics and mood stabilisers in the treatment of depressive symptoms in paediatric bipolar disorder. J Child Psychol Psychiatry 2017;58:865-79.**n; more comprehensive SR selected**

Ayani N, Sakuma M, Morimoto T, et al. The epidemiology of adverse drug events and medication errors among psychiatric inpatients in Japan: the JADE study. BMC Psychiatry 2016;16:303.**n; study type**

Bai Y, Liu T, Xu A, et al. Comparison of common side effects from mood stabilizers and antipsychotics between pediatric and adult patients with bipolar disorder: a systematic review of randomized, double-blind, placebo-controlled trials. Expert Opin Drug Saf 2019;18:703-17.**n; more comprehensive SR selected**
Bailly D. [Pharmacological treatment of bipolar disorder in children and adolescents]. Encephale 2017;43:254-8.**n; more comprehensive SR selected**
Balijepalli C, Druyts E, Zoratti MJ, et al. Change in Prolactin Levels in Pediatric Patients Given Antipsychotics for Schizophrenia and Schizophrenia Spectrum Disorders: A Network Meta-Analysis. Schizophr Res Treatment 2018;2018:1543034.**n; more comprehensive SR selected**
Ballon JS, Pajvani UB, Mayer LE, et al. Pathophysiology of drug induced weight and metabolic effects: findings from an RCT in healthy volunteers treated with olanzapine, iloperidone, or placebo. J Psychopharmacol 2018;32:533-40.**n; population**
Baptista T, Carrizo E, Rojas N, et al. Miocarditis inducida por clozapina durante la evaluacion observacional, transversal y ongitudinal: comparacion con otros antipsicoticos en ambientes naturalisticos. Invest Clin 2016;57:352-63.**n; language**
Barcones MF, MacDowell KS, Garcia-Bueno B, et al. Cardiovascular Risk in Early Psychosis: Relationship with Inflammation and Clinical Features 6 Months after Diagnosis. Int J Neuropsychopharmacol 2018;21:410-22.**n; research question**
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O'Donoghue B, Francey SM, Nelson B, et al. Staged treatment and acceptability guidelines in early psychosis study (STAGES): A randomized placebo controlled trial of intensive psychosocial treatment plus or minus antipsychotic medication for first-episode psychosis with low-risk of self-harm or aggression. Study protocol and baseline characteristics of participants. Early Interv Psychiatry 2019;13:953-60.**n; protocol**
Oshikoya KA, Carroll R, Aka I, et al. Adverse Events Associated with Risperidone Use in Pediatric Patients: A Retrospective Biobank Study. Drugs Real World Outcomes 2019;6:59-71.**n; no control group**
Pacchiarotti I, Leon-Caballero J, Murru A, et al. Mood stabilizers and antipsychotics during breastfeeding: Focus on bipolar disorder. Eur Neuropsychopharmacol 2016;26:1562-78.**n; population**
Page CB, Parker LE, Rashford SJ, et al. A Prospective Before and After Study of Droperidol for Prehospital Acute Behavioral Disturbance. Prehosp Emerg Care 2018;22:713-21.**n; comparison**
Page CB, Parker LE, Rashford SJ, et al. A Prospective Study of the Safety and Effectiveness of Droperidol in Children for Prehospital Acute Behavioral Disturbance. Prehosp Emerg Care 2019;23:519-26.**n; no control group**
Pagsberg AK, Tarp S, Glintborg D, et al. Acute Antipsychotic Treatment of Children and Adolescents With Schizophrenia-Spectrum Disorders: A Systematic Review and Network Meta-Analysis. J Am Acad Child Adolesc Psychiatry 2017;56:191-202.**n; more comprehensive SR selected**
Palanca-Maresca I, Ruiz-Antoran B, Centeno-Soto GA, et al. Prevalence and Risk Factors of Prolonged Corrected QT Interval Among Children and Adolescents Treated With Antipsychotic Medications: A Long-Term Follow-Up in a Real-World Population. J Clin Psychopharmacol 2017;37:78-83.**n; no control group**
Pan YJ, Yeh LL, Chan HY, et al. Transformation of excess mortality in people with schizophrenia and bipolar disorder in Taiwan. Psychol Med 2017;47:2483-93.**n; population**
Park SI, An H, Kim A, et al. An analysis of QTc prolongation with atypical antipsychotic medications and selective serotonin reuptake inhibitors using a large ECG record database. Expert Opin Drug Saf 2016;15:1013-9.**n; comparison**
Percinel I, Yazici KU. The Use of Aripiprazole in Young Children with Autism Spectrum Disorders: The Treatment and 16 Week Follow-Up of a 23-Month-old Male Patient. J Child Adolesc Psychopharmacol 2016;26:855-7.**n; study type**
