PROPOSAL FOR THE ADDITION OF A SELECTED SQUARE BOX SYMBOL TO RISPERIDONE FOR THE TREATMENT OF ADULTS WITH SCHIZOPHRENIA AND RELATED CHRONIC PSYCHOTIC DISORDERS TO THE WHO MODEL LIST OF ESSENTIAL MEDICINES

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APPENDICES

1. Summary statement of the proposal for the addition of a selected square box symbol to risperidone to the WHO EML core list

In this application, we propose the addition of a "restricted" square box symbol to **risperidone** to the core list of the WHO Model List of Essential Medicines (EML), section 24.1 "Medicines for mental and behavioural disorders >> Medicines used in psychotic disorders" including **aripiprazole, olanzapine, paliperidone,** and **quetiapine** as therapeutic alternatives. This proposal is based on the following elements:

a. In recent years, the scientific evidence on the comparative efficacy and tolerability of antipsychotics has notably grown. Current clinical guidelines suggest tailoring the choice of antipsychotic treatment based on individual characteristics, weighing expected benefits and harms. Currently, the EML includes **haloperidol, chlorpromazine** and **fluphenazine decanoate/enantate** (each marked with a square box indicating first-generation antipsychotics (FGAs) as therapeutic alternatives) and **risperidone**, which is the only representative of second-generation antipsychotics (SGAs). Although risperidone is supported by evidence, some individuals might not benefit from this medication, or experience adverse events, requiring an alternative treatment;

b. According to the most recent, high-quality meta-analytical evidence on the acute and maintenance treatment of schizophrenia and other chronic psychoses, most oral SGAs are similarly effective and tolerable. Aiming to identify the SGAs supported by the best-quality evidence, we selected those: (a) performing better than placebo in terms of efficacy for both acute and maintenance treatment; (b) performing better/no worse than placebo in terms of acceptability (overall dropout rate) for both acute and maintenance treatment; (c) having a moderate-to-high certainty of evidence according to the CINeMA appraisal for the majority (≥3/4) of these outcomes;

c. As a subsequent step, we critically appraised available information on possible cost, cost-effectiveness, regulatory and accessibility issues for each of the previously selected oral SGAs. We found that most oral SGAs are currently available as generics, are included in many national pharmacopoeias, and are cost-effective. However, we outlined major regulatory and accessibility issues for some of them;

d. This selection process was aligned with the work carried out by the Evidence Review Team involved in the updating of the mhGAP Guidelines for psychosis, in order to increase consistency between these two interrelated documents;

e. According to these criteria, the following antipsychotics survived the selection process: **risperidone** (already included in the EML), **aripiprazole, olanzapine, paliperidone,** and **quetiapine.** Of relevance, these SGAs did not show clinically relevant differences of efficacy and acceptability compared to risperidone for both acute and maintenance treatment.

2. Consultation with WHO technical departments

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3. Other organization(s) consulted and/or supporting the submission.

Prof. Stefan Leucht, Dr. Irene Bighelli, and Dr. Caroline Lorenz (Technical University of Munich, Germany) were consulted as experts of meta-analytical synthesis in the field of psychopharmacology, and as part of the Evidence Review Team for the update of the mhGAP Guidelines, currently underway.

4. Key information for the proposed medicines.

Table 1. ATC code, dosage forms and therapeutic indications of interest for this proposal

INN	ATC Code	Dosage form(s) and strength(s)	EMA indication (ICD-11 code)	FDA indication (ICD-11 code)
aripiprazole	N05AX12	Tablet: 5, 10, 15, 30 mg	Schizophrenia (in adults and in adolescents aged 15-17) (ICD-11 code: 6A20)	Schizophrenia (in adults and children aged 13-17) (ICD-11 code: 6A20)
olanzapine	N05AH03	Tablet: 5, 10, 20 mg Orodispersible tablets: 5, 10, 20 mg	Schizophrenia (ICD-11 code: 6A20)	Schizophrenia (in adults and adolescents aged 13-17) (ICD-11 code: 6A20)
paliperidone	N05AX13	Modified-release tablet: 3, 6, 9 mg	Schizophrenia (in adults and in adolescents 15-17) (ICD-11 code: 6A20); schizoaffective disorder (ICD-11 code: 6A21)	Schizophrenia (in adults and children aged 12-17) (ICD-11 code: 6A20); schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers and/or antidepressants (ICD-11 code: 6A21)
quetiapine	N05AH04	Tablet (immediate-release): 25, 100, 150, 200, 300 mg Modified-release tablet: 50, 150, 200, 300, 400 mg	Schizophrenia (ICD-11 code: 6A20)	Schizophrenia (in adults and adolescents aged 13-17) (ICD-11 code: 6A20)
risperidone	N05AX08	Tablet: 1, 2, 3, 4, 6 mg	Schizophrenia (ICD-11 code: 6A20)	Schizophrenia (in adults and adolescents aged 13-17)

5. Proposal for an individual medicine or representative of a pharmacological class / therapeutic group.

We are proposing the addition of a "selected" square box to oral risperidone in the section 24.1 "Medicines for mental and behavioral disorders >> Medicines used in psychotic disorders", indicating that the following medicines (in their oral formulation) can be regarded as valid therapeutic alternatives:

- **aripiprazole** for the acute and maintenance treatment of schizophrenia and related chronic psychoses in adults, in its oral formulation with a dose regimen between 10 and 30 mg per day;
- **olanzapine** for the acute and maintenance treatment of schizophrenia and related chronic psychoses in adults, in its oral formulation with a dose regimen between 5 and 20 mg per day;
- **paliperidone** for the acute and maintenance treatment of schizophrenia and related chronic psychoses in adults, in its oral formulation with a dose regimen comprised between 3 and 12 mg per day;
- **quetiapine** for the acute and maintenance treatment of schizophrenia and related chronic psychoses in adults, in its oral formulation with a dose regimen comprised between 50 and 800 mg per day.

Dose ranges are those reported in the British National Formulary (1), which are consistent with those indicated by the International Consensus (ICS) for the treatment of acute psychosis (2). Furthermore, a recent systematic review and network meta-analysis showed that "standard" doses indicated by the ICS are the most effective also for relapse prevention (3), and generally fall below the "critical dose" of 5 mg equivalents of risperidone indicated by Leucht and colleagues (4) (Table 2), above which the balance between efficacy and tolerability is arguably unsatisfactory, as there is no gain in efficacy, while adverse events steadily increase.

Table 2. Risperidone equivalent doses for selected antipsychotics compared to the "standard" dose

Antipsychotic	**Dose equivalent to risperidone 1 mg**	**Dose equivalent to risperidone 5 mg**	**«Standard» dose (target range for acute treatment)**
Aripiprazole	1,8 mg	9 mg	15-30 mg
Olanzapine	2,4 mg	12 mg	10-20 mg
Paliperidone	2,1 mg	10,5 mg	6-9 mg
Quetiapine	77 mg	385 mg	400-800 mg
Risperidone	1 mg	5 mg	4-6 mg

6. Information supporting the public health relevance.

It has been estimated that about 24 million people in the world have schizophrenia (5). The prevalence of schizophrenia ranges from 0.2 to 0.4% across countries, while its incidence was found to be 18.7 per 100 000 person-years (6). Globally, 129 million disability-adjusted life-years are attributable to mental health disorders, 11.7% of which specifically to schizophrenia-spectrum disorders. Schizophrenia is also associated with relevant direct and indirect health care costs, and it is considered the most costly mental health condition per person globally (5, 7).

In addition to the large burden of disease caused by schizophrenia-spectrum disorders, there is a well-known relationship between schizophrenia and stress-related non-communicable diseases (8). People with schizophrenia have a reduced life expectancy compared to the general population, calculated to be around 15-20 years (9, 10). While suicide explains some of this reduced life expectancy, physical diseases probably account for the overwhelming majority of premature mortality (10, 11).

According to data from large early psychosis treatment programs (12), the majority of individuals at their first episode of psychosis will respond to a combination of pharmacological and psychosocial treatment, reaching functional recovery. However, most of them (up to 65%) will have at least one relapse, often related to treatment inefficacy, poor treatment adherence, or both. About 60% of individuals overall will have a chronically relapsing/remitting course of disease, with about 15% being resistant to pharmacological treatment.

According to current evidence, regular pharmacological treatment from the early phases of disease may represent a key point for preserving neurocognitive abilities, preventing structural brain changes, and hindering the progression towards chronic functional deterioration, resulting in better life conditions and increased survival (13). However, treatment adherence is a major issue, considering that up to half individuals suffering from schizophrenia may not take their medications as prescribed and that only one out of three persons with schizophrenia are fully adherent to antipsychotic treatment, increasing the risk of relapse (14-17).

In recent years, the scientific evidence on the comparative efficacy and tolerability of antipsychotics has notably grown. Not all antipsychotics are equally effective and tolerable, and not all are supported by high-quality evidence (18-23). Both clinical response and individual vulnerability to adverse events are highly heterogeneous among individuals, therefore practitioners should be tailoring the choice of antipsychotic treatment based on individual characteristic, weighing expected benefits and harms (24).

The median value for treatment coverage in low and middle-income countries (LMIC) has been estimated around 30% (25). This suggests that roughly two thirds (70%) of people with schizophrenia-spectrum disorders in LMICs do not receive adequate treatment. The treatment gap for schizophrenic disorders was

larger in lower-income countries (89%) than in lower-middle-income (69%) and upper-middle-income countries (63%). The size of the treatment gap shows a significant negative association with the prevalence of schizophrenic disorders in the general population, gross national income, availability of psychiatric hospital beds, number of psychiatrists per 100,000 population and number of nurses in mental health facilities per 100,000 population (25). Further, few countries are aligned with the general principle of providing full access to essential psychotropic medicines, with low availability and high costs being major barriers (26).

7. Treatment details

Second-generation (or "atypical") antipsychotics (SGAs) are generally indicated as group of medications with: (a) relatively lower affinity for $D_{2/3}$ receptors, and possibly a higher dissociation rate constant compared to FGAs, and consequently lower risk of extrapyramidal symptoms; (b) an higher ratio of binding to the serotonin 2A receptor (5-HT2A) relative to binding to the dopamine $D_{2/3}$ receptor; (c) a preferential affinity for the limbic, as opposed to motor, areas of the striatum. However, medications currently labelled as SGAs are fairly heterogeneous in both chemical, pharmacological and clinical terms, and the concept of "atypicality" has been broadly challenged (27).

With the exception of the Royal Australian and New Zealand College of Psychiatrists (RANZCP) guidelines, which clearly indicate SGAs as the first-choice treatment (and particularly, amisulpride, aripiprazole, risperidone, quetiapine, ziprasidone), most clinical guidelines do not provide indication on which antipsychotic to choose, generally agreeing on the importance of tailoring the choice on individual patients' characteristics, actively involving patients and caregivers in a shared decision-making process (Table 3).

Table 3. Excerpts from national and international guidelines on the pharmacological treatment of schizophrenia and other chronic psychoses

Source	Year	Excerpts from the guideline
Scottish Intercollegiate Guidelines Network (SIGN) (28)	2013	▪ Healthcare professionals and service users should work together to find the most appropriate medication and the lowest effective dose. There should be detailed discussion with service users outlining the potential benefits and harms of individual medications. Service user preference should be elicited and taken into account.
The National Institute for Health and Care Excellence (NICE) (24)	2014	▪ The choice of antipsychotic medication should be made by the service user and healthcare professional together, taking into account the views of the carer if the service user agrees. Provide information and discuss the likely benefits and possible side effects of each drug, including: metabolic (including weight gain and diabetes); extrapyramidal (including akathisia, dyskinesia and dystonia); cardiovascular (including prolonging the QT interval); hormonal (including increasing plasma prolactin); other (including unpleasant subjective experiences).
The Royal Australian and New Zealand College of Psychiatrists (RANZCP) (29)	2016	▪ Acute phase. Where possible, the choice of antipsychotic medicine should take into consideration prior response to treatment, side effects and the person's preference. Oral SGAs are usually the treatment of choice, in view of their generally lower risk of extrapyramidal side effects, compared with FGAs. Long-acting injectable antipsychotic agents, particularly SGAs, provide an important treatment option in all phases of the disease for people whose adherence to oral treatment is poor […] ▪ Maintenance phase. In established illness, it is generally considered advisable to continue maintenance treatment with the prescribed antipsychotic to which the person responded in the acute episode, as long as the efficacy and benefits outweigh the side effects. However, if the drug is causing adverse effects such as weight gain, then switching to a drug with less potential for causing these side effects should be considered […]. If dose reduction is indicated, it should be performed gradually to avoid withdrawal effects and rebound psychoses […]

WHO Mental Health Gap Action Programme (mhGAP), Version 2.0 (30)	2016	▪ Begin antipsychotic medication. Start with a low dose within the therapeutic range and increase slowly to the lowest effective dose, in order to reduce the risk of side-effects. ▪ Antipsychotics should routinely be offered to a person with psychosis. ▪ Start antipsychotic medication immediately. See Table 1 [including haloperidol, risperidone, chlorpromazine, or fluphenazine enanthate/decanoate]. ▪ Second-generation antipsychotics (with the exception of clozapine which is indicated for treatment resistant psychosis) can be offered for the treatment of psychotic disorders (including schizophrenia). There is no clinically relevant advantage of one second-generation antipsychotic over others and choice should be based on availability, cost, patient preferences and possible adverse effects associated with each medication. Strength of recommendation: LOW; Quality of evidence: CONDITIONAL (see here)
The American Psychiatric Association (APA) (31)	2020	▪ An evidence-based ranking of FGAs and SGAs or an algorithmic approach to antipsychotic selection is not possible […]. […] there is no definitive evidence that one antipsychotic will have consistently superior efficacy compared with another, with the possible exception of clozapine. ▪ Consequently, the choice of a particular antipsychotic agent will typically occur in the context of discussion with the patient about the likely benefits and possible side effects of medication options and will incorporate patient preferences; the patient's past responses to treatment (including symptom response and tolerability); the medication's side-effect profile (see Table 6); the presence of physical health conditions that may be affected by medication side effects; and other medication-related factors such as available formulations, potential for drug-drug interactions, receptor binding profiles, and pharmacokinetic considerations.

The mhGAP provides generic information on how to safely introduce antipsychotics and monitor possible side-effects, including "monitoring weight, blood pressure, fasting sugar, cholesterol and ECG for persons on antipsychotics if possible". The APA guideline (31) provides detailed indications for the monitoring of physical health in people with schizophrenia, including the assessment of specific side effects of treatments, provides detailed indications for the monitoring of physical health in people with schizophrenia, including the assessment of the lipid panel, fasting blood glucose, screening for diabetes and cardiac risk factors, ECG, prolactin levels, and the assessment of movement disorders with structured instruments.

8. Review of benefits: summary of evidence of comparative effectiveness

We searched electronic databases PubMed, CENTRAL, and Web of Science Core Collection for the most updated systematic reviews on the topic of antipsychotics' efficacy, acceptability, tolerability and safety in adults with schizophrenia-spectrum disorders. The following terms were searched in the title/abstract: (schizophrenia OR schizoaffective OR psychosis OR psychotic) AND (antipsychotic* OR neuroleptic) AND (acute treatment OR long-term treatment OR maintenance treatment) AND review (last update of the search: 25th November, 2022). After having screened 1430 titles and abstracts, and subsequently 57 full-texts articles, we identified two systematic reviews and network meta-analyses (19, 20) (Table 4). Additional material, retrieved by revising the bibliography of included systematic reviews, included two network meta-analyses (21, 23) and two pairwise meta-analysis of randomized trials (32, 33) (Table 5).