Petric D, Racki V, Gaco N, et al. Retrospective Analysis of the Effectiveness and Tolerability of Long-Acting Paliperidone Palmitate Antipsychotic in Adolescent First-Episode Schizophrenia Patients. J Child Adolesc Psychopharmacol 2019;29:197-204.**n; sample size**
Pillay J, Boylan K, Newton A, et al. Harms of Antipsychotics in Children and Young Adults: A Systematic Review Update. Can J Psychiatry 2018;63:661-78.**n; summary of AHRQ 2017**
Poels EMP, Schrijver L, Kamperman AM, et al. Long-term neurodevelopmental consequences of intrauterine exposure to lithium and antipsychotics: a systematic review and meta-analysis. Eur Child Adolesc Psychiatry 2018;27:1209-30.**n; population**

Pope S, Zaraa SG. Efficacy of Long-Acting Injectable Antipsychotics in Adolescents. J Child Adolesc Psychopharmacol 2016;26:391-4.**n; study type**
Post RM, Yatham LN, Vieta E, et al. Beyond evidence-based treatment of bipolar disorder: Rational pragmatic approaches to management. Bipolar Disord 2019;21:650-9.**n; publication type**
Pozzi M, Pisano S, Bertella S, et al. Persistence in Therapy With Risperidone and Aripiprazole in Pediatric Outpatients: A 2-Year Naturalistic Comparison. J Clin Psychiatry 2016;77:e1601-e9.**n; outcome**
Pozzi M, Pisano S, Marano G, et al. Weight-Change Trajectories of Pediatric Outpatients Treated with Risperidone or Aripiprazole in a Naturalistic Setting. J Child Adolesc Psychopharmacol 2019;29:133-40.**n; comparison**
Pringsheim T, Ho J, Sarna JR, et al. Feasibility and Relevance of Antipsychotic Safety Monitoring in Children With Tourette Syndrome: A Prospective Longitudinal Study. J Clin Psychopharmacol 2017;37:498-504.**n; sample size**
Rachamallu V, Elberson BW, Vutam E, et al. Off-Label Use of Clozapine in Children and Adolescents-A Literature Review. Am J Ther 2019;26:e406-e16.**n; more comprehensive SR selected**
Reutfors J, Clapham E, Bahmanyar S, et al. Suicide risk and antipsychotic side effects in schizophrenia: nested case-control study. Hum Psychopharmacol 2016;31:341-5.**n; study type**
Riahi F, Tashakori A, Abdi L. Comparison between the efficacies of Risperidone with Haloperidol in the treatment of attention-deficit hyperactivity disorder (ADHD) among preschoolers: a randomized double-blind clinical trial. Electron Physician 2016;8:2840-8.**n; sample size**
Rice JN, Gillett CB, Malas NM. The Impact of Psychotropic Medications on Bone Health in Youth. Curr Psychiatry Rep 2018;20:104.**n; not an SR**
Richardson CM, Davis EA, Vyas GR, et al. Evaluation of the Safety of Clozapine Use in Patients With Benign Neutropenia. J Clin Psychiatry 2016;77:e1454-e9.**n; study type**
Ringen PA, Faerden A, Antonsen B, et al. Cardiometabolic risk factors, physical activity and psychiatric status in patients in long-term psychiatric inpatient departments. Nord J Psychiatry 2018;72:296-302.**n; study type**
Rizzo R, Pavone P. Aripiprazole for the treatment of irritability and aggression in children and adolescents affected by autism spectrum disorders. Expert Rev Neurother 2016;16:867-74.**n; more comprehensive SR selected**
Rotharmel M, Szymoniak F, Pollet C, et al. Eleven Years of Clozapine Experience in Autism Spectrum Disorder: Efficacy and Tolerance. J Clin Psychopharmacol 2018;38:577-81.**n; sample size**
Saatcioglu O, Kalkan M, Fistikci N, et al. Relationship Between Metabolic Syndrome and Clinical Features, and Its Personal-Social Performance in Patients with Schizophrenia. Psychiatr Q 2016;87:265-80.**n; population**
Safavi P, Hasanpour-Dehkordi A, AmirAhmadi M. Comparison of risperidone and aripiprazole in the treatment of preschool children with disruptive behavior disorder and attention deficit-hyperactivity disorder: A randomized clinical trial. J Adv Pharm Technol Res 2016;7:43-7.**n; sample size**
Sallee F, Kohegyi E, Zhao J, et al. Randomized, Double-Blind, Placebo-Controlled Trial Demonstrates the Efficacy and Safety of Oral Aripiprazole for the Treatment of Tourette's Disorder in Children and Adolescents. J Child Adolesc Psychopharmacol 2017;27:771-81.**n; comparison no statistics**
Savitz AJ, Xu H, Gopal S, et al. Efficacy and safety of paliperidone palmitate 3-month formulation in Latin American patients with schizophrenia: A subgroup analysis of data from two large phase 3 randomized, double-blind studies. Braz J Psychiatry 2019;41:499-510.**n; population**
Scahill L, Jeon S, Boorin SJ, et al. Weight Gain and Metabolic Consequences of Risperidone in Young Children With Autism Spectrum Disorder. J Am Acad Child Adolesc Psychiatry 2016;55:415-23.**n; comparison**

Schneider-Thoma J, Efthimiou O, Bighelli I, et al. Second-generation antipsychotic drugs and short-term somatic serious adverse events: a systematic review and meta-analysis. Lancet Psychiatry 2019;6:753-65.**n; outcome**
Schoenbaum M, Sutherland JM, Chappel A, et al. Twelve-Month Health Care Use and Mortality in Commercially Insured Young People With Incident Psychosis in the United States. Schizophr Bull 2017;43:1262-72.**n; intervention**
Schottle D, Janetzky W, Luedecke D, et al. Effectiveness of aripiprazole once-monthly in schizophrenia patients pretreated with oral aripiprazole: a 6-month, real-life non-interventional study. BMC Psychiatry 2018;18:365.**n; population**
Schroder C, Dorks M, Kollhorst B, et al. Extent and Risks of Antipsychotic Off-Label Use in Children and Adolescents in Germany Between 2004 and 2011. J Child Adolesc Psychopharmacol 2017;27:806-13.**n; comparison**
Schurhoff F, Fond G, Berna F, et al. [The 10-year findings from the FondaMental Academic Center of Expertise for Schizophrenia (FACE-SZ): Review and recommendations for clinical practice]. Encephale 2019;45:9-14.**n; population**
Shafiq S, Pringsheim T. Using antipsychotics for behavioral problems in children. Expert Opin Pharmacother 2018;19:1475-88.**n; more comprehensive SR selected**
Sheridan DC, Hendrickson RG, Lin AL, et al. Adolescent Suicidal Ingestion: National Trends Over a Decade. J Adolesc Health 2017;60:191-5.**n; study type**
Si T, Zhuo J, Turkoz I, et al. Once-monthly injection of paliperidone palmitate in patients with recently diagnosed and chronic schizophrenia: a post-hoc comparison of efficacy and safety. Expert Opin Pharmacother 2017;18:1799-809.**n; population**
Sjo CP, Stenstrom AD, Bojesen AB, et al. Development of Metabolic Syndrome in Drug-Naive Adolescents After 12 Months of Second-Generation Antipsychotic Treatment. J Child Adolesc Psychopharmacol 2017;27:884-91.**n; no control group**
Slooff VD, van den Dungen DK, van Beusekom BS, et al. Monitoring Haloperidol Plasma Concentration and Associated Adverse Events in Critically Ill Children With Delirium: First Results of a Clinical Protocol Aimed to Monitor Efficacy and Safety. Pediatr Crit Care Med 2018;19:e112-e9.**n; sample size**
Spettigue W, Norris ML, Maras D, et al. Evaluation of the Effectiveness and Safety of Olanzapine as an Adjunctive Treatment for Anorexia Nervosa in Adolescents: An Open-Label Trial. J Can Acad Child Adolesc Psychiatry 2018;27:197-208.**n; sample size**
Spiller HA, Ackerman JP, Smith GA, et al. Suicide attempts by self-poisoning in the United States among 10-25 year olds from 2000 to 2018: substances used, temporal changes and demographics. Clin Toxicol (Phila) 2019:1-12.**n; study type**
Stassinos G, Klein-Schwartz W. Comparison of pediatric atypical antipsychotic exposures reported to U.S. poison centers. Clin Toxicol (Phila) 2017;55:40-5.**n; outcome**
Stassinos G, Klein-Schwartz W. Asenapine, iloperidone and lurasidone exposures in young children reported to U.S. poison centers. Clin Toxicol (Phila) 2018;56:355-9.**n; comparison**
Steinauer LM, Leung JG, Burkey BW, et al. A Retrospective Multicenter Evaluation of Clozapine Use in Pediatric Patients Admitted for Acute Psychiatric Hospitalization. J Child Adolesc Psychopharmacol 2018;28:615-9.**n; sample size**
Stepanova E, Grant B, Findling RL. Asenapine Treatment in Pediatric Patients with Bipolar I Disorder or Schizophrenia: A Review. Paediatr Drugs 2018;20:121-34.**n; not an SR**
Strawn JR, Geracioti L, Rajdev N, et al. Pharmacotherapy for generalized anxiety disorder in adult and pediatric patients: an evidence-based treatment review. Expert Opin Pharmacother 2018;19:1057-70.**n; not an SR**
Stringaris A, Vidal-Ribas P, Brotman MA, et al. Practitioner Review: Definition, recognition, and treatment challenges of irritability in young people. J Child Psychol Psychiatry 2018;59:721-39.**n; study type**
Stroup TS, Bareis NA, Rosenheck RA, et al. Heterogeneity of Treatment Effects of Long-Acting Injectable Antipsychotic Medications. J Clin Psychiatry 2018;80.**n; population**