Table 4. Key systematic reviews and network meta-analyses identified by the search process

First author, journal, year	Population	Interventions and comparisons	Outcomes of interest for the application	Design	N. of studies included (primary outcome)	N. of participants included (primary outcome)
Huhn, Lancet 2019	Adults with multiple-episode schizophrenia-spectrum disorders, suffering from acute symptoms	Antipsychotics, placebo (oral formulation)	Efficacy (mean change at rating scale scores); acceptability (overall dropouts)	Network meta-analysis of randomized controlled trials	218	40 815
Schneider-Thoma, Lancet 2022	Clinically stable adults with schizophrenia-spectrum disorders	Antipsychotics, placebo (oral and long-acting formulation)	Efficacy (relapse prevention); acceptability (overall dropouts)	Network meta-analysis of randomized controlled trials	100	16 812

Table 5. Additional systematic reviews and meta-analyses identified by the search process

First author, journal, year	Population	Interventions and comparisons	Outcomes of interest for the application	Design	N. of studies included (primary outcome)	N. of participants included (primary outcome)
Ostuzzi, World Psychiatry 2022	Clinically stable adults with schizophrenia-spectrum disorders	Antipsychotics, placebo	Efficacy (relapse prevention); acceptability (overall dropouts)	Network meta-analysis of randomized controlled trials	92	22 645
Zhu, Lancet Psychiatry 2017	Adults with first-episode schizophrenia-spectrum disorders, suffering from acute symptoms	Antipsychotics, placebo	Efficacy (mean change at rating scale scores); acceptability (overall dropouts)	Network meta-analysis of randomized controlled trials	19	2669
Schneider-Thoma, Lancet Psychiatry, 2018	Any mental illness, with no age restrictions	Second-generation antipsychotics, placebo	Short-term mortality	Pairwise meta-analysis of randomized controlled trials	352	84 988
Schneider-Thoma, Lancet Psychiatry, 2019	Any mental illness, with no age restrictions	Second-generation antipsychotics, placebo	Short-term somatic serious adverse events	Pairwise meta-analysis of randomized controlled trials	314	67 642

Evidence from included reviews

Huhn and colleagues performed a network meta-analysis including both placebo-controlled and head-to-head randomized controlled trials comparing 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia (19). Overall, they included 402 RCTs and 53 463 participants, of which 218 (54%) with 40 815 (76%) participants provided data for the primary outcome analysis (change in overall symptoms at the end of the study). Most antipsychotics (26 over 31, 81%) outperformed placebo, with SMDs ranging between -0.89 (clozapine) to -0.26 (brexpiprazole). Effect sizes and 95% Credible Intervals (95% CrI) were largely overlapping. Certainty of evidence according to the CINeMA approach was “high” only for risperidone and paliperidone, and “moderate” for amisulpride, zotepine, olanzapine, perphenazine, haloperidol, and quetiapine (Figure 1). When considering head-to-head comparisons, clozapine, amisulpride, zotepine, olanzapine, and risperidone appeared among the best performing medications. Amisulpride outperformed risperidone (SMD -0.18; 95% CI -0.33 to -0.02), which in turn outperformed quetiapine (SMD -0.13; 95% CI -0.23 to -0.04), aripiprazole (SMD -0.14; 95% CI -0.25 to -0.03), ziprasidone (SMD -0.14; 95% CI -0.25 to -0.03), sertindole (SMD -0.15; 95% CI -0.30 to -0.01), asenapine (SMD -0.16; 95% CI -0.30 to -0.02), lurasidone (SMD -0.19; 95% CI -0.32 to -0.05), cariprazine (SMD -0.21; 95% CI -0.36 to -0.05), iloperidone (SMD -0.22; 95% CI -0.34 to -0.10), and brexpiprazole (SMD -0.29; 95% CI -0.45 to -0.14). Most of these

comparisons barely reach statistical significance and, most importantly, differences are clinically negligible (Cohen's $d < 0.2$)(34), with the exception of cariprazine, iloperidone and brexpiprazole, for which the difference is small ($0.2 < \text{Cohen's } d < 0.5$).

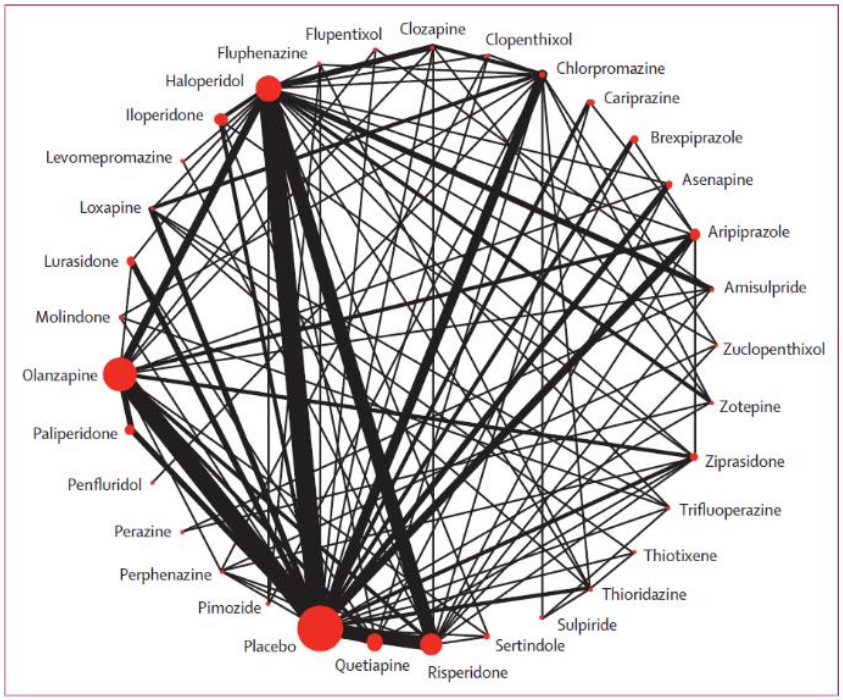
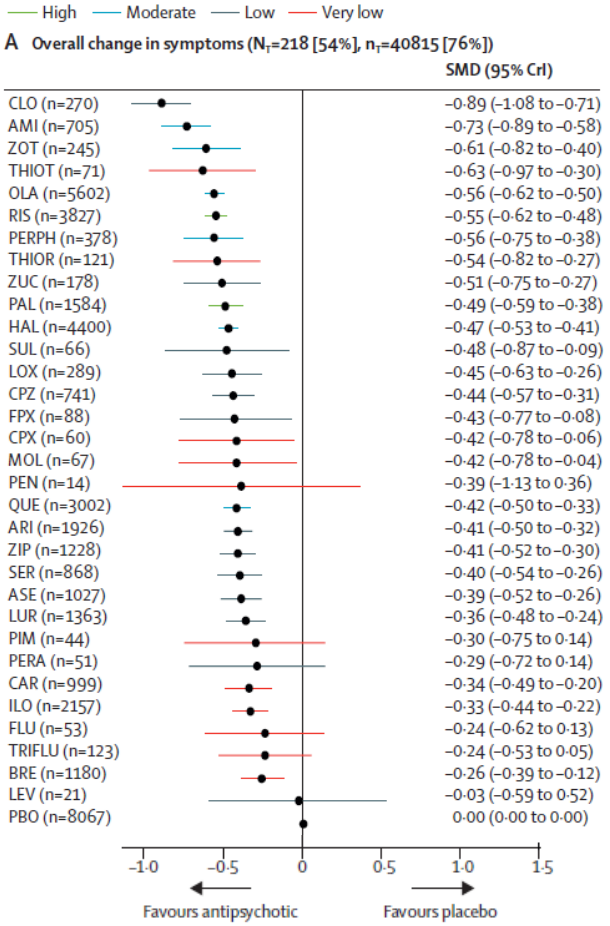


Figure 1: **Network plot of overall efficacy**
The size of the nodes corresponds to the number of participants assigned to each treatment. Treatments with direct comparisons are linked with a line; its thickness corresponds to the number of trials evaluating the comparison.



Treatments are ranked according to their surface under the curve cumulative ranking and compared with placebo. Effect sizes are presented as standardised mean difference or risk ratio with 95% CrIs. The evidence is graded using the CINeMA system (Confidence in Network Meta-Analysis), an adaption of the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach for network meta-analysis. Colours indicate the confidence in the evidence: green=high, blue=moderate, grey=low, red=very low. NT=total number of trials reporting the outcome (percentage of sample). nT=total number of participants available for the respective outcome (percentage of sample). SMD=standardised mean difference. CrI=credible interval. RR=risk ratio. AMI=amisulpride. ARI=aripiprazole. ASE=asenapine. BRE=brexpiprazole. CAR=cariprazine. CLO=clozapine. CPX=clopenthixol. CPZ=chlorpromazine. FLU=fluphenazine. FPX=flupentixol. HAL=haloperidol. ILO=iloperidone. LEV=levomepromazine. LOX=loxapine. LUR=lurasidone. MOL=molindone. OLA=olanzapine. PAL=paliperidone. PBO=placebo. PEN=penfluridol. PERA=perazine. PERPH=perphenazine. PIM=pimozide. QUE=quetiapine. RIS=risperidone. SER=sertindole. SUL=sulpiride. THIOR=thioridazine. THIOT=thiotixene. TRIFLU=trifluoperazine. ZIP=ziprasidone. ZOT=zotepine. ZUC=zuclopenthixol.

Figure 1. Results of the network meta-analysis on the acute treatment of schizophrenia for the outcome efficacy. Adapted from Huhn et al. 2019 *[open access article]*

Schneider-Thoma and colleagues performed a network meta-analysis including both placebo-controlled and head-to-head randomized controlled trials comparing 32 oral and long-acting antipsychotics for the prevention relapse in adults with schizophrenia or schizoaffective disorder with stable symptoms who were already treated with antipsychotics (20). Overall, they included 125 RCTs and 18 152 participants, of which 100 (80%) with 16 812 (93%) participants provided data for the primary outcome (risk of relapse). Most antipsychotics (26 over 31, 81%) outperformed placebo, with SMDs ranging between -0.89 (clozapine) to -0.26 (brexpiprazole). Effect sizes were and 95% Credible Intervals (95% CrI) were largely overlapping. Certainty of evidence according to the CINeMA approach "moderate" for most of the best performing medications, with the exception of fluphenazine oral, tiotixene oral, and iloperidone oral (rated as "low") (Figure 2). When considering head-to-head comparisons, clozapine, amisulpride, zotepine, olanzapine, and risperidone appeared among the best performing medications, while in most cases differences were small or non-significant. No statistically significant differences emerged when comparing risperidone and other oral SGAs head-to-head.

Antipsychotic treatment (n. of participants)	RR (95% CrI)	Events (95% CrI)	CINeMA
Zuclopenthixol long-acting injectable (n=56)	0.07 (0.00-0.34)	4% (0-20)	Moderate
Paliperidone oral (n=170)	0.20 (0.05-0.41)	12% (3-25)	Moderate
Olanzapine oral (n=1180)	0.20 (0.09-0.38)	12% (6-23)	Moderate
Fluphenazine oral (n=90)	0.22 (0.05-0.49)	13% (3-30)	Low
Fluphenazine long-acting injectable (n=338)	0.22 (0.12-0.35)	13% (7-21)	Moderate
Zotepine oral (n= 63)	0.24 (0.02-0.65)	14% (1-39)	Moderate
Risperidone long-acting injectable (n=1099)	0.45 (0.12-0.47)	15% (7-28)	Moderate
Pimozide oral (n=202)	0.47 (0.12-047)	16% (7-28)	Moderate
Haloperidol oral (n=1020)	0.47 (0.14-0.45)	16% (8-27)	Moderate
Tiotixene oral (n=19)	0.49 (0.02-0.82)	17% (1-49)	Low
Sertindole oral (n=272)	0.49 (0.07-0.65)	17% (4-39)	Moderate
Risperidone oral (r=1018)	0.49 (0.14-0.49)	17% (8-30)	Moderate
Penfluridol oral (n=230)	0.49 (0.14-0.51)	17% (8-30)	Moderate
Olanzapine long-acting injectable (n=863)	0.49 (0.07-0.63)	17% (4-38)	Moderate
Paliperidone long-acting injectable (n=848)	0.31(0.16-0.48)	18% (10-29)	Moderate
Iloperidone oral (n=153)	0.32 (0.07-0.74)	19% (4-44)	Low
Haloperidol long-acting injectable (n=461)	0.32 (0.16-0.54)	19% (10-32)	Moderate
Aripiprazole oral (n=952)	0.32 (0.14-0.56)	19% (8-34)	Moderate
Aripiprazole long-acting injectable (n=910)	0.32 (0.14-0.57)	19% (8-34)	Moderate
Chlorpromazine oral (n=443)	0.34 (0.16-0.54)	20% (10-32)	Moderate
Asenapine oral (n=194)	0.35 (0.07-0.79)	21% (4-47)	Moderate
Ziprasidone oral (n=355)	0.40 (0.14-0.74)	24% (8-44)	Moderate
Flupentixol long-acting injectable (n=137)	0.41 (0.09-0.87)	25% (6-52)	Moderate
Trifluoperazine oral (n=353)	0.44 (0.42-0.71)	26% (13-42)	Moderate
Quetiapine oral (n=939)	0.47 (0.44-0.72)	28% (14-43)	Moderate
Brexpiprazole oral (n=97)	0.48 (0.12-0.95)	29% (7-57)	Low
Thioridazine oral (n=52)	0.49 (0.09-0.98)	30% (6-59)	Low
Clopenthixol long-acting injectable (n=30)	0.51 (0.02-1.18)	30% (1-71)	Low
Lurasidone oral (n=571)	0.63 (0.25-1.02)	38% (15-61)	Low
Cariprazine oral (n=101)	0.65 (0.16-1.14)	39% (10-69)	Low
Placebo (n=2916)	1 (ref)	60%	

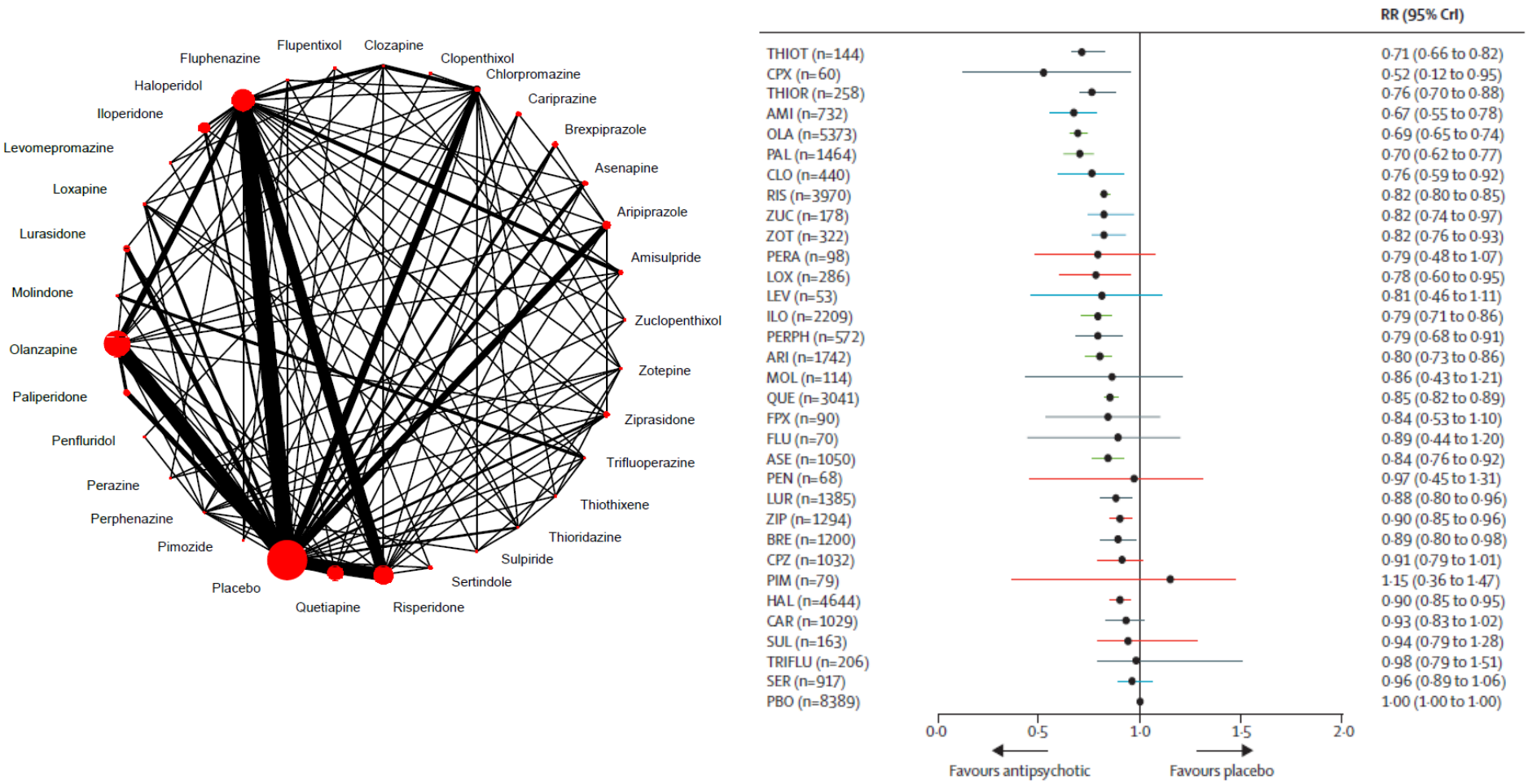
Figure 2. Results of the network meta-analysis on the relapse prevention of schizophrenia for the outcome efficacy. Treatments are ordered according to the mean effect size. RR<1 favour the antipsychotic over placebo. Crl=credible interval; RR=risk ratio. Adapted from Schneider-Thoma et al. 2022

In addition to these two network meta-analyses, we found two further systematic review and meta-analyses, which confirm and expand the above-described results on antipsychotics' efficacy. In particular:

- Zhu et al. performed a network meta-analysis comparing antipsychotics and placebo in the acute treatment of first-episode psychosis (21), including 19 RCTs and 2669 participants. In terms of overall change in symptoms (assessed with validated rating scales measuring psychopathology), among 7 oral medications included, amisulpride, olanzapine, ziprasidone and risperidone were significantly superior to haloperidol. In general, this analysis was limited to the relatively small number of RCTs and medications included, and the certainty of evidence according to CINeMA was generally low;
- Ostuzzi et al. performed a network meta-analysis including clinically stable adults with schizophrenia spectrum disorder (23). As compared to the NMA by Schneider-Thoma et al., Ostuzzi et al. additionally included those RCTs where mean severity scores of participants (e.g. Brief Psychiatric Rating Scale, BPRS) at baseline indicated relatively low levels of psychopathology, according to commonly employed cut-offs. This led to the inclusion of 14 RCTs (1486 individuals) that would have been otherwise excluded. Further, Schneider-Thoma et al. excluded individuals with prominent negative symptoms, considering that the definition of "relapse" for these individuals might be particularly challenging, while Ostuzzi et al. did not apply this exclusion criterion. Overall, results of the two NMAs were consistent in terms of both efficacy, tolerability and acceptability of treatments. Ostuzzi et al. included in the primary analysis (relapse) 92 trials (22 645 participants). Some differences emerged in terms of rating of the certainty of evidence according to CINeMA. According to Ostuzzi et al., certainty was "high" for the following treatments: amisulpride oral, olanzapine oral and LAI, aripiprazole oral and LAI, paliperidone oral, and ziprasidone oral.