Sun AY, Woods S, Findling RL, et al. Safety considerations in the psychopharmacology of pediatric bipolar disorder. Expert Opin Drug Saf 2019;18:777-94.**n; more comprehensive SR selected**
Suvitaival T, Mantere O, Kieseppa T, et al. Serum metabolite profile associates with the development of metabolic co-morbidities in first-episode psychosis. Transl Psychiatry 2016;6:e951.**n; study type**
Suzuki H, Hibino H, Inoue Y, et al. Treatment retention of risperidone long-acting injection in patients with early-onset schizophrenia in Japan. Asian J Psychiatr 2017;27:137-8.**n; publication type**
Taipale H, Mittendorfer-Rutz E, Alexanderson K, et al. Antipsychotics and mortality in a nationwide cohort of 29,823 patients with schizophrenia. Schizophr Res 2018;197:274-80.**n; population no subgroup children**
Targum SD, Risinger R, Du Y, et al. Effect of patient age on treatment response in a study of the acute exacerbation of psychosis in schizophrenia. Schizophr Res 2017;179:64-9.**n; population**
Tarraf C, Naja WJ. Aripiprazole-Induced Hyperlipidemia: An Update. Prim Care Companion CNS Disord 2016;18.**n; population**
Taylor JH, Jakubovski E, Gabriel D, et al. Predictors and Moderators of Antipsychotic-Related Weight Gain in the Treatment of Early-Onset Schizophrenia Spectrum Disorders Study. J Child Adolesc Psychopharmacol 2018;28:474-84.**n; not a research question**
Teodorescu A, Ifteni P, Moga MA, et al. Dilemma of treating schizophrenia during pregnancy: a Case series and a review of literature. BMC Psychiatry 2017;17:311.**n; population**
Tiihonen J, Mittendorfer-Rutz E, Majak M, et al. Real-World Effectiveness of Antipsychotic Treatments in a Nationwide Cohort of 29823 Patients With Schizophrenia. JAMA Psychiatry 2017;74:686-93.**n; no subgroup children**
Tiihonen J, Mittendorfer-Rutz E, Torniainen M, et al. Mortality and Cumulative Exposure to Antipsychotics, Antidepressants, and Benzodiazepines in Patients With Schizophrenia: An Observational Follow-Up Study. Am J Psychiatry 2016;173:600-6.**n; population**
Tromans S, Adams C. Brief Report: Autism Spectrum Disorder: A Comprehensive Survey of Randomized Controlled Trials. J Autism Dev Disord 2018;48:3228-32.**n; not a research question**
Tveito M, Smith RL, Molden E, et al. Age Impacts Olanzapine Exposure Differently During Use of Oral Versus Long-Acting Injectable Formulations: An Observational Study Including 8,288 Patients. J Clin Psychopharmacol 2018;38:570-6.**n; populatoin**
Uguz F. Second-Generation Antipsychotics During the Lactation Period: A Comparative Systematic Review on Infant Safety. J Clin Psychopharmacol 2016;36:244-52.**n; population**
Ulloa RE, Perez-Garza R, Arce S, et al. A prospective study of adverse effects of antipsychotics in adolescents with schizophrenia during a 6-month follow-up. Int Clin Psychopharmacol 2019;34:33-6.**n; sample size**
Upadhyay N, Patel A, Chan W, et al. Reversibility of psychotropic medication induced weight gain among children and adolescents with bipolar disorders. Psychiatry Res 2019;276:151-9.**n; not a research question**
Vaidyanathan S, Rajan TM, Chandrasekaran V, et al. Pre-school attention deficit hyperactivity disorder: 12 weeks prospective study. Asian J Psychiatr 2019;48:101903.**n; sample size**
van der Schans J, Vardar S, Cicek R, et al. An explorative study of school performance and antipsychotic medication. BMC Psychiatry 2016;16:332.**n; study type**
van Schalkwyk GI, Lewis AS, Beyer C, et al. Efficacy of antipsychotics for irritability and aggression in children: a meta-analysis. Expert Rev Neurother 2017;17:1045-53.**n; outcome**
Vandenberghe F, Najar-Giroud A, Holzer L, et al. Second-Generation Antipsychotics in Adolescent Psychiatric Patients: Metabolic Effects and Impact of an Early Weight Change to Predict Longer Term Weight Gain. J Child Adolesc Psychopharmacol 2018;28:258-65.**n; no control group**
Vieta E, Montes JM. A Review of Asenapine in the Treatment of Bipolar Disorder. Clin Drug Investig 2018;38:87-99.**n; unclear methodology**
Vitale SG, Lagana AS, Muscatello MR, et al. Psychopharmacotherapy in Pregnancy and Breastfeeding. Obstet Gynecol Surv 2016;71:721-33.**n; population**

Vuk A, Kuzman MR, Baretic M, et al. Diabetic ketoacidosis associated with antipsychotic drugs: case reports and a review of literature. Psychiatr Danub 2017;29:121-35.**n; study type**
Wang S, Wei YZ, Yang JH, et al. The efficacy and safety of aripiprazole for tic disorders in children and adolescents: A systematic review and meta-analysis. Psychiatry Res 2017;254:24-32.**n; more comprehensive SR selected**
Wang Z, Ho PWH, Choy MTH, et al. Advances in Epidemiological Methods and Utilisation of Large Databases: A Methodological Review of Observational Studies on Central Nervous System Drug Use in Pregnancy and Central Nervous System Outcomes in Children. Drug Saf 2019;42:499-513.**n; population**
Wei YJ, Liu X, Rao N, et al. Physical Health Outcomes in Preschoolers with Prior Authorization for Antipsychotics. J Child Adolesc Psychopharmacol 2017;27:833-9.**n; study type**
Whicher CA, Price HC, Holt RIG. Mechanisms in endocrinology: Antipsychotic medication and type 2 diabetes and impaired glucose regulation. Eur J Endocrinol 2018;178:R245-r58.**n; not an SR**
Whittington C, Pennant M, Kendall T, et al. Practitioner Review: Treatments for Tourette syndrome in children and young people - a systematic review. J Child Psychol Psychiatry 2016;57:988-1004.**n; more comprehensive SR selected**
Williamson DR, Frenette AJ, Burry L, et al. Pharmacological interventions for agitation in patients with traumatic brain injury: protocol for a systematic review and meta-analysis. Syst Rev 2016;5:193.**n; protocol**
Williamson E, Sathe NA, Andrews JC, et al. Medical Therapies for Children With Autism Spectrum Disorder-An Update. AHRQ Comparative Effectiveness Reviews 2017.**n; more comprehensive SR selected**
Wimberley T, MacCabe JH, Laursen TM, et al. Mortality and Self-Harm in Association With Clozapine in Treatment-Resistant Schizophrenia. Am J Psychiatry 2017;174:990-8.**n; population**
Wohkittel C, Gerlach M, Taurines R, et al. Relationship between clozapine dose, serum concentration, and clinical outcome in children and adolescents in clinical practice. J Neural Transm (Vienna) 2016;123:1021-31.**n; not a research question**
Wu CS, Gau SS. Association Between Antipsychotic Treatment and Advanced Diabetes Complications Among Schizophrenia Patients With Type 2 Diabetes Mellitus. Schizophr Bull 2016;42:703-11.**n; population**
Wu CS, Wang SC, Yeh IJ, et al. Comparative risk of seizure with use of first- and second-generation antipsychotics in patients with schizophrenia and mood disorders. J Clin Psychiatry 2016;77:e573-9.**n; no subgroup children**
Wubeshet YS, Mohammed OS, Desse TA. Prevalence and management practice of first generation antipsychotics induced side effects among schizophrenic patients at Amanuel Mental Specialized Hospital, central Ethiopia: cross-sectional study. BMC Psychiatry 2019;19:32.**n; population**
Wurtz AML, Hostrup Vestergaard C, Rytter D, et al. Prenatal exposure to antipsychotic medication and use of primary health care system in childhood: a population-based cohort study in Denmark. Clin Epidemiol 2017;9:657-66.**n; population**
Xia L, Li WZ, Liu HZ, et al. Olanzapine Versus Risperidone in Children and Adolescents with Psychosis: A Meta-Analysis of Randomized Controlled Trials. J Child Adolesc Psychopharmacol 2018;28:244-51.**n; more comprehensive SR selected**
Yalcin O, Kaymak G, Erdogan A, et al. A Retrospective Investigation of Clozapine Treatment in Autistic and Nonautistic Children and Adolescents in an Inpatient Clinic in Turkey. J Child Adolesc Psychopharmacol 2016;26:815-21.**n; sample size**
Yang C, Hao Z, Zhu C, et al. Interventions for tic disorders: An overview of systematic reviews and meta analyses. Neurosci Biobehav Rev 2016;63:239-55.**n; more comprehensive SR selected**
Yang C, Yi Q, Zhang L, et al. Safety of aripiprazole for tics in children and adolescents: A systematic review and meta-analysis. Medicine (Baltimore) 2019;98:e15816.**n; more comprehensive SR selected**
Zhai D, Lang Y, Dong G, et al. QTc interval lengthening in first-episode schizophrenia (FES) patients in the earliest stages of antipsychotic treatment. Schizophr Res 2017;179:70-4.**n; population**

23.4.1 Exclusions for update 1

1. Alonso-Pedrero L, Bes-Rastrollo M, Marti A. Effects of antidepressant and antipsychotic use on weight gain: A systematic review. Obes Rev 2019;20:1680-90.**n; no additional studies found**