9. Review of harms and toxicity: summary of evidence of comparative safety

The NMA by Huhn and colleagues on the acute treatment of adults with multi-episode schizophrenia (19) provides data on the "acceptability" of treatments (all-cause discontinuation), which is generally considered a pragmatic proxy of the balance between desirable and undesirable effects of medications. This analysis included 226 RCTs and 42 672 participants, showing the majority of the included medications to be significantly more acceptable than placebo, and none of them to be less acceptable than placebo. Certainty of evidence according to the CINeMA approach was "high" for olanzapine, paliperidone, risperidone, iloperidone, aripiprazole, quetiapine, asenapine, and "moderate" for amisulpride, clotiapine, zuclopenthixol, zotepine, and levomepromazine (Figure 3). When considering head-to-head comparisons between risperidone and other SGAs, the former was outperformed by olanzapine (RR 0.93, 95% CI 0.87 to 0.98), and outperformed lurasidone (RR 0.90, 95% CI 0.84 to 0.98), ziprasidone (RR 0.88, 95% CI 0.80 to 0.96), brexpiprazole (RR 0.89, 95% CI 0.83 to 0.97), cariprazine (RR 0.87, 95% CI 0.81 to 0.94) and sertindole (RR 0.81, 95% CI 0.70 to 0.90). In all cases, differences between risperidone and other SGAs were clinically and statistically very small.



The evidence is graded using the CINeMA system (Confidence in Network Meta-Analysis), an adaption of the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach for network meta-analysis. Colours indicate the confidence in the evidence: green=high, blue=moderate, grey=low, red=very low. NT=total number of trials reporting the outcome (percentage of sample). nT=total number of participants available for the respective outcome (percentage of sample). SMD=standardised mean difference. CrI=credible interval. RR=risk ratio. AMI=amisulpride. ARI=aripiprazole. ASE=asenapine. BRE=brexpiprazole. CAR=cariprazine. CLO=clozapine. CPX=clopenthixol. CPZ=chlorpromazine. FLU=fluphenazine. FPX=flupentixol. HAL=haloperidol. ILO=iloperidone. LEV=levomepromazine. LOX=loxapine. LUR=lurasidone. MOL=molindone. OLA=olanzapine. PAL=paliperidone. PBO=placebo. PEN=penfluridol. PERA=perazine. PERPH=perphenazine. PIM=pimozide. QUE=quetiapine. RIS=risperidone. SER=sertindole. SUL=sulpiride. THIOR=thioridazine. THIOT=thiotixene. TRIFLU=trifluoperazine. ZIP=ziprasidone. ZOT=zotepine. ZUC=zuclopenthixol.

Figure 3. Results of the network meta-analysis on the acute treatment of schzophrenia for the outcome “all-cause discontinuation”. Adapted from Huhn et al. 2019 *[open access article]*

The NMA by Schneider-Thoma and colleagues on the prevention relapse in clinically adults with schizophrenia or schizoaffective disorder (20) showed that the risk of discontinuation for any reason significantly favored most of the included antipsychotics over placebo, and none of them was significantly worse than placebo. The number of RCTs and participants included in this analysis was not clearly reported. Certainty of evidence according to the CINeMA approach "moderate" for most of the medications, with the exception of sertindole oral, rated as "high", and zotepine and cariprazine rated as "low" (Figure 4). When considering head-to-head comparisons between risperidone and other SGAs, the former outperformed lurasidone (RR 2.28, 95% CI 1.29 to 3.84) and cariprazine (RR 3.26, 95% CI 1.13 to 7.43), and there were no statistical differences with the remaining SGAs.

Antipsychotic treatment (n. of participants)	RR (95% CrI)	Events (95% CrI)	CINeMa
FLU oral (n=117)	0.15 (0.08 to 0.28)	10% (5% to 18%)	Moderate
CPX LAI (n=30)	0.20 (0.03 to 0.58)	13% (2% to 38%)	Moderate
PEN oral (n=212)	0.26 (0.15 to 0.40)	17% (10% to 26%)	Moderate
PIM oral (n=219)	0.32 (0.20 to 0.45)	21% (13% to 29%)	Moderate
ZUC LAI (n=56)	0.35 (0.11 to 0.72)	23% (7% to 47%)	Moderate
OLA oral (n=1263)	0.35 (0.24 to 0.47)	23% (16% to 31%)	Moderate
FPX LAI (n=107)	0.35 (0.13 to 0.67)	23% (8% to 44%)	Moderate
FLU LAI (n=327)	0.37 (0.24 to 0.50)	24% (16% to 33%)	Moderate
RIS oral (n=999)	0.40 (0.28 to 0 54)	26% (18% to 35%)	Moderate
CPZ oral (n=338)	0.42 (0.28 to 0.58)	27% (18% to 38%)	Moderate
THIOR oral (n=37)	0.43 (0.13 to 0.83)	28% (8% to 54%)	Moderate
RIS LAI (n=767)	0.45 (0.30 to 0.62)	29% (19% to 40%)	Moderate
HAL LAI (n=450)	0.45 (0.30 to 0.61)	29% (19% to 39%)	Moderate
ZIP oral (n=355)	0.46 (0.26 to 0.66)	30% (17% to 43%)	Moderate
OLA LAI (n=863)	0.46 (0.26 to 0.66)	30% (17% to 43%)	Moderate
TRI oral (n=353)	0.47 (0.32 to 0.65)	31% (21% to 42%)	Moderate
ARI LAI (n=910)	0.47 (0.34 to 0.62)	31% (22% to 40%)	Moderate
HAL oral (n=808)	0.49 (0.35 to 0.63)	32% (23% to 41%)	Moderate
ASE oral (n=194)	0.53 (0.30 to 0.76)	34% (19% to 50%)	Moderate
QUE oral (n=939)	0.55 (0.40 to 0.71)	36% (26% to 46%)	Moderate
SER oral (n=131)	0.56 (0.26 to 0.86)	37% (17% to 56%)	High
PAL LAI (n=848)	0 56 (0 43 to 0 67)	37% (28% to 44%)	Moderate
PAL oral (n=170)	0.58 (0.37 to 0.79)	38% (24% to 51%)	Moderate
ARI oral (n=776)	0.60 (0.43 to 0.76)	39% (28% to 49%)	Moderate
LUR oral (n=571)	0.67 (0.46 to 0.87)	44% (30% to 57%)	Moderate
ZOT oral (n=63)	0.69 (0.30 to 1.03)	45% (19% to 67%)	Low
BRE oral (n=97)	0.70 (0.39 to 0.98)	46% (25% to 64%)	Moderate
CAR oral (n=101)	0.80 (0.46 to 1.07)	52% (30% to 69%)	Low
PLB (n=2683)	Reference	65%	

Figure 4. Results of the network meta-analysis on the relapse prevention of schzophrenia for the outcome "discontinuation for any reason". Treatments are ordered according to the mean effect size. RR<1 favour the antipsychotic over placebo. Crl=credible interval; RR=risk ratio.Adapted from Schneider-Thoma et al. 2022

In addition to these two network meta-analyses, we found additional systematic reviews and meta-analyses, which confirm and expand the above-described results on antipsychotics' possible undesirable effects. In particular:

- The NMA by Zhu et al. on the acute treatment of first-episode psychosis (21) showed a significantly lower risk of all-cause discontinuation for oral aripiprazole, quetiapine, risperidone and olanzapine compared to haloperidol. As above, the certainty of evidence according to CINeMA was generally low due to the relatively small number of individuals included;
- The NMA by Ostuzzi et al. on clinically stable adults with schizophrenia spectrum disorder (23) were generally consistent with the NMA by Schneider-Thoma and colleagues (20) in terms of acceptability of treatments (discontinuation for any reason). Ostuzzi et al. included in this analysis 87 trials and 21 772 participants, showing none of the antipsychotic included to be significantly less acceptable than placebo. In this NMA, the CINeMA appraisal was not performed for secondary outcomes;
- Schneider-Thoma et al. performed a pairwise meta-analysis including RCTs comparing mortality risk between SGAs and placebo across multiple diagnoses (32). The main analysis included 352 RCTs and 84 988 participants, showing no significant differences between antipsychotic drugs and placebo in terms of mortality by any cause (OR 1.19; 95% CI 0.93–1.53), from natural causes (OR 1.29; 95% CI 0.85–1.94), from suicide (OR 1.15; 95% CI 0.47–2.81), and from other non-natural causes (OR 1.55; 95% CI 0.66–3.63). This finding was confirmed in the subgroup of people with schizophrenia (mortality by any cause: OR 0.69; 95% CI 0.35–1.35);
- Schneider-Thoma et al. performed a pairwise meta-analysis including RCTs comparing the risk of somatic serious adverse events between SGAs and placebo across multiple diagnoses (33). The main analysis included 314 RCTs and 67 642 participants. The subgroup analysis on each antipsychotic included, and considering the most conservative approach (possibly overestimating the number of serious adverse events), showed a significantly higher risk of serious adverse events for haloperidol (OR 1.61; 95% CI 1.07–2.43), olanzapine (OR 1.35; 95% CI 1.04–1.74), and risperidone (OR 1.33; 95% CI 1.04–1.70) as compared to placebo, while for the other medications no significant differences emerged.

We considered "overall dropouts" as proxy of acceptability of treatments, however the original meta-analyses explored also individual adverse events, although data were generally lacking and of poor quality (22). Additional information on adverse events can be derived from the Summary of Product Characteristics, Labelling and Package Leaflet, released by the EMA (see Appendix 1).

Overview of the evidence

In the previous sections, we reviewed current scientific literature in order to identify which SGAs are supported by the best-quality evidence according to the following criteria:

a) performing better than placebo in terms of efficacy for both acute and maintenance treatment;
b) performing better/no worse than placebo in terms of acceptability (overall dropout rate) for both acute and maintenance treatment;
c) having a moderate-to-high certainty of evidence according to the CINeMA appraisal for the majority (≥3/4) of these outcomes.

Table 6 and 7 show the effect sizes and the certainty of evidence according to the CINeMA appraisal for efficacy and acceptability.

The following antipsychotics met the criteria for selection: **aripiprazole, asenapine, olanzapine, paliperidone, quetiapine, risperidone, sertindole,** and **zotepine** (see Table 6).

Importantly, when comparing risperidone to other selected SGAs, statistically significant differences were relatively few and clinically negligible.

Second-generation antipsychotics	ACUTE TREATMENT (Huhn 2019)		MAINTENANCE TREATMENT (Schneider-Thoma 2022)		Meeting pre-defined quality criteria
	Efficacy (mean change; SMD (95% CI); negative values favour APs)	Acceptability (overall discontinuation; RR (95% CI); lower values favour APs)	Efficacy (relapse; RR (95% CI); lower values favour APs)	Acceptability (overall discontinuation; RR (95% CI); lower values favour APs)	
Amisulpride	**-0.73 (-0.89 to -0.58) +++**	**0.67 (0.55 to 0.78) +++**	NA	NA	No
Aripiprazole	-0.41 (-0.50 to -0.32) ++	**0.80 (0.73 to 0.86) ++++**	**0.32 (0.14 to 0.56) +++**	**0.60 (0.43 to 0.76) +++**	Yes
Asenapine	-0.39 (-0.52 to 0.26) ++	**0.84 (0.76 to 0.92) ++++**	**0.35 (0.07 to 0.74) +++**	**0.53 (0.30 to 0.76) +++**	Yes
Brexpiprazole	-0.26 (-0.39 to -0.12) +	0.89 (0.80 to 0.98) ++	0.48 (0.12 to 0.95) +	**0.70 (0.39 to 0.98) +++**	No
Cariprazine	-0.34 (-0.49 to -0.20) +	0.93 (0.83 to 1.02) ++	0.65 (0.16 to 1.14) +	0.80 (0.46 to 1.07) ++	No
Clozapine	-0.89 (-1.08 to -0.71) ++	**0.76 (0.59 to 0.92) +++**	NA	NA	No
Iloperidone	-0.33 (-0.44 to 0.22) +	**0.79 (0.71 to 0.86) ++++**	0.32 (0.07 to 0.74) ++	NA	No
Lurasidone	-0.36 (-0.48 to -0.24) ++	0.88 (0.80 to 0.96) ++	0.63 (0.25 to 1.02) +	**0.67 (0.46 to 0.87) +++**	No
Olanzapine	**-0.56 (-0.62 to -0.50) +++**	**0.69 (0.65 to 0.74) ++++**	**0.20 (0.09 to 0.38) +++**	**0.35 (0.24 to 0.47) +++**	Yes
Paliperidone	**-0.49 (-0.59 to -0.38) ++++**	**0.70 (0.62 to 0.77) ++++**	**0.20 (0.05 to 0.41) +++**	**0.58 (0.37 to 0.79) +++**	Yes
Quetiapine	**-0.42 (-0.50 to -0.33) +++**	**0.85 (0.82 to 0.89) ++++**	**0.47 (0.24 to 0.72) +++**	**0.55 (0.40 to 0.71) +++**	Yes
Risperidone	**-0.55 (-0.62 to -0.48) ++++**	**0.82 (0.80 to 0.85) ++++**	**0.29 (0.14 to 0.49) ++**	**0.40 (0.28 to 0.54) +++**	Yes
Sertindole	-0.40 (-0.54 to 0.26) ++	**0.96 (0.89 to 1.06) +++**	**0.29 (0.07 to 0.65) +++**	**0.56 (0.26 to 0.86) ++++**	No
Sulpride	-0.48 (-0.87 to -0.09) ++	0.94 (0.79 to 1.28) +	NA	NA	No
Ziprasidone	-0.42 (-0.52 to 0.30) ++	0.90 (0.85 to 0.95) +	**0.40 (0.14 to 0.74) +++**	**0.46 (0.26 to 0.66) +++**	No
Zotepine	**-0.61 (-0.82 to -0.40) +++**	**0.82 (0.76 to 0.93) +++**	**0.24 (0.02 to 0.65) +++**	0.69 (0.30 to 1.03) ++	No

Table 6. Overview of the certainty of evidence (CINeMA) of each SGA compared to placebo for the outcomes efficacy and acceptability, for both acute and maintenance treatment. Comparisons showing statistically significant differences and that are supported by moderate-to-high certainty of evidence are in boldface. Legend: NA=not available; NS=no significant differences vs. placebo; +=very low certainty; ++=low certainty; +++=moderate certainty; ++++=high certainty.

10. Summary of available data on comparative cost and cost-effectiveness

In this and the following section, we will critically appraise available information on possible cost, cost-effectiveness, regulatory and accessibility issues for each of the previously selected oral SGAs.

As a premise, schizophrenia-spectrum disorders come with an extremely high cost for affected individuals, healthcare systems and society. Findings from the 2016 Global Burden of Diseases Study indicate that schizophrenia contributes 13.4 million years of life lived with disability to burden of disease globally (Charlson *et al.*, 2018). Total costs associated with schizophrenia in the US have been estimated for the year 2019 at 343.2 billion, consisting of approximately 20% direct costs and more than 70% indirect costs, accounting for loss of working power and need for assistance (Kadakia *et al.*, 2022). In addition, patients suffering from schizophrenia are known to be 2.5 times more at risk of all-causes mortality (35), with consequently further increase in healthcare costs (36).

First-generation antipsychotics (FGAs) are generally cheaper than second-generation antipsychotics (SGAs), however it is challenging to rule out the comparative cost-effectiveness of these two classes of medications, mostly because of differences in terms of side effects profile. For instance, FGAs might be associated with an increased occurrence of tardive dyskinesia and an exacerbation of negative symptoms (37). SGAs are sometimes recommended as first-line treatment for schizophrenia by clinical guidelines because of their better short-term tolerability (particularly on extrapyramidal symptoms), although the burden of long-term endocrine and metabolic symptoms (e.g., hyperprolactinaemia, weight gain, glucose intolerance) and associated cardiovascular risk might be extremely relevant (38). However, SGAs are a heterogeneous class, and tolerability profiles might notably differ across different medications (39, 40).