2. Blader JC, Pliszka SR, Kafantaris V, et al. Stepped Treatment for Attention-Deficit/Hyperactivity Disorder and Aggressive Behavior: A Randomized, Controlled Trial of Adjunctive Risperidone, Divalproex Sodium, or Placebo After Stimulant Medication Optimization. J Am Acad Child Adolesc Psychiatry 2020.**n, sample size**
3. Campbell CT, Grey E, Munoz-Pareja J, et al. An Evaluation of Risperidone Dosing for Pediatric Delirium in Children Less Than or Equal to 2 Years of Age. Ann Pharmacother 2020;54:464-9.**n; sample size**
4. Capino AC, Thomas AN, Baylor S, et al. Antipsychotic Use in the Prevention and Treatment of Intensive Care Unit Delirium in Pediatric Patients. J Pediatr Pharmacol Ther 2020;25:81-95.**n, ICU setting**
5. Chang MY, Lin KL, Wang HS, et al. Drug-Induced Extrapyramidal Symptoms at the Pediatric Emergency Department. Pediatr Emerg Care 2020;36:468-72.**n; study type**
6. Clapham E, Boden R, Reutfors J, et al. Exposure to risperidone versus other antipsychotics and risk of osteoporosis-related fractures: a population-based study. Acta Psychiatr Scand 2020;141:74-83.**n; adult population**
7. Cole JB, Klein LR, Strobel AM, et al. The Use, Safety, and Efficacy of Olanzapine in a Level I Pediatric Trauma Center Emergency Department Over a 10-Year Period. Pediatr Emerg Care 2020;36:70-6.**n; no control group**
8. Cortese S, Novins DK. Editorial: Why JAACAP Published an "Inconclusive" Trial: Optimize, Optimize, Optimize Psychostimulant Treatment. J Am Acad Child Adolesc Psychiatry 2020.**n; publication type**
9. Coustals N, Ménard ML, Cohen D. Aripiprazole in Children and Adolescents. J Child Adolesc Psychopharmacol 2020.**n; no additional studies found**
10. Druschky K, Bleich S, Grohmann R, et al. Severe parkinsonism under treatment with antipsychotic drugs. Eur Arch Psychiatry Clin Neurosci 2020;270:35-47.**n; adult population**
11. Egglefield K, Cogan L, Leckman-Westin E, et al. Antipsychotic Medication Adherence and Diabetes-Related Hospitalizations Among Medicaid Recipients With Diabetes and Schizophrenia. Psychiatr Serv 2020;71:236-42.**n; study type**
12. Fountain JS, Tomlin AM, Reith DM, et al. Fatal Toxicity Indices for Medicine-Related Deaths in New Zealand, 2008-2013. Drug Saf 2020;43:223-32.**n; study type**
13. Friedman N, Shoshani-Levy M, Brent J, et al. Fatalities in poisoned patients managed by medical toxicologists. Clin Toxicol (Phila) 2020;58:688-91.**n; outcomes**
14. Grover S, Shouan A, Chakrabarti S, et al. Haematological side effects associated with clozapine: A retrospective study from India. Asian J Psychiatr 2020;48:101906.**n; no separate analysis for <18y**
15. Gurka MJ, Siddiqi SU, Filipp SL, et al. Attention deficit hyperactivity disorder medications and BMI trajectories: The role of medication type, sex and age. Pediatr Obes 2020:e12738.**n; no quantitative results**
16. Hayden JD, Horter L, Parsons T, III, et al. Metabolic Monitoring Rates of Youth Treated with Second-Generation Antipsychotics in Usual Care: Results of a Large US National Commercial Health Plan. J Child Adolesc Psychopharmacol 2020;30:119-22.**n; outcome**
17. Hutchins LM, Shipman A, Zimmerman KO, et al. Evaluation of QTc Interval Effects of Antipsychotic Medications for Intensive Care Unit Delirium in Pediatric Patients. J Pediatr Pharmacol Ther 2021;26:87-91.**n; sample size**
18. Kakko K, Pihlakoski L, Keskinen P, et al. Current follow-up practices often fail to detect metabolic and neurological adverse reactions in children treated with second-generation antipsychotics. Acta Paediatr 2020;109:342-8.**n; comparison**
19. Katz C, Randall JR, Leong C, et al. Psychotropic medication use before and after suicidal presentations to the emergency department: A longitudinal analysis. Gen Hosp Psychiatry 2020;63:68-75.**n; adult population**
20. Kim HA, Lee JW, Kim SJ, et al. Second-generation antipsychotics activate platelets in antipsychotic-naive and antipsychotic-free patients with schizophrenia: A retrospective study. Int J Psychiatry Med 2020;55:105-13.**n; no control group**
21. Kloosterboer SM, de Winter BCM, Reichart CG, et al. Risperidone plasma concentrations are associated with side effects and effectiveness in children and adolescents with autism spectrum disorder. Br J Clin Pharmacol 2020.**n; sample size**

22. Lamy M, Pedapati EV, Dominick KL, et al. Recent Advances in the Pharmacological Management of Behavioral Disturbances Associated with Autism Spectrum Disorder in Children and Adolescents. Paediatr Drugs 2020;22:473-83.**n; narrative review**
23. Lauriello J, Claxton A, Du Y, et al. Beyond 52-Week Long-Term Safety: Long-Term Outcomes of Aripiprazole Lauroxil for Patients With Schizophrenia Continuing in an Extension Study. J Clin Psychiatry 2020;81.**n; adult population**
24. Lee ES, Kronsberg H, Findling RL. Psychopharmacologic Treatment of Schizophrenia in Adolescents and Children. Child Adolesc Psychiatr Clin N Am 2020;29:183-210.**n; not an SR**
25. Lee SR, Kim SM, Oh MY, et al. Efficacy of Olanzapine for High and Moderate Emetogenic Chemotherapy in Children. Children (Basel) 2020;7.**n; sample size**
26. Maan JS, Ershadi M, Khan I, et al. Quetiapine. StatPearls 2020.**n; not an SR**
27. Mano-Sousa BJ, Pedrosa AM, Alves BC, et al. Effects of risperidone in autistic children and young adults: A Systematic Review and Meta-Analysis. Curr Neuropharmacol 2020.**n; SR yielded no new references**
28. McCoy JJ, Aldy K, Arnall E, et al. Treatment of Headache in the Emergency Department: Haloperidol in the Acute Setting (THE-HA Study): A Randomized Clinical Trial. J Emerg Med 2020;59:12-20.**n; sample size of subgroup children too small**
29. McIntyre RS, Berk M, Brietzke E, et al. Bipolar disorders. Lancet 2020;396:1841-56.**n; publication type**
30. Menard ML, Fernandez A, Thummler S, et al. [Review of the prescription of antipsychotics in children]. Rev Prat 2020;70:502-6.**n, not an SR**
31. Menard ML, Thummler S, Giannitelli M, et al. Incidence of adverse events in antipsychotic-naive children and adolescents treated with antipsychotic drugs: Results of a multicenter naturalistic study (ETAPE). Eur Neuropsychopharmacol 2019;29:1397-407.**n; no control group**
32. Mosheva M, Korotkin L, Gur RE, et al. Effectiveness and side effects of psychopharmacotherapy in individuals with 22q11.2 deletion syndrome with comorbid psychiatric disorders: a systematic review. Eur Child Adolesc Psychiatry 2020;29:1035-48.**n; SR does not contain eligible studies**
33. Naik RD, V S, Singh V, et al. Olanzapine for Prevention of Vomiting in Children and Adolescents Receiving Highly Emetogenic Chemotherapy: Investigator-Initiated, Randomized, Open-Label Trial. J Clin Oncol 2020;38:3785-93.**n; comparison**
34. Poweleit EA, Colestock M, Kantemneni EC, et al. Cariprazine in Youth with Bipolar and Psychotic Disorders: A Retrospective Chart Review. J Child Adolesc Psychopharmacol 2020;30:267-72.**n; sample size**
35. Pozzi M, Ferrentino RI, Scrinzi G, et al. Weight and body mass index increase in children and adolescents exposed to antipsychotic drugs in non-interventional settings: a meta-analysis and meta-regression. Eur Child Adolesc Psychiatry 2020.**n; no additional studies found**
36. Reurts EE, Troost PW, Dinnissen M, et al. Aripiprazole in youth with intellectual disabilities: A retrospective chart study. J Intellect Disabil 2020:1744629520905175.**n; sample size**
37. Rodrigues R, Lai MC, Beswick A, et al. Practitioner Review: Pharmacological treatment of attention-deficit/hyperactivity disorder symptoms in children and youth with autism spectrum disorder: a systematic review and meta-analysis. J Child Psychol Psychiatry 2020.**n; no additional studies found**
38. Ruda D, Einarsson G, Matthiassen JB, et al. Measuring movements in adolescents with psychosis using the Microsoft Kinect sensor: a pilot study exploring a new tool for assessing aspects of antipsychotic-induced parkinsonism. Child Adolesc Ment Health 2020;25:79-94.**n; sample size**
39. Schneider M, Regente J, Greiner T, et al. Neuroleptic malignant syndrome: evaluation of drug safety data from the AMSP program during 1993-2015. Eur Arch Psychiatry Clin Neurosci 2020;270:23-33.**n; adult population**
40. Solmi M, Fornaro M, Ostinelli EG, et al. Safety of 80 antidepressants, antipsychotics, anti-attention-deficit/hyperactivity medications and mood stabilizers in children and adolescents with psychiatric disorders: a large scale systematic meta-review of 78 adverse effects. World Psychiatry 2020;19:214-32.**n; no additional studies found**
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3. Chow R, Herrstedt J, Aapro M, et al. Olanzapine for the prophylaxis and rescue of chemotherapy-induced nausea and vomiting: a systematic review, meta-analysis, cumulative meta-analysis and fragility assessment of the literature. Support Care Cancer 2021;29:3439-59.**n; SR included one study in 14 children**