In resource-limited countries, the use of FGAs is prevalent and SGAs are usually reserved in case of serious collateral effects or inefficacy (41, 42). There is debate around whether a routine use of SGAs in these countries could be favorable in terms of medical-economic resources as compared to FGAs, despite their higher procurement cost. Current evidence on the matter is scant and controversial. Among SGAs, olanzapine and risperidone often appear to have the most favorable cost-effectiveness profile. Here we list some of the most relevant studies informing on this issue:

- In a multi-center randomized controlled trial conducted in the UK, the relative costs and efficacy of conventional versus atypical antipsychotics were compared in more than 200 patients with a diagnosis of chronic psychosis (schizophrenia, schizoaffective disorder, delusional disorder) for whom a medication change was needed. Results suggested that switching to FGAs was generally associated with lower costs and higher quality adjusted life years (QALYs) if compared to SGAs (43);
- Obradovic et al. carried out a pharmacoeconomic analysis modeling clinical and economic outcomes of various antipsychotics in both oral (amisulpride, aripiprazole, haloperidol, olanzapine, quetiapine,

risperidone, ziprasidone) and long-acting formulation (haloperidol and risperidone) over a 1-year horizon. They concluded that the most cost-effective strategies were haloperidol, haloperidol decanoate and olanzapine. Among SGAs, olanzapine and risperidone were found to be the most favorable treatments for outpatients with chronic schizophrenia (44);

- In a study conducted in Singapore modelling the cost-effectiveness of 11 oral antipsychotics both FGAs and SGAs (amisulpride, aripiprazole, chlorpromazine, haloperidol, olanzapine, paliperidone, quetiapine, risperidone, sulpiride, trifluoperazine, ziprasidone) for psychotic relapse-prevention over a life-time, olanzapine emerged as the most favorable treatment with the highest quality-adjusted life-years gained and the lowest lifetime costs, while ziprasidone, aripiprazole and paliperidone seemed the least favorable (45);
- A cohort study carried out in Germany using data from a statutory sickness fund, including more than 3000 patients diagnosed with schizophrenia, found no differences between atypical versus typical antipsychotics in terms of re-hospitalization rates (46);
- Findings from a large-scale study in Taiwan including more than 3000 patients recruited from 1999 to 2004 and treated for first episode psychosis indicated that haloperidol was more expensive if compared with olanzapine, zotepine or quetiapine when considering total hospitalization expenses and overall treatment costs (47);
- In another cost-effectiveness analysis modeled after the Ugandan health care system, risperidone was deemed to be potentially cost-saving compared to haloperidol and quetiapine (48);
- A review of the literature by Hargraves et al. states that there is insufficient evidence to distinguish the relative total cost of care associated with risperidone versus olanzapine, although available evidence suggests the difference is small (49);
- A recent cost-analysis carried out in the UK from National Health Service perspective between 2016 and 2017 evaluated the use of paliperidone instead of most the commonly prescribed amisulpride. Results indicated that paliperidone was associated with an incremental cost-effectiveness ratio of £10,941 per added Quality Adjusted Life Year, below the suggested NHS threshold of £20–30,000, leading to the conclusion that it should be preferred to amisulpride (50);
- Newer antipsychotics on the market, such as asenapine, ziprasidone and lurasidone have also been the subject of pharmacoeconomic studies using Markov models with promising results in terms of cost-effectiveness, mostly attributable to the lower incidence of cardiometabolic side-effects (51-53).

Moreover, different medicine formulations might also have an impact on cost-effectiveness. Several studies showed that olanzapine orodispersible treatment (ODT) is generally preferred by patients to the standard oral treatment (SOT) and therefore tend to associate with better treatment adherence and lower relapse risk (54). In a 12-week randomized, cross-over, multinational, open-label study, 175 patients suffering from schizophrenia were randomly assigned to olanzapine ODT or SOT for 6 weeks and then switched to the other

formulation. Results indicate that 61% of the sample preferred the ODT formulation, whereas only 27% favored SOT and 12% expressed no preference at all (55). In addition to that, olanzapine ODT has proven particularly useful when treatment needs to be administered under difficult circumstances, such as in case of acutely ill non-compliant or agitated patients, allowing a reduction in nursing burden (56, 57). According to some cost-effectiveness analysis, olanzapine ODT also seems to offer a favorable pharmacoeconomic profile compared to the corresponding OST and to other antipsychotics. Ascher-Svanum et al. (58) compared the cost-effectiveness of olanzapine, aripiprazole and risperidone ODT and SOT using a 1-year Monte Carlo Micro-simulation economic model. Although olanzapine ODT was more expensive than olanzapine SOT and risperidone SOT, it proved to be cost-effective (ICER 19,643$ and ICER 39,966$ respectively), due to lower relapse and hospitalization rates. Moreover, if compared to risperidone and aripiprazole ODT, olanzapine ODT was not only less expensive but also more effective (58). A similar cost-effectiveness analysis carried out in China yielded consistent results with olanzapine-ODT demonstrating to be cost-effective compared to olanzapine-SOT (ICER 16,798$ per QALY gained), which in turn was cost-effective (-15,477$ per QALY gained) compared to aripiprazole-SOT over a 1-year horizon (59).

Table 7 provides some examples of the cost of generic second-generation antipsychotics (SGAs) available on the market in different countries.

Table 7. Cost of selected second-generation antipsychotics in different countries expressed in US dollars (currency converter: xe.com). We reported the general patient charge for generic medications (or for the original brand if generic was unavailable).

	Italy	U.K.	U.S.	India	Australia	South Africa
Aripiprazole tablets	5 mg (28 u) = 19,86 $ 10 mg (28 u) = 19,86 $ 15 mg (28 u) = 19,86 $	5 mg (28 u) = 115,30 $ 10 mg (28 u) = 115,30 $ 15 mg (28 u) = 115,30 $ 30 mg (28 u) = 230,59 $	5 mg (30 u) = 608,22 $ 10 mg (30 u) = 620,53 $ 15 mg (30 u) = 640,67 $ 20 mg (30 u) = 817,82 $	5 mg (10 u) = 0,41 $ 10 mg (10 u) = 0,70 $ 15 mg (10 u) = 1,00 $ 20 mg (10 u) = 1,68 $ 30 mg (10 u) = 1,74 $	10 mg (30 u) = 29,10 $ 15 mg (30 u) = 29,10 $ 20 mg (30 u) = 29,10 $ 30 mg (30 u) = 29,10 $	5 mg (30 u) = 10,23 $ 10 mg (30 u) = 18,73 $ 15 mg (30 u) = 30,00 $
Asenapine sublingual tablets	5 mg (60 u) = 146,06 $ 10 mg (60 u) = 146,06 $	5 mg (60 u) = 123,17 $ 10 mg (60 u) = 123,17 $	5 mg (60 u) = 914,29 $ 10 mg (60 u) = 1164 ,15 $	5 mg (10 u) = 0,69 $	5 mg (60 u) = 29,44 $ 10 mg (60 u) = 29,44 $	NA
Olanzapine tablets	2,5 mg (28 u) = 10,08 $ 5 mg (28 u) = 19,86 $ 10 mg (28 u) = 34,12 $	2,5 mg (28 u) = 26,23 $ 5 mg (28 u) = 52,46 $ 7,5 mg (28 u) = 74,75 $ 10 mg (28 u) = 104,92 $ 15 mg (28 u) = 143,07 $ 20 mg (28 u) = 190,76 $	5 mg (30 u) = 147,33 $ 7,5 mg (30 u) = 174,82 $ 10 mg (30 u) = 208,25 $ 15 mg (30 u) = 301,47 $ 20 mg (30 u) = 379,42 $	5 mg (10 u) = 0,30 $ 10 mg (10 u) = 0,63 $ 15 mg (10 u) = 0,88 $ 20 mg (10 u) = 1,05 $	5 mg (28 u) = 16,09 $ 10 mg (28 u) = 19,90 $ 15 mg (28 u) = 23,69 $ 20 mg (28 u) = 27,48 $	5 mg (28 u) = 16,01 $ 10 mg (28 u) = 19,20 $
Olanzapine orally disintegrating tablets	2,5 mg (28 u) = 10,25 $ 5 mg (28 u) = 20,19 $ 10 mg (28 u) = 34,70 $	5 mg (28 u) = 48,93 $ 10 mg (28 u) = 88,86 $ 15 mg (28 u) = 133,47 $ 20 mg (28 u) = 177,96 $	5 mg (30 u) = 295,94 $ 10 mg (30 u) = 302,72 $ 15 mg (30 u) = 337,23 $ 20 mg (30 u) = 523,19 $	2,5 mg (10 u) = 0,31 $ 5 mg (10 u) = 0,45 $ 10 mg (10 u) = 0,88 $ 15 mg (10 u) = 1,08 $	5 mg (28 u) = 15,07 $ 10 mg (28 u) = 17,56 $ 15 mg (28 u) = 20,30 $ 20 mg (28 u) = 23,03 $	5 mg (28 u) = 16,81 $ 10 mg (28 u) = 51,94 $
Paliperidone tablets	3 mg (28 u) = 61,35 $ 6 mg (28 u) = 61,35 $ 9 mg (28 u) = 103,53 $	3 mg (28 u) = 116,78 $ 6 mg (28 u) = 116,78 $ 9 mg (28 u) = 175,16 $	1,5 mg (30 u) = 662,94 $ 3 mg (30 u) = 668,87 $ 6 mg (30 u) = 639,13 $	3 mg (10 u) = 0,51 $ 6 mg (10 u) = 0,96 $ 9 mg (10 u) = 1,30 $	3 mg (28 u) = 29,44 $ 6 mg (28 u) = 29,44 $ 9 mg (28 u) = 29,44 $	3 mg (28 u) = 121,21 $ 6 mg (28 u) = 121,21 $ 9 mg (28 u) = 143,55 $
Quetiapine tablets extended-release (XR)	50 mg (60 u) = 32,07 $ 150 mg (60 u) = 48,71 $ 200 mg (60 u) = 64,94 $ 300 mg (60 u) = 73,21 $ 400 mg (60 u) = 97,41 $	50 mg (60 u) = 10,79 $ 150 mg (60 u) = 23,40 $ 200 mg (60 mg) = 23,40 $ 300 mg (60 u) = 40,50 $ 400 mg (60 u) = 50,01 $	50 mg (60 u) = 394,11 $ 150 mg (60 u) = 684,03 $ 200 mg (60 u) = 751,46 $ 300 mg (60 u) = 950,65 $ 400 mg (60 u) = 1166,30 $	50 mg (10 u) = 0,50 $ 100 mg (10 u) = 0,69 $ 200 mg (10 u) = 1,30 $ 300 mg (10 u) = 1,83 $ 400 mg (10 u) = 2,32 $	50 mg (60 u) = 20,31 $ 150 mg (60 u) = 23,63 $ 200 mg (60 u) = 29,10 $ 300 mg (60 u) = 29,10 $ 400 mg (60 u) = 29,10 $	50 mg (60 u) = 21,06 $ 150 mg (60 u) = 25,62 $ 200 mg (60 u) = 43,66 $ 300 mg (60 u) = 39,56 $ 400 mg (60 u) = 46,76 $
Quetiapine tablets immediate-release (IR)	100 mg (60 u) = 40,74 $ 200 mg (60 u) = 50,93 $ 300 mg (60 u) = 61,11 $	25 mg (60 u) = 58,34 $ 100 mg (60 u) = 162,93 $ 150 mg (60 u) = 135,77 $ 200 mg (60 u) = 162,93 $ 300 mg (60 u) = 244,90 $	25 mg (60 u) = 84,89 $ 50 mg (60 u) = 130,66 $ 100 mg (60 u) = 135,32 $ 200 mg (60 u) = 222,93 $ 300 mg (60 u) = 323,65 $ 400 mg (60 u) = 369,39 $	25 mg (10 u) = 0,27 $ 100 mg (10 u) = 0,50 $ 200 mg (10 u) = 1,00 $ 300 mg (10 u) = 1,31 $	25 mg (60 u) = 16,32 $ 200 g (60 u) = 27,72 $ 300 mg (60 u) = 29,10 $	200 mg (60 u) = 25,09 $ 300 mg (60 u) = 30,69 $ 400 mg (60 u) = 45,14 $
Risperidone tablets	1 mg (60 u) = 14,90 $ 2 mg (60 u) = 27,55 $ 3 mg (60 u) = 38,85 $ 4 mg (60 u) = 64,41 $	1 mg (60 u) = 21,08 $ 2 mg (60 u) = 72,15 $ 3 mg (60 u) =106,10 $ 4 mg (60 u) = 140,06 $ 6 mg (28 u) = 99,04 $	1 mg (60 u) = 91,37 $ 2 mg (60 u) = 101,43 $ 3 mg (60 u) = 167,94 $ 4 mg (60 u) = 190,83 $	1 mg (10 u) = 0,15 $ 2 mg (10 u) = 0,32 $ 3 mg (10 u) = 0,32 $ 4 mg (10 u) = 0,45 $	1 mg (60 u) = 16,59 $ 2 mg (60 u) = 22,09 $ 3 mg (60 u) = 27,38 $ 4 mg (60 u) = 29,10 $	1 mg (60 u) = 26,48 $ 2 mg (60 u) = 56,53 $ 3 mg (60 u) = 87,76 $

Sertindole	NA	NA	NA	NA	NA	NA
Ziprasidone tablets	20 mg (56 u) = 115,56 $ 40 mg (56 u) = 115,56 $ 60 mg (56 u) = 115,52 $ 80 mg (56 u) = 251,70 $	NA	20 mg (30 u) = 217,95 $ 40 mg (30 u) = 190,24 $ 60 mg (30 u) = 213,88 $ 80 mg (30 u) = 201,27 $	20 mg (10 u) = 0,36 $ 40 mg (50 u) = 0,89 $ 60 mg (10 u) = 0,22 $ 80 mg (10 u) = 0,30 $	20 mg (60 u) = 29,44 $ 40 mg (60 u) = 29,44 $ 60 mg (60 u) = 29,44 $ 80 mg (60 u) = 29,44 $	20 mg (60 u) = 78,99 $ 40 mg (60 u) = 82,78 $ 60 mg (60 u) = 111,15 $ 80 mg (60 u) = 135,97 $
Zotepine	NA	NA	NA	NA	NA	NA

Legend: mg=milligrams; NA=not available; u= units.

Sources:
Italy: generic price as indicated by the Italian National agency (see this link, last accessed 29.11.2022) or in the package leaflet (for Asenapine and Ziprasidone)
UK: non-proprietary or generic price as reported in the British National Formulary 83, 2022
US: average retail pharmacy price extracted from https://www.goodrx.com (accessed 29.11.2022)
South Africa: https://medicineprices.org.za/ (last accessed 29.11.2022)
Australia: https://www.pbs.gov.au/medicine/item/11877D-11879F-3169T-8789N (last accessed 29.11.2022)
India: median retail price extracted from https://www.medindia.net/drug-price/ (last accessed 29.11.2022)

11. Regulatory status, market availability and pharmacopoeial standards

Current approval and patent status

- Aripiprazole was approved by the FDA in November 2002 (trade name Abilify®, Application n. 021436; Company: Otsuka Pharmaceutical Co., Ltd) and by the EMA in June 2004 (trade name: Abilify®; Agency product n. EMEA/H/C/000471; Marketing-authorization holder: Otsuka Pharmaceutical Netherlands B.V.). Otsuka's patent expired in 2015 and many generic versions of the medication are now available worldwide.
- Asenapine was approved by the FDA in August 2009 (trade name Saphris®, Application n. 022117; Company: Allergan) and by the EMA in September 2010 (trade name: Sycrest®; Agency product n. EMEA/H/C/001177; Marketing-authorization holder: N. V. Organon). Allergan's patent for asenapine expired in June 2020 and generic versions of the medication can currently be produced and marketed, although they are still unavailable in most countries worldwide.
- Olanzapine was approved by the FDA on September 30th, 1996 (trade name Zyprexa®, Application n. 022264; Company: Eli Lilly and Company, Inc.) and by the EMA on September 27th, 1996 (trade name: Zyprexa®; Agency product n. EMEA/H/C/000115; Marketing-authorization holder: Eli Lilly Nederland B.V.). Eli Lilly's patent expired in 2011 and many generic versions of the medication are now available worldwide.
- Paliperidone was approved by the FDA on December 19th, 2006 (trade name: Invega®, Application n. 021999; Company: Jansen Pharms, Inc.) and by the EMA on June 24th 2007 (trade name: Invega®; Agency product n. EMEA/H/C/000746; Marketing-authorisation holder: Janssen-Cilag International N.V.). Many generic versions of the medication are now available worldwide.
- Quetiapine was approved by the FDA on September 26th, 1997 (trade name: Seroquel®, Application n. 020639; Company: Zeneca Pharmaceuticals, Inc.) and was first authorized in the European area in July 1997. AstraZeneca's patent expired in 2012 for quetiapine IR and in 2017 for quetiapine ER; many generic versions of the medication are now available worldwide.
- Sertindole was developed by the Danish pharmaceutical company H. Lundbeck and was initially authorized in the UK in May 1996 and subsequently in several other EU Member States through the Mutual Recognition procedure. In June 1999, following a referral presented by the Netherlands in November 1998, the authorization was suspended due to an alleged increased risk of sudden cardiac death. After a careful re-evaluation of the additional information submitted by the manufacturer and a redefinition of dosing, contraindications and monitoring requirements, the European Committee for Proprietary Medicinal Products recommended to lift the suspension in October 2001, a decision that was ratified by the European Commission in June 2002 (EMA)[1]. However, the medication is currently

[1] https://www.ema.europa.eu/en/medicines/human/referrals/sertindole (last accessed 29.11.2022)

produced and marketed only in some European countries, under special safety conditions. Sertindole was never approved by the FDA and consequently never entered the US market. The medication was deemed insufficiently safe by the FDA advisory panel in 2009, despite the unanimous acknowledgement of its clinical efficacy (AACAP)[2].