4. Chung YS, Shao SC, Chi MH, et al. Comparative cardiometabolic risk of antipsychotics in children, adolescents and young adults. Eur Child Adolesc Psychiatry 2021;30:769-83.**n; included in update 1**
5. Correll CU, Cortese S, Croatto G, et al. Efficacy and acceptability of pharmacological, psychosocial, and brain stimulation interventions in children and adolescents with mental disorders: an umbrella review. World Psychiatry 2021;20:244-75.**n; outcomes, no new studies identified**
6. Cortese S, Novins DK. Editorial: Why JAACAP Published an "Inconclusive" Trial: Optimize, Optimize, Optimize Psychostimulant Treatment. J Am Acad Child Adolesc Psychiatry 2021;60:213-5.**n; publication type**
7. Coustals N, Ménard ML, Cohen D. Aripiprazole in Children and Adolescents. J Child Adolesc Psychopharmacol 2021;31:4-32.**n; no new studies identified**
8. Cox JH, Cavanna AE. Aripiprazole for the treatment of Tourette syndrome. Expert Rev Neurother 2021;21:381-91.**n; no new studies identified**
9. D'Alò GL, De Crescenzo F, Amato L, et al. Impact of antipsychotics in children and adolescents with autism spectrum disorder: a systematic review and meta-analysis. Health Qual Life Outcomes 2021;19:33.**n; 1 new study identified; did not meet sample size criteria**
10. Di X, Chen M, Shen S, et al. Antipsychotic use and Risk of Venous Thromboembolism: A Meta-Analysis. Psychiatry Res 2021;296:113691.**n; population age**
11. Gurka MJ, Siddiqi SU, Filipp SL, et al. Attention deficit hyperactivity disorder medications and BMI trajectories: The role of medication type, sex and age. Pediatr Obes 2021;16:e12738.**n; no numerical results**
12. Houghton R, van den Bergh J, Law K, et al. Risperidone versus aripiprazole fracture risk in children and adolescents with autism spectrum disorders. Autism Res 2021.**n; outcome**
13. Hughes KM, Thorndyke A, Tillman EM. Incidence of Corrected QT Prolongation With Concomitant Methadone and Atypical Antipsychotics in Critically Ill Children. J Pediatr Pharmacol Ther 2021;26:271-6.**n; ICU population**
14. Hutchins LM, Shipman A, Zimmerman KO, et al. Evaluation of QTc Interval Effects of Antipsychotic Medications for Intensive Care Unit Delirium in Pediatric Patients. J Pediatr Pharmacol Ther 2021;26:87-91.**n; ICU population**
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16. Khalil H, Hoppe D, Ameen N. Characteristics of voluntary reporting of adverse drug events related to antipsychotics in Australia: 14-year analysis. Ther Adv Drug Saf 2021;12:20420986211012854.**n; no control group; study type**

17. Kloosterboer SM, de Winter BCM, Reichart CG, et al. Risperidone plasma concentrations are associated with side effects and effectiveness in children and adolescents with autism spectrum disorder. Br J Clin Pharmacol 2021;87:1069-81.**n; sample size**
18. Liviskie C, McPherson C. Delirium in the NICU: Risk or Reality? Neonatal Netw 2021;40:103-12.**n; NICU population**
19. Malashock HR, Yeung C, Roberts AR, et al. Pediatric Methamphetamine Toxicity: Clinical Manifestations and Therapeutic Use of Antipsychotics-One Institution's Experience. J Med Toxicol 2021;17:168-75.**n; sample size**
20. Mano-Sousa BJ, Pedrosa AM, Alves BC, et al. Effects of Risperidone in Autistic Children and Young Adults: A Systematic Review and Meta-Analysis. Curr Neuropharmacol 2021;19:538-52.**n; review no new studies identified**
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23. Persico AM, Ricciardello A, Lamberti M, et al. The pediatric psychopharmacology of autism spectrum disorder: A systematic review - Part I: The past and the present. Prog Neuropsychopharmacol Biol Psychiatry 2021;110:110326.**n; SR no new studies identified**
24. Preti A, Raballo A, Meneghelli A, et al. Antipsychotics are related to psychometric conversion to psychosis in ultra-high-risk youth. Early Interv Psychiatry 2021.**n; outcome**
25. Rodrigues R, Lai MC, Beswick A, et al. Practitioner Review: Pharmacological treatment of attention-deficit/hyperactivity disorder symptoms in children and youth with autism spectrum disorder: a systematic review and meta-analysis. J Child Psychol Psychiatry 2021;62:680-700.**n; SR no new studies identified**
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