- Zotepine is not approved by either FDA or EMA. In 1993 it was classified by the FDA as an inactive substance and, even in subsequent analyses, it never achieved sufficient effect to be further studied[3].

Table 8 shows current authorized indications according to FDA and EMA, and Table 9 shows and inclusion of selected medications in some relevant national and international pharmacopoeias.

Table 8. Current FDA and EMA indication for the selected oral SGAs

Medication	FDA indication	EMA indication
Aripiprazole	▪ schizophrenia (in adults and children aged 13-17) ▪ acute treatment of manic and mixed episodes associated with bipolar I (in adults and children aged 10 and up) ▪ adjunctive treatment of major depressive disorder ▪ irritability associated with autistic disorder (in children aged 6 to 17) ▪ treatment of Tourette's disorder (in children aged 6 to 18)	▪ schizophrenia (in adults and in adolescents aged 15-17) ▪ treatment of moderate to severe manic episodes in bipolar I disorder (in adults and - only for severe episodes- in adolescents aged 13-17) ▪ prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment.
Asenapine	▪ schizophrenia ▪ acute monotherapy treatment of manic or mixed episodes (in adults and children aged 10 and up) ▪ adjunctive treatment to lithium or valproate in adults for bipolar disorder ▪ maintenance monotherapy for bipolar disorder treatment in adults	▪ moderate to severe manic episodes associated with bipolar I disorder in adults

[2] https://www.aacap.org/App_Themes/AACAP/docs/Advocacy/regulatory_issues/2009/FDA_Psychopharm_Hearing_Summary_Final.pdf (last accessed 29.11.2022)

[3] https://pubchem.ncbi.nlm.nih.gov/compound/Zotepine (last accessed 29.11.2022)

Olanzapine standard and orodispersible tablets	▪ schizophrenia (in adults and adolescents aged 13-17) ▪ acute treatment of manic or mixed episodes associated with bipolar I disorder (in adults and adolescents aged 13-17) ▪ maintenance treatment of bipolar I disorder (in adults and adolescents aged 13-17) ▪ bipolar I acute manic and mixed episodes as adjunctive with lithium or valproate (in adults) ▪ depressive episodes associated with bipolar I disorder in adults and children/adolescents (ages 10-17) in combination with fluoxetine ▪ treatment-resistant depression in adults in combination with fluoxetine	▪ schizophrenia initial treatment and maintenance treatment for patients who have shown good response to olanzapine ▪ acute treatment of moderate to severe manic episode ▪ prevention of recurrence in patients with bipolar disorder whose manic episode has responded well to initial treatment with olanzapine
Paliperidone	▪ schizophrenia (in adults and children aged 12-17) ▪ schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers and/or antidepressants	▪ treatment of schizophrenia (in adults and in adolescents 15-17) ▪ schizoaffective disorder
Quetiapine extended-release (XR)	▪ schizophrenia ▪ manic or mixed episodes associated with bipolar I disorder ▪ depressive episodes associated to bipolar disorder ▪ major depressive disorder as adjunctive therapy to antidepressants	▪ schizophrenia ▪ acute treatment of moderate to severe manic episodes in bipolar disorder ▪ acute treatment of major depressive episodes in bipolar disorder ▪ prevention of recurrence of manic or depressive episodes in patients with bipolar disorder who previously responded to quetiapine treatment ▪ add-on treatment of major depressive episodes in patients with major depressive disorder
Quetiapine immediate-release (IR)	▪ schizophrenia (in adults and adolescents aged 13-17) ▪ depressive episodes associated with bipolar disorder ▪ acute manic episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex (in adults and children aged 10-17) ▪ maintenance treatment of bipolar I disorder as adjunct therapy to lithium or divalproex	▪ schizophrenia ▪ acute treatment of moderate to severe manic episodes in bipolar disorder ▪ acute treatment of major depressive episodes in bipolar disorder ▪ prevention of recurrence of manic or depressive episodes in patients with bipolar disorder who previously responded to quetiapine treatment
Risperidone	▪ schizophrenia (in adults and adolescents aged 13-17) ▪ bipolar I acute manic or mixed episodes as monotherapy (in adults and children aged ten and up) ▪ bipolar I acute manic and mixed episodes as adjunctive with lithium or valproate (in adults) ▪ autism-associated irritability in children aged five and up.	▪ schizophrenia ▪ manic episodes associated with bipolar disorders ▪ short-term treatment of persistent aggression in patients with moderate to severe Alzheimer's dementia ▪ short-term treatment of persistent aggression in conduct disorder in children aged five and up
Sertindole	Not approved	▪ schizophrenia
Zotepine	Not approved	Not approved

Table 9. Availability of reference standards in the British, United States, European and International pharmacopoeias.

Medication	Indian Pharmacopoeia 2018	US Pharmacopoeia 2020	British Pharmacopoeia 2022	Brazilian Pharmacopoeia 2022	International Pharmacopoeia 2020
Aripiprazole	Aripiprazole Aripiprazole tablets	Aripiprazole Aripiprazole tablets Aripiprazole ODT	Aripiprazole	Not included	Not included
Asenapine	Asenapine Maleate	Not included	Not included	Not included	Not included
Olanzapine	Olanzapine Olanzapine Tablets Olanzapine and Fluoxetine Tablets	Olanzapine Olanzapine tablets Olanzapine and fluoxetine capsules Olanzapine ODT	Olanzapine Olanzapine embonate monohydrate	Not included	Not included
Paliperidone	Paliperidone	Paliperidone	Not included	Not included	Not included
Quetiapine	Quetiapine Fumarate Quetiapine Tablets	Quetiapine tablets Quetiapine extended-release tablets Quetiapine Fumarate	Quetiapine Fumarate	Not included	Not included
Risperidone	Not included	Risperidone Risperidone oral solution Risperidone tablets Risperidone ODTs	Risperidone	Not included	Not included
Sertindole	Not included	Not included	Not included	Not included	Not included
Zotepine	Not included	Not included	Not included	Not included	Not included

Sources:
India: www.ipc.gov.in (last accessed 29.11.2022)
US: http://www.usp.org/ (last accessed 29.11.2022)
Britain: https://www.pharmacopoeia.com/ (last accessed 29.11.2022)
Brazil: http://portal.anvisa.gov.br/farmacopeiabrasileira (last accessed 29.11.2022)
International Pharmacopoeia: https://apps.who.int/phint/en/p/about/ (last accessed 29.11.2022)

According to a recent analysis based on a sample of 112 national essential medicine lists, the inclusion of SGAs within the national/international lists of essential medicines is still quite rare. While first-generation antipsychotics such as haloperidol and chlorpromazine are among the most frequently included psychotropic medications, second-generation antipsychotics such as risperidone and clozapine are far less represented. The inclusion of these medications seems affected by the socio-economic status of the Country, SGAs being more often included in the lists of high-income countries and only in a minority of lower-middle income countries (26).

Relevant differences exist among National Medicines Lists/Formularies, for instance:

- Afghanistan: the "National Essential Medicines List of Afghanistan (2014)"[4] includes no second-generation antipsychotics;

[4] https://pdf.usaid.gov/pdf_docs/pa00n5m9.pdf

- Brazil: the "Relação Nacional de Medicamentos Essenciais (2020)"[5] includes risperidone, clozapine, olanzapine and quetiapine;
- China: the "National Essential Medicines List (2018)"[6] includes risperidone, olanzapine, clozapine, quetiapine, paliperidone, aripiprazole, amisulpride and sulpiride;
- India: the "National List of Essential Medicines of India (2015)"[7] includes risperidone and clozapine;
- Nigeria: the "Essential Medicines List, 6th Edition (2016)"[8] includes only risperidone;
- South Africa: the "Standard Treatment Guidelines and Essential Drugs List for South Africa – Hospital level – Adults (2019)"[9] includes risperidone, clozapine, olanzapine and quetiapine;
- the "MSF Essential Drugs (August 2022)"[10] includes risperidone and olanzapine.

Overview of the assessment of costs, cost-effectiveness, availability and regulatory status

When examining oral SGAs supported by the best-quality evidence on efficacy and tolerability, we found that most of them are currently available as generics in many countries worldwide, have an overall favorable cost-effectiveness profile, and are currently approved by the largest national and international regulatory agencies for the treatment of schizophrenia. However, we found major issues for the following medications:

- **asenapine** has been approved for schizophrenia by the FDA, but not by the EMA (which approved only the indication for bipolar disorder); is not available as generic in most countries; and is not included in any of the selected national and international pharmacopoeias that we assessed;
- **sertindole** has been approved for schizophrenia by the EMA, but not by the FDA; is available only in relatively few European Countries; and is not included in any of the selected national and international pharmacopoeias that we assessed;
- **zotepine** has not been approved by EMA and FDA, and is not included in any of the selected national and international pharmacopoeias that we assessed.

Therefore, we considered **asenapine, sertindole** and **zotepine** not eligible for inclusion in the WHO EML.

[5] https://bvsms.saude.gov.br/bvs/publicacoes/relacao_medicamentos_rename_2020.pdf

[6] ww.nhc.gov.cn/ewebeditor/uploadfile/2018/10/20181025183346942.pdf

[7] https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=MTUyNw==

[8] https://www.health.gov.ng/doc/Essential%20Medicine%20List%20(2016)%206th%20Revision.pdf

[9] http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

[10] https://medicalguidelines.msf.org/sites/default/files/pdf/guideline-339-en-2022-08-25.pdf

Final selection

In conclusion, after revising the best available evidence on oral SGAs, and critically appraising their cost, cost-effectiveness, availability and regulatory status, we propose **aripiprazole, olanzapine, paliperidone** and **quetiapine** to be included in a restricted square box as therapeutic alternatives of **risperidone** for the treatment of schizophrenia and other related psychoses.

	Meeting pre-defined criteria for high-quality evidence*	**Cost, cost-effectiveness, availability, regulatory issues**	**Eligible for inclusion in the WHO EML?**
Aripiprazole	Yes	Minor	Yes
Asenapine	Yes	**Major**	No
Olanzapine	Yes	Minor	Yes
Paliperidone	Yes	Minor	Yes
Quetiapine	Yes	Minor	Yes
Risperidone	Yes	Minor	Yes
Sertindole	Yes	**Major**	No
Zotepine	Yes	**Major**	No

* see Table 6

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APPENDICES

APPENDIX 1: Excerpts from EMA Annex III of aripiprazole, olanzapine, paliperidone, and quetiapine

Aripiprazole

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Common side effects (may affect up to 1 in 10 people): • diabetes mellitus, • difficulty sleeping, • feeling anxious, • feeling restless and unable to keep still, difficulty sitting still, • akathisia (an uncomfortable feeling of inner restlessness and a compelling need to move constantly), • uncontrollable twitching, jerking or writhing movements, • trembling, • headache, • tiredness, • sleepiness, • light-headedness, • shaking and blurred vision, • decreased number of or difficulty making bowel movements, • indigestion, • feeling sick, • more saliva in mouth than normal, • vomiting, • feeling tired. Uncommon side effects (may affect up to 1 in 100 people): • increased or decreased blood levels of the hormone prolactin, • too much sugar in the blood, • depression, • altered or increased sexual interest, • uncontrollable movements of mouth, tongue and limbs (tardive dyskinesia), • muscle disorder causing twisting movements (dystonia), • restless legs, • double vision, • eye sensitivity to light, • fast heartbeat, • a fall in blood pressure on standing up which causes dizziness, light-headedness or fainting, • hiccups. The following side effects have been reported since the marketing of oral aripiprazole but the frequency for them to occur is not known: • low levels of white blood cells, • low levels of blood platelets, • allergic reaction (e.g. swelling in the mouth, tongue, face and throat, itching, hives), • onset or worsening of diabetes, ketoacidosis (ketones in the blood and urine) or coma, • high blood sugar, • not enough sodium in the blood, • loss of appetite (anorexia), • weight loss, • weight gain, • thoughts of suicide, suicide attempt and suicide, • feeling aggressive, • agitation, • nervousness, • combination of fever, muscle stiffness, faster breathing, sweating, reduced consciousness and sudden changes in blood pressure and heart rate, fainting (neuroleptic malignant syndrome), • seizure, • serotonin syndrome (a reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles), • speech disorder, • fixation of the eyeballs in one position, • sudden unexplained death, • life-threatening irregular heartbeat, • heart attack, • slower heartbeat, • blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing (if you notice any of these symptoms, seek medical advice immediately), • high blood pressure, • fainting, • accidental inhalation of food with risk of pneumonia (lung infection), • spasm of the muscles around the voice box, • inflammation of the pancreas, • difficulty swallowing, • diarrhoea, • abdominal discomfort, • stomach discomfort, • liver failure, • inflammation of the liver, • yellowing of the skin and white part of eyes, • reports of abnormal liver tests values, • skin rash, • skin sensitivity to light, • baldness, • excessive sweating, • serious allergic reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). DRESS appears initially as flu-like symptoms with a rash on the face and then with an extended rash, high temperature, enlarged lymph nodes, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia), • abnormal muscle breakdown which can lead to kidney problems, • muscle pain, • stiffness, • involuntary loss of urine (incontinence), • difficulty in passing urine, • withdrawal symptoms in newborn babies in case of exposure during pregnancy, • prolonged and/or painful erection, • difficulty controlling core body temperature or overheating, • chest pain, • swelling of hands, ankles or feet, • in blood tests: increased or fluctuating blood sugar, increased glycosylated haemoglobin. • Inability to resist the impulse, drive or temptation to perform an action that could be harmful to you or others, which may include: - strong impulse to gamble excessively despite serious personal or family consequences - altered or increased sexual interest and behaviour of significant concern to you or to others, for example, an increased sexual drive - uncontrollable excessive shopping - binge eating (eating large amounts of food in a short time period) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger) - a tendency to wander away. Tell your doctor if you experience any of these behaviours; he/she will discuss ways of managing or reducing the symptoms. In elderly patients with dementia, more fatal cases have been reported while taking aripiprazole. In addition, cases of stroke or "mini" stroke have been reported.

Olanzapine

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Tell your doctor immediately if you have: • unusual movement (a common side effect that may affect up to 1 in 10 people) mainly of the face or tongue; • blood clots in the veins (an uncommon side effect that may affect up to 1 in 100 people) especially in the legs (symptoms include swelling, pain, and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing. If you notice any of these symptoms seek medical advice immediately; • a combination of fever,

faster breathing, sweating, muscle stiffness and drowsiness or sleepiness (the frequency of this side effect cannot be estimated from the available data). Very common side effects (may affect more than 1 in 10 people) include weight gain; sleepiness; and increases in levels of prolactin in the blood. In the early stages of treatment, some people may feel dizzy or faint (with a slow heart rate), especially when getting up from a lying or sitting position. This will usually pass on its own but if it does not, tell your doctor. Common side effects (may affect up to 1 in 10 people) include changes in the levels of some blood cells, circulating fats and early in treatment, temporary increases in liver enzymes; increases in the level of sugars in the blood and urine; increases in levels of uric acid and creatine phosphokinase in the blood; feeling more hungry; dizziness; restlessness; tremor; unusual movements(dyskinesias); constipation; dry mouth; rash; loss of strength; extreme tiredness; water retention leading to swelling of the hands, ankles or feet; fever; joint pain; and sexual dysfunctions such as decreased libido in males and females or erectile dysfunction in males. Uncommon side effects (may affect up to 1 in 100 people) include hypersensitivity (e.g. swelling in the mouth and throat, itching, rash); diabetes or the worsening of diabetes, occasionally associated with ketoacidosis (ketones in the blood and urine) or coma; seizures, usually associated with a history of seizures (epilepsy); muscle stiffness or spasms (including eye movements); restless legs syndrome; problems with speech; stuttering; slow heart rate; sensitivity to sunlight; bleeding from the nose; abdominal distension; drooling; memory loss or forgetfulness; urinary incontinence; lack of ability to urinate; hair loss; absence or decrease in menstrual periods; and changes in breasts in males and females such as an abnormal production of breast milk or abnormal growth. Rare side effects (may affect up to 1 in 1000 people) include lowering of normal body temperature; abnormal rhythms of the heart; sudden unexplained death; inflammation of the pancreas causing severe stomach pain, fever and sickness; liver disease appearing as yellowing of the skin and white parts of the eyes; muscle disease presenting as unexplained aches and pains; and prolonged and/or painful erection. Very rare side effects include serious allergic reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). DRESS appears initially as flu-like symptoms with a rash on the face and then with an extended rash, high temperature, enlarged lymph nodes, increased levels of liver enzymes seen on blood tests and an increase in a type of white blood cells (eosinophilia). While taking olanzapine, elderly patients with dementia may suffer from stroke, pneumonia, urinary incontinence, falls, extreme tiredness, visual hallucinations, a rise in body temperature, redness of the skin and have trouble walking. Some fatal cases have been reported in this particular group of patients. In patients with Parkinson's disease ZYPREXA may worsen the symptoms.

Paliperidone

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Tell your doctor immediately if you: • experience blood clots in the veins, especially in the legs (symptoms include swelling, pain, and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty breathing. If you notice any of these symptoms seek medical advice immediately. • have dementia and experience a sudden change in your mental state or sudden weakness or numbness of your face, arms or legs, especially on one side, or slurred speech, even for a short period of time. These may be signs of a stroke. • experience fever, muscle stiffness, sweating or a lowered level of consciousness (a disorder called "Neuroleptic Malignant Syndrome"). Immediate medical treatment may be needed. • are a man and experience prolonged or painful erection. This is called priapism. Immediate medical treatment may be needed. • experience involuntary rhythmic movements of the tongue, mouth and face. Withdrawal of paliperidone may be needed. • experience a severe allergic reaction characterised by fever, swollen mouth, face, lip or tongue, shortness of breath, itching, skin rash and sometimes drop in blood pressure (amounting to an 'anaphylactic reaction'). Very common: may affect more than 1 in 10 people • difficulty falling or staying asleep • parkinsonism: This condition may include slow or impaired movement, sensation of stiffness or tightness of the muscles (making your movements jerky), and sometimes even a sensation of movement "freezing up" and then restarting. Other signs of parkinsonism include a slow shuffling walk, a tremor while at rest, increased saliva and/or drooling, and a loss of expression on the face. • restlessness • feeling sleepy or less alert • headache. Common side effects: may affect up to 1 in 10 people • infection of the chest (bronchitis), common cold symptoms, sinus infection, urinary tract infection, feeling like you have the flu • weight gain, increased appetite, weight loss, decreased appetite • elated mood (mania), irritability, depression, anxiety • dystonia: This is a condition involving slow or sustained involuntary contraction of muscles. While it can involve any part of the body (and may result in abnormal posture), dystonia often involves muscles of the face, including abnormal movements of the eyes, mouth, tongue or jaw. • dizziness • dyskinesia: This is a condition involving involuntary muscle movements, and can include repetitive, spastic or writhing movements, or twitching. • tremor (shaking) • blurry vision • an interruption in conduction between the upper and lower parts of the heart, abnormal electrical conduction of the heart, prolongation of the QT interval from your heart, slow heart rate, rapid heart rate • low blood pressure upon standing (consequently, some people taking INVEGA may feel faint, dizzy, or may pass out when they stand up or sit

up suddenly), high blood pressure • sore throat, cough, stuffy nose • abdominal pain, abdominal discomfort, vomiting, nausea, constipation, diarrhoea, indigestion, dry mouth, toothache • increased liver transaminases in your blood • itching, rash • bone or muscle ache, back pain, joint pain • loss of menstrual periods • fever, weakness, fatigue (tiredness). 49 Uncommon side effects: may affect up to 1 in 100 people • pneumonia, infection of the breathing passages, bladder infection, ear infection, tonsillitis • white blood cell count decreased, decrease in platelets (blood cells that help you stop bleeding), anaemia, decrease in red blood cells • INVEGA can raise your levels of a hormone called "prolactin" found on a blood test (which may or may not cause symptoms). When symptoms of high prolactin occur, they may include: (in men) breast swelling, difficulty in getting or maintaining erections, or other sexual dysfunction, (in women) breast discomfort, leakage of milk from the breasts, missed menstrual periods, or other problems with your cycle. • diabetes or worsening diabetes, high blood sugar, increased waist size, loss of appetite resulting in malnutrition and low body weight, high blood triglycerides (a fat) • sleep disorder, confusion, decreased sexual drive, inability to reach orgasm, nervousness, nightmares • tardive dyskinesia (twitching or jerking movements that you cannot control in your face, tongue, or other parts of your body). Tell your doctor immediately if you experience involuntary rhythmic movements of the tongue, mouth and face. Withdrawal of INVEGA may be needed. • convulsion (fits), fainting, a restless urge to move parts of your body, dizziness upon standing, disturbance in attention, problems with speech, loss or abnormal sense of taste, reduced sensation of skin to pain and touch, a sensation of tingling, pricking, or numbness of skin • oversensitivity of the eyes to light, eye infection or "pink eye", dry eye • a sensation of spinning (vertigo), ringing in the ears, ear pain • irregular heartbeat, abnormal electrical tracing of the heart (electrocardiogram or ECG), a fluttering or pounding feeling in your chest (palpitations) • low blood pressure • shortness of breath, wheezing, nosebleeds • swollen tongue, stomach or intestinal infection, difficulty swallowing, excessive passing of gas or wind • increased GGT (a liver enzyme called gamma-glutamyltransferase) in your blood, increased liver enzymes in your blood • hives (or "nettle rash"), hair loss, eczema, acne • an increase of CPK (creatine phosphokinase) in your blood, an enzyme which is sometimes released with muscle breakdown, muscle spasms, joint stiffness, joint swelling, muscle weakness, neck pain • incontinence (lack of control) of urine, frequent passing of urine, inability to pass urine, pain when passing urine • erectile dysfunction, ejaculation disorder • missed menstrual periods or other problems with your cycle (females), leakage of milk from the breasts, sexual dysfunction, breast pain, breast discomfort • swelling of the face, mouth, eyes, or lips, swelling of the body, arms or legs • chills, an increase in body temperature • a change in the way you walk • feeling thirsty • chest pain, chest discomfort, feeling unwell • fall. Rare side effects: may affect up to 1 in 1,000 people • eye infection, fungal infection of the nails, infection of the skin, skin inflammation caused by mites • dangerously low numbers of a certain type of white blood cell needed to fight infection in your blood • decrease in the type of white blood cells that help to protect you against infection, increase in eosinophils (a type of white blood cell) in your blood • severe allergic reaction characterised by fever, swollen mouth, face, lip or tongue, shortness of breath, itching, skin rash and sometimes drop in blood pressure, allergic reaction • sugar in the urine • inappropriate secretion of a hormone that controls urine volume • life-threatening complications of uncontrolled diabetes • dangerously excessive intake of water, low blood sugar, excessive drinking of water, increased cholesterol in your blood • sleep walking • not moving or responding while awake (catatonia) • lack of emotion • neuroleptic malignant syndrome (confusion, reduced or loss of consciousness, high fever, and severe muscle stiffness) • loss of consciousness, balance disorder, abnormal coordination • blood vessel problems in the brain, coma due to uncontrolled diabetes, unresponsive to stimuli, low level of consciousness, shaking of the head • glaucoma (increased pressure within the eyeball), increased tears, redness of the eyes, problems with movement of your eyes, eye rolling • atrial fibrillation (an abnormal heart rhythm), rapid heartbeat upon standing • blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing. If you notice any of these symptoms seek medical advice immediately • decreased oxygen in parts of your body (because of decreased blood flow), flushing • trouble breathing during sleep (sleep apnea), fast, shallow breathing • pneumonia caused by inhaling food, congestion of breathing passages, voice disorder • a blockage in the bowels, stool incontinence, very hard stool, lack of bowel muscle movement that causes blockage • yellowing of the skin and the eyes (jaundice) • inflammation of the pancreas • serious allergic reaction with swelling that may involve the throat and lead to difficulty breathing • thickening of the skin, dry skin, skin redness, skin discolouration, flaky itchy scalp or skin, dandruff • breakdown of muscle fibers and pain in muscles (rhabdomyolysis), abnormal posture • priapism (a prolonged penile erection that may require surgical treatment) • development of breasts in men, enlargement of the glands in your breasts, discharge from the breasts, vaginal discharge • a delay in menstrual periods, breast enlargement • very low body temperature, a decrease in body temperature • symptoms of drug withdrawal. Not known: frequency cannot be estimated from the available data • lung congestion • increased insulin (a hormone that controls blood sugar levels) in your blood. The following side effects have been seen with the use of another

medicine called risperidone that is very similar to paliperidone, so these can also be expected with INVEGA: sleep-related eating disorder, other types of blood vessel problems in the brain, crackly lung sounds, and severe or life-threatening rash with blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body (Stevens-Johnson syndrome/toxic epidermal necrolysis). Eye problems during cataract surgery may also occur. During cataract surgery, a condition called intraoperative floppy iris syndrome (IFIS) can happen if you take or have taken INVEGA. If you need to have cataract surgery, be sure to tell your eye doctor if you take or have taken this medicine.

Quetiapine

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients of this product. Concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV-protease inhibitors, azole-antifungal agents, erythromycin, clarithromycin and nefazodone, is contraindicated. (See section 4.5).

4.4 Special warnings and precautions for use

As Seroquel XR is indicated for the treatment of schizophrenia, bipolar disorder and add-on treatment of major depressive episodes in patients with MDD, the safety profile should be considered with respect to the individual patient's diagnosis and the dose being administered. Long-term efficacy and safety in patients with MDD has not been evaluated as add-on therapy, however long-term efficacy and safety has been evaluated in adult patients as monotherapy (see Section 5.1). Children and adolescents (10 to 17 years of age) Seroquel XR is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. Clinical trials with Seroquel have shown that in addition to the known safety profile identified in adults (see section 4.8), certain adverse events occurred at a higher frequency in children and adolescents compared to adults (increased appetite, elevations in serum prolactin and extrapyramidal symptoms) and one was identified that has not been previously seen in adult studies (increases in blood pressure). Changes in thyroid function tests have also been observed in children and adolescents. Furthermore, the long-term safety implications of treatment with Seroquel on growth and maturation have not been studied beyond 26 weeks. Long-term implications for cognitive and behavioural development are not known. In placebo-controlled clinical trials with children and adolescent patients treated with Seroquel, quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for schizophrenia and bipolar mania (see section 4.8). Suicide/suicidal thoughts or clinical worsening: Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. In addition, physicians should consider the potential risk of suicide-related events after abrupt cessation of quetiapine treatment, due to the known risk factors for the disease being treated. Other psychiatric conditions for which Seroquel XR is prescribed can also be associated with an increased risk of suicide related events. In addition, these conditions may be co-morbid with major depressive episodes. The same precautions observed when treating patients with major depressive episodes should therefore be observed when treating patients with other psychiatric disorders. Patients with a history of suicide related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta analysis of placebo controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old. Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present. In shorter-term placebo controlled clinical studies of patients with major depressive episodes in bipolar disorder an increased risk of suicide-related events was observed in young adults patients (younger than 25 years of age) who were treated with quetiapine as compared to those treated with placebo (3.0% vs. 0%, respectively). In clinical studies of patients with MDD the incidence of suicide-related events observed in young adult patients (younger than 25 years of age) was 2.1% (3/144) for quetiapine and 1.3% (1/75) for placebo. Extrapyramidal symptoms: In placebo controlled clinical trials of adult patients quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for major depressive episodes in bipolar disorder and major depressive disorder (see sections 4.8 and 5.1). The use of quetiapine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental. Tardive Dyskinesia: If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of Seroquel XR

should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment (see Section 4.8). Somnolence and dizziness: Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation (see Section 4.8). In clinical trials for treatment of patients with bipolar depression and major depressive disorder, onset was usually within the first 3 days of treatment and was predominantly of mild to moderate intensity. Bipolar depression patients and patients with major depressive episodes in MDD experiencing somnolence of severe intensity may require more frequent contact for a minimum of 2 weeks from onset of somnolence, or until symptoms improve and treatment discontinuation may need to be considered. Quetiapine treatment has been associated with orthostatic hypotension and related dizziness (see Section 4.8) which, like somnolence has onset usually during the initial dose-titration period. This could increase the occurrence of accidental injury (fall), especially in the elderly population. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication. Cardiovascular: Seroquel XR should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. Quetiapine may induce orthostatic hypotension especially during the initial dose-titration period and therefore dose reduction or more gradual titration should be considered if this occurs. A slower titration regimen could be considered in patients with underlying cardiovascular disease. Seizures: In controlled clinical trials there was no difference in the incidence of seizures in patients treated with quetiapine or placebo. As with other antipsychotics, caution is recommended when treating patients with a history of seizures (see Section 4.8). Neuroleptic Malignant Syndrome: Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including quetiapine (see section 4.8). Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatinine phosphokinase. In such an event, Seroquel XR should be discontinued and appropriate medical treatment given. Severe Neutropenia: Severe neutropenia (neutrophil count <0.5 X 10^9/L) has been uncommonly reported in quetiapine clinical trials. Most cases of severe neutropenia have occurred within a couple of months of starting therapy with quetiapine. There was no apparent dose relationship. During post-marketing experience, resolution of leucopenia and/or neutropenia has followed cessation of therapy with quetiapine. Possible risk factors for neutropenia include pre-existing low white cell count (WBC) and history of drug induced neutropenia. Quetiapine should be discontinued in patients with a neutrophil count <1.0 X 10^9 /L. Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5 X 10^9 /L). (See section 5.1). Interactions: See also section 4.5. Concomitant use of quetiapine with a strong hepatic enzyme inducer such as carbamazepine or phenytoin substantially decreases quetiapine plasma concentrations, which could affect the efficacy of quetiapine therapy. In patients receiving a hepatic enzyme inducer, initiation of Seroquel XR treatment should only occur if the physician considers that the benefits of Seroquel XR outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate). Weight: Weight gain has been reported in patients who have been treated with quetiapine, and should be monitored and managed as clinically appropriate as in accordance with utilised antipsychotic guidelines (see Sections 4.8 and 5.1). Hyperglycaemia: Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with any antipsychotic agent including quetiapine, should be observed for signs and symptoms of hyperglycaemia, (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly. Lipids: Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol have been observed in clinical trials with quetiapine (see section 4.8). Lipid changes should be managed as clinically appropriate. Metabolic Risk: Given the observed changes in weight, blood glucose (see hyperglycemia) and lipids seen in clinical studies, there may be possible worsening of the metabolic risk profile in individual patients, which should be managed as clinically appropriate (see also section 4.8). QT Prolongation: In clinical trials and use in accordance with the SPC, quetiapine was not associated with a persistent increase in absolute QT intervals. In post marketing, QT prolongation was reported with quetiapine at the therapeutic doses (see Section 4.8) and in overdose (see Section 4.9). As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also caution should be exercised when quetiapine is prescribed either with medicines known to increase QT interval, or with concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia (see section 4.5). Withdrawal: Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability have been described after abrupt cessation of quetiapine. Gradual withdrawal over a period of at least one to two weeks is advisable.(see section 4.8) Elderly patients with dementia-related psychosis: Seroquel XR is not approved for the treatment of dementia-related psychosis. An approximately 3-fold increased risk of

cerebrovascular adverse events has been seen in randomized placebo controlled trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Seroquel XR should be used with caution in patients with risk factors for stroke. In a meta-analysis of atypical antipsychotics, it has been reported that elderly patients with dementiarelated psychosis are at an increased risk of death compared to placebo. However in two 10-week placebo controlled quetiapine studies in the same patient population (n=710; mean age: 83 years; range: 56-99 years) the incidence of mortality in quetiapine treated patients was 5.5% versus 3.2% in the placebo group. The patients in these trials died from a variety of causes that were consistent with expectations for this population. These data do not establish a causal relationship between quetiapine treatment and death in elderly patients with dementia. Dysphagia: Dysphagia (See section 4.8 Undesirable effects) has been reported with quetiapine. Quetiapine should be used with caution in patients at risk for aspiration pneumonia. Venous Thromboembolism (VTE): Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with SEROQUEL XR and preventive measures undertaken. Additional information: Quetiapine data in combination with divalproex or lithium in acute moderate to severe manic episodes is limited; however, combination therapy was well tolerated (see section 4.8 and 5.1). The data showed an additive effect at week 3. Lactose: Seroquel XR tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

[…]

4.8 Undesirable effects

The most commonly reported Adverse Drug Reactions (ADRs) with quetiapine are somnolence, dizziness, dry mouth, mild asthenia, constipation, tachycardia, orthostatic hypotension and dyspepsia. As with other antipsychotics, weight gain, syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral oedema, have been associated with quetiapine. The incidences of ADRs associated with quetiapine therapy, are tabulated below according to the format recommended by the Council for International Organizations of Medical Sciences (CIOMS III Working Group 1995).

The frequencies of adverse events are ranked according to the following: Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100, rare (≥1/10,000, <1/1000) and very rare (<1/10,000).	
Blood and lymphatic system disorders	
Common:	Leucopenia [1]
Uncommon:	Eosinophilia, Thrombocytopenia
Unknown:	Neutropenia [1]
Immune system disorders	
Uncommon:	Hypersensitivity
Very rare:	Anaphylactic reaction[6]
Endocrine disorders	
Common:	*Hyperprolactinemia*[16]
Metabolism and nutritional disorders	
Common:	Increased appetite
Very rare:	Diabetes Mellitus [1,5,6,]
Psychiatric disorders	
Common:	Abnormal dreams and nightmares
	Suicidal ideation and suicidal behaviour[20]
Nervous system disorders	
Very common:	Dizziness[4, 17], somnolence [2, 17], headache
Common:	Syncope [4, 17]
	Extrapyramidal symptoms[1, 21], Dysarthria
Uncommon:	Seizure [1], Restless legs syndrome, Tardive dyskinesia [1, 6]
Cardiac disorders	
Common:	Tachycardia [4]
Eye Disorders	
Common:	Vision blurred
Vascular disorders	
Common:	Orthostatic hypotension [4, 17]
Rare:	Venous thromboembolism[1]
Respiratory, thoracic and mediastinal disorder	
Common:	Rhinitis
Gastrointestinal disorders	
Very common:	Dry mouth
Common:	Constipation, dyspepsia
Uncommon:	Dysphagia[8]
Hepato-biliary disorders	
Rare:	Jaundice[6]
Very rare:	Hepatitis [6]
Skin and subcutaneous tissue disorders	
Very rare:	Angioedema[6], Stevens-Johnson syndrome[6]
Reproductive system and breast disorders	
Rare:	Priapism, Galactorrhoea
General disorders and administration site conditions	
Very common	Withdrawal (discontinuation) symptoms [1, 10]
Common:	Mild asthenia, peripheral oedema, irritability
Rare:	Neuroleptic malignant syndrome [1]
Investigations	
Very common	Elevations in serum triglyceride levels [11]
	Elevations in total cholesterol (predominantly LDL cholesterol) [12], Decreases in HDL cholesterol[18], Weight gain[9]
Common:	Elevations in serum transaminases (ALT, AST)[3], decreased neutrophil count, blood glucose increased to hyperglycaemic levels [7]
Uncommon:	Elevations in gamma-GT levels[3], Platelet count decreased[14],
	QT prolongation [1,13, 19]
Rare	Elevations in blood creatine phosphokinase[15]

(1) See Section 4.4. (2) Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of quetiapine. (3) Asymptomatic elevations in serum transaminase (ALT, AST) or gamma-GT-levels have been observed in some patients administered quetiapine. These elevations were usually reversible on continued quetiapine treatment. (4) As with other antipsychotics with alpha1 adrenergic blocking activity, quetiapine may commonly induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period. (See section 4.4). (5) Exacerbation of pre-existing diabetes has been reported in very rare cases. (6) Calculation of Frequency for these ADR's have only been taken from postmarketing data with the immediate release formulation of Seroquel (7) Fasting blood glucose ≥126mg/dL (≥7.0 mmol/L) or a non fasting blood glucose ≥200mg/dL (≥11.1 mmol/L) on at least one occasion (8) An increase in the rate of dysphagia with quetiapine vs. placebo was only observed in the clinical trials in bipolar depression (9) Based on >7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment. (10) The following withdrawal symptoms have been observed most frequently in acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms: insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability. The incidence of these reactions had decreased significantly after 1 week postdiscontinuation. (11) Triglycerides ≥200 mg/dL (≥2.258 mmol/L) (patients ≥18 years of age) or ≥150 mg/dL (≥1.694 mmol/L) (patients 18 years of age): >20 µg/L (>869.56 pmol/L) males; >30 µg/L (>1304.34 pmol/L) females at any time. (17) May lead to falls. (18) HDL cholesterol: <40 mg/dL (1.025 mmol/L) males; <50 mg/dL (1.282 mmol/L) females at any time. (19) Incidence of patients who have a QTc shift from <450 msec to ≥450 msec with a ≥30 msec increase. In placebo-controlled trials with quetiapine the mean change and the incidence of patients who have a shift to a clinically significant level is similar between quetiapine and placebo (20) Cases of suicidal ideation and suicidal behaviours have been reported during Seroquel XR therapy or early after treatment discontinuation (see Sections 4.4 and 5.1). (21) See Section 5.1. Cases of QT prolongation, ventricular arrhythmia, sudden unexplained death, cardiac arrest and torsades de pointes have been reported with the use of neuroleptics and are considered class effects. Quetiapine treatment was associated with small dose-related decreases in thyroid hormone levels, particularly total T4 and free T4. The reduction in total and free T4 was maximal within the first two to four weeks of Seroquel treatment, with no further reduction during long-term treatment. In nearly all cases, cessation of Seroquel treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. Smaller decreases in total T3 and reverse T3 were seen only at higher doses. Levels of TBG were unchanged and in general, reciprocal increases in TSH were not observed, with no indication that quetiapine causes clinically relevant hypothyroidism.

APPENDIX 2: GRADE/CINeMA Tables

Acute treatment of schizophrenia-spectrum disorders

Outcome: change in overall symptoms at the end of the study (figures and tables adapted from the Supplementary material of Huhn et al., 2019) *[open access article]*

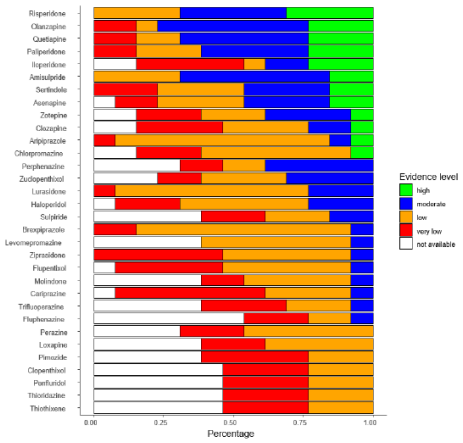

Figure 15.2: Confidence in evidence for all antipsychotics compared to placebo
In this figure we present a summary of the confidence in the evidence for the individual drugs compared to placebo according to CINeMA (Confidence in Network Meta-analysis). The 13 outcomes presented in Figures 2 and 3 were considered. The bars present the percentage of outcomes with each evidence level (e.g. for olanzapine 23% of the reported outcomes had a high evidence level, 54% a moderate, 8% a low and 15% a very low one). The antipsychotics with the largest proportion of outcomes ranked with high certainty of evidence are presented on top (e.g. for risperidone 31% of the outcomes had a high level of evidence). As CINeMA does not consider comparisons for which no data are available, we added this information in the white bars (e.g. for thiothixene for 46% of the outcomes no data were available at all). Colour code: green=high, blue=moderate, orange=low, red=very low, white=percentage of outcomes with no data available.

Comparison	Nature of evidence	Confidence level	Downgrading
Amisulpride vs. Aripiprazole	indirect	moderate	Heterogeneity
Amisulpride vs. Asenapine	indirect	moderate	Heterogeneity
Amisulpride vs. Brexpiprazole	indirect	high	
Amisulpride vs. Cariprazine	indirect	low	Study limitations, Heterogeneity
Amisulpride vs. Chlorpromazine	indirect	moderate	Imprecision
Amisulpride vs. Clopenthixol	indirect	low	Imprecision, Heterogeneity
Amisulpride vs. Clozapine	indirect	low	Imprecision, Heterogeneity
Amisulpride vs. Flupentixol	mixed	very low	Study limitations, Imprecision, Incoherence
Amisulpride vs. Fluphenazine	indirect	moderate	Imprecision
Amisulpride vs. Haloperidol	mixed	moderate	Heterogeneity
Amisulpride vs. Iloperidone	indirect	high	
Amisulpride vs. Levomepromazine	indirect	moderate	Imprecision
Amisulpride vs. Loxapine	indirect	moderate	Imprecision
Amisulpride vs. Lurasidone	indirect	moderate	Heterogeneity
Amisulpride vs. Molindone	indirect	low	Imprecision, Heterogeneity
Amisulpride vs. Olanzapine	mixed	very low	Imprecision, Heterogeneity, Incoherence
Amisulpride vs. Paliperidone	indirect	moderate	Imprecision
Amisulpride vs. Penfluridol	indirect	very low	Study limitations, Serious Imprecision
Amisulpride vs. Perazine	mixed	moderate	Imprecision
Amisulpride vs. Perphenazine	indirect	low	Imprecision, Heterogeneity

Comparison	Nature of evidence	Confidence level	Downgrading
Amisulpride vs. Pimozide	indirect	very low	Study limitations, Imprecision, Heterogeneity
Amisulpride vs. Placebo	indirect	moderate	Publication Bias
Amisulpride vs. Quetiapine	indirect	moderate	Heterogeneity
Amisulpride vs. Risperidone	mixed	low	Imprecision, Incoherence
Amisulpride vs. Sertindole	indirect	moderate	Heterogeneity
Amisulpride vs. Sulpiride	indirect	low	Serious Imprecision
Amisulpride vs. Thioridazine	indirect	very low	Study limitations, Serious Imprecision
Amisulpride vs. Thiothixene	indirect	very low	Study limitations, Serious Imprecision
Amisulpride vs. Trifluoperazine	indirect	low	Study limitations, Heterogeneity
Amisulpride vs. Ziprasidone	indirect	moderate	Heterogeneity
Amisulpride vs. Zotepine	indirect	low	Serious Imprecision
Amisulpride vs. Zuclopenthixol	indirect	low	Imprecision, Heterogeneity
Aripiprazole vs. Asenapine	indirect	very low	Study limitations, Serious Imprecision
Aripiprazole vs. Brexpiprazole	mixed	very low	Imprecision, Heterogeneity, Incoherence
Aripiprazole vs. Cariprazine	mixed	very low	Study limitations, Serious Imprecision, Incoherence
Aripiprazole vs. Chlorpromazine	indirect	very low	Study limitations, Serious Imprecision
Aripiprazole vs. Clopenthixol	indirect	very low	Study limitations, Serious Imprecision
Aripiprazole vs. Clozapine	indirect	moderate	Study limitations
Aripiprazole vs. Flupentixol	indirect	very low	Study limitations, Serious Imprecision
Aripiprazole vs. Fluphenazine	indirect	very low	Study limitations, Serious Imprecision
Aripiprazole vs. Haloperidol	mixed	very low	Study limitations, Imprecision, Heterogeneity, Incoherence
Aripiprazole vs. Iloperidone	indirect	very low	Study limitations, Imprecision, Heterogeneity

Comparison	Nature of evidence	Confidence level	Downgrading
Aripiprazole vs. Levomepromazine	indirect	low	Serious Imprecision
Aripiprazole vs. Loxapine	indirect	very low	Study limitations, Serious Imprecision
Aripiprazole vs. Lurasidone	indirect	low	Serious Imprecision
Aripiprazole vs. Molindone	indirect	very low	Study limitations, Serious Imprecision
Aripiprazole vs. Olanzapine	mixed	very low	Study limitations, Imprecision, Heterogeneity
Aripiprazole vs. Paliperidone	indirect	low	Imprecision, Heterogeneity
Aripiprazole vs. Penfluridol	indirect	very low	Study limitations, Serious Imprecision
Aripiprazole vs. Perazine	indirect	low	Serious Imprecision
Aripiprazole vs. Perphenazine	indirect	low	Imprecision, Heterogeneity
Aripiprazole vs. Pimozide	indirect	very low	Study limitations, Serious Imprecision
Aripiprazole vs. Placebo	mixed	low	Study limitations, Publication Bias
Aripiprazole vs. Quetiapine	indirect	low	Serious Imprecision
Aripiprazole vs. Risperidone	mixed	very low	Imprecision, Heterogeneity, Incoherence
Aripiprazole vs. Sertindole	indirect	very low	Study limitations, Serious Imprecision
Aripiprazole vs. Sulpiride	indirect	very low	Study limitations, Serious Imprecision
Aripiprazole vs. Thioridazine	indirect	very low	Study limitations, Serious Imprecision
Aripiprazole vs. Thiothixene	indirect	very low	Study limitations, Serious Imprecision
Aripiprazole vs. Trifluoperazine	indirect	very low	Study limitations, Serious Imprecision
Aripiprazole vs. Ziprasidone	mixed	very low	Study limitations, Serious Imprecision
Aripiprazole vs. Zotepine	indirect	low	Imprecision, Heterogeneity
Aripiprazole vs. Zuclopenthixol	indirect	very low	Study limitations, Serious Imprecision
Asenapine vs. Brexpiprazole	indirect	low	Imprecision, Heterogeneity

Comparison	Nature of evidence	Confidence level	Downgrading
Asenapine vs. Cariprazine	indirect	very low	Study limitations, Serious Imprecision
Asenapine vs. Chlorpromazine	indirect	very low	Study limitations, Serious Imprecision
Asenapine vs. Clopenthixol	indirect	very low	Study limitations, Serious Imprecision
Asenapine vs. Clozapine	indirect	moderate	Study limitations
Asenapine vs. Flupentixol	indirect	very low	Study limitations, Serious Imprecision
Asenapine vs. Fluphenazine	indirect	very low	Study limitations, Serious Imprecision
Asenapine vs. Haloperidol	mixed	very low	Study limitations, Imprecision, Heterogeneity, Incoherence
Asenapine vs. Iloperidone	indirect	very low	Study limitations, Serious Imprecision
Asenapine vs. Levomepromazine	indirect	low	Serious Imprecision
Asenapine vs. Loxapine	indirect	very low	Study limitations, Serious Imprecision
Asenapine vs. Lurasidone	indirect	low	Serious Imprecision
Asenapine vs. Molindone	indirect	very low	Study limitations, Serious Imprecision
Asenapine vs. Olanzapine	mixed	low	Study limitations, Imprecision
Asenapine vs. Paliperidone	indirect	low	Imprecision, Heterogeneity
Asenapine vs. Penfluridol	indirect	very low	Study limitations, Serious Imprecision
Asenapine vs. Perazine	indirect	low	Serious Imprecision
Asenapine vs. Perphenazine	indirect	low	Imprecision, Heterogeneity
Asenapine vs. Pimozide	indirect	very low	Study limitations, Serious Imprecision
Asenapine vs. Placebo	mixed	low	Study limitations, Publication Bias
Asenapine vs. Quetiapine	indirect	low	Serious Imprecision
Asenapine vs. Risperidone	mixed	very low	Imprecision, Heterogeneity, Incoherence
Asenapine vs. Sertindole	indirect	very low	Study limitations, Serious Imprecision

Comparison	Nature of evidence	Confidence level	Downgrading
Asenapine vs. Sulpiride	indirect	very low	Study limitations, Serious Imprecision
Asenapine vs. Thioridazine	indirect	very low	Study limitations, Serious Imprecision
Asenapine vs. Thiothixene	indirect	very low	Study limitations, Serious Imprecision
Asenapine vs. Trifluoperazine	indirect	very low	Study limitations, Serious Imprecision
Asenapine vs. Ziprasidone	indirect	very low	Study limitations, Serious Imprecision
Asenapine vs. Zotepine	indirect	low	Imprecision, Heterogeneity
Asenapine vs. Zuclopenthixol	indirect	very low	Study limitations, Serious Imprecision
Brexpiprazole vs. Cariprazine	indirect	very low	Study limitations, Serious Imprecision
Brexpiprazole vs. Chlorpromazine	indirect	very low	Study limitations, Imprecision, Heterogeneity
Brexpiprazole vs. Clopenthixol	indirect	very low	Study limitations, Serious Imprecision
Brexpiprazole vs. Clozapine	indirect	moderate	Study limitations
Brexpiprazole vs. Flupentixol	indirect	low	Serious Imprecision
Brexpiprazole vs. Fluphenazine	indirect	very low	Study limitations, Serious Imprecision
Brexpiprazole vs. Haloperidol	indirect	low	Study limitations, Imprecision
Brexpiprazole vs. Iloperidone	indirect	low	Serious Imprecision
Brexpiprazole vs. Levomepromazine	indirect	low	Serious Imprecision
Brexpiprazole vs. Loxapine	indirect	very low	Study limitations, Imprecision, Heterogeneity
Brexpiprazole vs. Lurasidone	indirect	low	Imprecision, Heterogeneity
Brexpiprazole vs. Molindone	indirect	very low	Study limitations, Serious Imprecision
Brexpiprazole vs. Olanzapine	indirect	moderate	Heterogeneity
Brexpiprazole vs. Paliperidone	indirect	moderate	Imprecision
Brexpiprazole vs. Penfluridol	indirect	very low	Study limitations, Serious Imprecision

Comparison	Nature of evidence	Confidence level	Downgrading
Brexpiprazole vs. Perazine	indirect	low	Serious Imprecision
Brexpiprazole vs. Perphenazine	indirect	moderate	Imprecision
Brexpiprazole vs. Pimozide	indirect	very low	Study limitations, Serious Imprecision
Brexpiprazole vs. Placebo	mixed	very low	Publication Bias, Heterogeneity, Serious Incoherence
Brexpiprazole vs. Quetiapine	mixed	very low	Study limitations, Imprecision, Heterogeneity, Incoherence
Brexpiprazole vs. Risperidone	indirect	moderate	Heterogeneity
Brexpiprazole vs. Sertindole	indirect	low	Imprecision, Heterogeneity
Brexpiprazole vs. Sulpiride	indirect	very low	Study limitations, Serious Imprecision
Brexpiprazole vs. Thioridazine	indirect	very low	Study limitations, Imprecision, Heterogeneity
Brexpiprazole vs. Thiothixene	indirect	low	Study limitations, Imprecision
Brexpiprazole vs. Trifluoperazine	indirect	very low	Study limitations, Serious Imprecision
Brexpiprazole vs. Ziprasidone	indirect	low	Imprecision, Heterogeneity
Brexpiprazole vs. Zotepine	indirect	moderate	Imprecision
Brexpiprazole vs. Zuclopenthixol	indirect	very low	Study limitations, Imprecision, Heterogeneity
Cariprazine vs. Chlorpromazine	indirect	very low	Study limitations, Serious Imprecision
Cariprazine vs. Clopenthixol	indirect	very low	Study limitations, Serious Imprecision
Cariprazine vs. Clozapine	indirect	moderate	Study limitations
Cariprazine vs. Flupentixol	indirect	very low	Study limitations, Serious Imprecision
Cariprazine vs. Fluphenazine	indirect	very low	Study limitations, Serious Imprecision
Cariprazine vs. Haloperidol	indirect	very low	Study limitations, Imprecision, Heterogeneity
Cariprazine vs. Iloperidone	indirect	very low	Study limitations, Serious Imprecision
Cariprazine vs. Levomepromazine	indirect	very low	Study limitations, Serious Imprecision

Comparison	Nature of evidence	Confidence level	Downgrading
Cariprazine vs. Loxapine	indirect	very low	Study limitations, Serious Imprecision
Cariprazine vs. Lurasidone	indirect	low	Serious Imprecision
Cariprazine vs. Molindone	indirect	very low	Study limitations, Serious Imprecision
Cariprazine vs. Olanzapine	indirect	low	Study limitations, Imprecision
Cariprazine vs. Paliperidone	indirect	very low	Study limitations, Imprecision, Heterogeneity
Cariprazine vs. Penfluridol	indirect	very low	Study limitations, Serious Imprecision
Cariprazine vs. Perazine	indirect	very low	Study limitations, Serious Imprecision
Cariprazine vs. Perphenazine	indirect	very low	Study limitations, Imprecision, Heterogeneity
Cariprazine vs. Pimozide	indirect	very low	Study limitations, Serious Imprecision
Cariprazine vs. Placebo	mixed	very low	Study limitations, Publication Bias, Heterogeneity, Serious Incoherence
Cariprazine vs. Quetiapine	indirect	very low	Study limitations, Imprecision, Heterogeneity
Cariprazine vs. Risperidone	mixed	low	Study limitations, Imprecision
Cariprazine vs. Sertindole	indirect	very low	Study limitations, Serious Imprecision
Cariprazine vs. Sulpiride	indirect	very low	Study limitations, Serious Imprecision
Cariprazine vs. Thioridazine	indirect	very low	Study limitations, Serious Imprecision
Cariprazine vs. Thiothixene	indirect	very low	Study limitations, Serious Imprecision
Cariprazine vs. Trifluoperazine	indirect	very low	Study limitations, Serious Imprecision
Cariprazine vs. Ziprasidone	indirect	very low	Study limitations, Serious Imprecision
Cariprazine vs. Zotepine	indirect	low	Study limitations, Imprecision
Cariprazine vs. Zuclopenthixol	indirect	very low	Study limitations, Serious Imprecision
Chlorpromazine vs. Clopenthixol	mixed	very low	Study limitations, Serious Imprecision
Chlorpromazine vs. Clozapine	mixed	low	Study limitations, Incoherence

Comparison	Nature of evidence	Confidence level	Downgrading
Chlorpromazine vs. Flupentixol	indirect	very low	Study limitations, Serious Imprecision
Chlorpromazine vs. Fluphenazine	mixed	very low	Study limitations, Serious Imprecision
Chlorpromazine vs. Haloperidol	mixed	very low	Study limitations, Serious Imprecision
Chlorpromazine vs. Iloperidone	indirect	very low	Study limitations, Imprecision, Heterogeneity
Chlorpromazine vs. Levomepromazine	indirect	low	Serious Imprecision
Chlorpromazine vs. Loxapine	mixed	very low	Study limitations, Serious Imprecision
Chlorpromazine vs. Lurasidone	indirect	low	Serious Imprecision
Chlorpromazine vs. Molindone	mixed	very low	Study limitations, Serious Imprecision
Chlorpromazine vs. Olanzapine	indirect	very low	Study limitations, Imprecision, Heterogeneity
Chlorpromazine vs. Paliperidone	indirect	low	Serious Imprecision
Chlorpromazine vs. Penfluridol	mixed	very low	Study limitations, Serious Imprecision
Chlorpromazine vs. Perazine	indirect	very low	Study limitations, Serious Imprecision
Chlorpromazine vs. Perphenazine	indirect	low	Serious Imprecision
Chlorpromazine vs. Pimozide	mixed	very low	Study limitations, Serious Imprecision
Chlorpromazine vs. Placebo	mixed	low	Study limitations, Publication Bias
Chlorpromazine vs. Quetiapine	mixed	very low	Study limitations, Serious Imprecision
Chlorpromazine vs. Risperidone	indirect	very low	Study limitations, Imprecision, Heterogeneity
Chlorpromazine vs. Sertindole	indirect	very low	Study limitations, Serious Imprecision
Chlorpromazine vs. Sulpiride	mixed	low	Serious Imprecision
Chlorpromazine vs. Thioridazine	mixed	very low	Study limitations, Serious Imprecision
Chlorpromazine vs. Thiothixene	indirect	very low	Study limitations, Serious Imprecision
Chlorpromazine vs. Trifluoperazine	indirect	very low	Study limitations, Serious Imprecision

Comparison	Nature of evidence	Confidence level	Downgrading
Chlorpromazine vs. Ziprasidone	indirect	very low	Study limitations, Serious Imprecision
Chlorpromazine vs. Zotepine	mixed	very low	Imprecision, Heterogeneity, Serious Incoherence
Chlorpromazine vs. Zuclopenthixol	mixed	low	Serious Imprecision
Clopenthixol vs. Clozapine	indirect	low	Study limitations, Imprecision
Clopenthixol vs. Flupentixol	indirect	very low	Study limitations, Serious Imprecision
Clopenthixol vs. Fluphenazine	indirect	very low	Study limitations, Serious Imprecision
Clopenthixol vs. Haloperidol	mixed	very low	Study limitations, Serious Imprecision
Clopenthixol vs. Iloperidone	indirect	very low	Study limitations, Serious Imprecision
Clopenthixol vs. Levomepromazine	indirect	low	Serious Imprecision
Clopenthixol vs. Loxapine	indirect	very low	Study limitations, Serious Imprecision
Clopenthixol vs. Lurasidone	indirect	low	Serious Imprecision
Clopenthixol vs. Molindone	indirect	very low	Study limitations, Serious Imprecision
Clopenthixol vs. Olanzapine	indirect	very low	Study limitations, Serious Imprecision
Clopenthixol vs. Paliperidone	indirect	low	Serious Imprecision
Clopenthixol vs. Penfluridol	indirect	very low	Study limitations, Serious Imprecision
Clopenthixol vs. Perazine	indirect	very low	Study limitations, Serious Imprecision
Clopenthixol vs. Perphenazine	mixed	low	Serious Imprecision
Clopenthixol vs. Pimozide	indirect	very low	Study limitations, Serious Imprecision
Clopenthixol vs. Placebo	mixed	very low	Study limitations, Publication Bias, Imprecision, Serious Incoherence
Clopenthixol vs. Quetiapine	indirect	very low	Study limitations, Serious Imprecision
Clopenthixol vs. Risperidone	indirect	very low	Study limitations, Serious Imprecision
Clopenthixol vs. Sertindole	indirect	very low	Study limitations, Serious Imprecision

Comparison	Nature of evidence	Confidence level	Downgrading
Clopenthixol vs. Sulpiride	indirect	very low	Study limitations, Serious Imprecision
Clopenthixol vs. Thioridazine	indirect	very low	Study limitations, Serious Imprecision
Clopenthixol vs. Thiothixene	indirect	very low	Study limitations, Serious Imprecision
Clopenthixol vs. Trifluoperazine	indirect	very low	Study limitations, Serious Imprecision
Clopenthixol vs. Ziprasidone	indirect	very low	Study limitations, Serious Imprecision
Clopenthixol vs. Zotepine	indirect	low	Serious Imprecision
Clopenthixol vs. Zuclopenthixol	indirect	very low	Study limitations, Serious Imprecision
Clozapine vs. Flupentixol	indirect	low	Study limitations, Imprecision
Clozapine vs. Fluphenazine	indirect	moderate	Study limitations
Clozapine vs. Haloperidol	mixed	low	Study limitations, Incoherence
Clozapine vs. Iloperidone	indirect	moderate	Study limitations
Clozapine vs. Levomepromazine	indirect	high	
Clozapine vs. Loxapine	indirect	low	Study limitations, Heterogeneity
Clozapine vs. Lurasidone	indirect	high	
Clozapine vs. Molindone	indirect	low	Study limitations, Imprecision
Clozapine vs. Olanzapine	mixed	very low	Study limitations, Heterogeneity, Serious Incoherence
Clozapine vs. Paliperidone	indirect	low	Study limitations, Heterogeneity
Clozapine vs. Penfluridol	indirect	very low	Study limitations, Serious Imprecision
Clozapine vs. Perazine	indirect	low	Study limitations, Imprecision
Clozapine vs. Perphenazine	indirect	moderate	Imprecision
Clozapine vs. Pimozide	indirect	low	Study limitations, Imprecision
Clozapine vs. Placebo	mixed	low	Study limitations, Publication Bias

Comparison	Nature of evidence	Confidence level	Downgrading
Clozapine vs. Quetiapine	indirect	moderate	Study limitations
Clozapine vs. Risperidone	mixed	very low	Study limitations, Heterogeneity, Serious Incoherence
Clozapine vs. Sertindole	indirect	moderate	Study limitations
Clozapine vs. Sulpiride	indirect	very low	Study limitations, Imprecision, Heterogeneity
Clozapine vs. Thioridazine	indirect	low	Study limitations, Imprecision
Clozapine vs. Thiothixene	indirect	very low	Study limitations, Serious Imprecision
Clozapine vs. Trifluoperazine	indirect	moderate	Study limitations
Clozapine vs. Ziprasidone	indirect	moderate	Study limitations
Clozapine vs. Zotepine	mixed	low	Imprecision, Incoherence
Clozapine vs. Zuclopenthixol	indirect	low	Study limitations, Imprecision
Flupentixol vs. Fluphenazine	indirect	very low	Study limitations, Serious Imprecision
Flupentixol vs. Haloperidol	indirect	very low	Study limitations, Serious Imprecision
Flupentixol vs. Iloperidone	indirect	low	Serious Imprecision
Flupentixol vs. Levomepromazine	indirect	low	Serious Imprecision
Flupentixol vs. Loxapine	indirect	very low	Study limitations, Serious Imprecision
Flupentixol vs. Lurasidone	indirect	low	Serious Imprecision
Flupentixol vs. Molindone	indirect	very low	Study limitations, Serious Imprecision
Flupentixol vs. Olanzapine	mixed	very low	Study limitations, Serious Imprecision
Flupentixol vs. Paliperidone	indirect	low	Serious Imprecision
Flupentixol vs. Penfluridol	indirect	very low	Study limitations, Serious Imprecision
Flupentixol vs. Perazine	indirect	very low	Study limitations, Serious Imprecision
Flupentixol vs. Perphenazine	indirect	low	Serious Imprecision

Comparison	Nature of evidence	Confidence level	Downgrading
Flupentixol vs. Pimozide	indirect	very low	Study limitations, Serious Imprecision
Flupentixol vs. Placebo	mixed	low	Publication Bias, Imprecision
Flupentixol vs. Quetiapine	indirect	low	Serious Imprecision
Flupentixol vs. Risperidone	indirect	low	Serious Imprecision
Flupentixol vs. Sertindole	indirect	low	Serious Imprecision
Flupentixol vs. Sulpiride	indirect	very low	Study limitations, Serious Imprecision
Flupentixol vs. Thioridazine	indirect	very low	Study limitations, Serious Imprecision
Flupentixol vs. Thiothixene	indirect	very low	Study limitations, Serious Imprecision
Flupentixol vs. Trifluoperazine	indirect	very low	Study limitations, Serious Imprecision
Flupentixol vs. Ziprasidone	indirect	very low	Study limitations, Serious Imprecision
Flupentixol vs. Zotepine	indirect	low	Serious Imprecision
Flupentixol vs. Zuclopenthixol	indirect	very low	Study limitations, Serious Imprecision
Fluphenazine vs. Haloperidol	mixed	very low	Study limitations, Serious Imprecision
Fluphenazine vs. Iloperidone	indirect	very low	Study limitations, Serious Imprecision
Fluphenazine vs. Levomepromazine	indirect	low	Serious Imprecision
Fluphenazine vs. Loxapine	indirect	very low	Study limitations, Serious Imprecision
Fluphenazine vs. Lurasidone	indirect	low	Serious Imprecision
Fluphenazine vs. Molindone	indirect	very low	Study limitations, Serious Imprecision
Fluphenazine vs. Olanzapine	indirect	very low	Study limitations, Imprecision, Heterogeneity
Fluphenazine vs. Paliperidone	indirect	very low	Study limitations, Serious Imprecision
Fluphenazine vs. Penfluridol	indirect	very low	Study limitations, Serious Imprecision
Fluphenazine vs. Perazine	indirect	very low	Study limitations, Serious Imprecision

Comparison	Nature of evidence	Confidence level	Downgrading
Fluphenazine vs. Perphenazine	indirect	low	Serious Imprecision
Fluphenazine vs. Pimozide	mixed	very low	Study limitations, Serious Imprecision
Fluphenazine vs. Placebo	mixed	very low	Study limitations, Publication Bias, Serious Imprecision
Fluphenazine vs. Quetiapine	indirect	very low	Study limitations, Serious Imprecision
Fluphenazine vs. Risperidone	indirect	very low	Study limitations, Imprecision, Heterogeneity
Fluphenazine vs. Sertindole	indirect	very low	Study limitations, Serious Imprecision
Fluphenazine vs. Sulpiride	indirect	very low	Study limitations, Serious Imprecision
Fluphenazine vs. Thioridazine	mixed	very low	Study limitations, Serious Imprecision
Fluphenazine vs. Thiothixene	indirect	very low	Study limitations, Serious Imprecision
Fluphenazine vs. Trifluoperazine	indirect	very low	Study limitations, Serious Imprecision
Fluphenazine vs. Ziprasidone	indirect	very low	Study limitations, Serious Imprecision
Fluphenazine vs. Zotepine	indirect	low	Imprecision, Heterogeneity
Fluphenazine vs. Zuclopenthixol	indirect	very low	Study limitations, Serious Imprecision
Haloperidol vs. Iloperidone	mixed	very low	Study limitations, Imprecision, Heterogeneity
Haloperidol vs. Levomepromazine	mixed	very low	Serious Imprecision, Serious Incoherence
Haloperidol vs. Loxapine	mixed	very low	Study limitations, Serious Imprecision, Incoherence
Haloperidol vs. Lurasidone	mixed	low	Imprecision, Heterogeneity
Haloperidol vs. Molindone	indirect	very low	Study limitations, Serious Imprecision
Haloperidol vs. Olanzapine	mixed	very low	Study limitations, Imprecision, Heterogeneity
Haloperidol vs. Paliperidone	indirect	low	Serious Imprecision
Haloperidol vs. Penfluridol	indirect	very low	Study limitations, Serious Imprecision
Haloperidol vs. Perazine	indirect	low	Serious Imprecision

Comparison	Nature of evidence	Confidence level	Downgrading
Haloperidol vs. Perphenazine	indirect	low	Serious Imprecision
Haloperidol vs. Pimozide	mixed	very low	Study limitations, Serious Imprecision
Haloperidol vs. Placebo	mixed	moderate	Study limitations
Haloperidol vs. Quetiapine	mixed	very low	Study limitations, Imprecision, Heterogeneity, Incoherence
Haloperidol vs. Risperidone	mixed	low	Imprecision, Heterogeneity
Haloperidol vs. Sertindole	mixed	very low	Imprecision, Heterogeneity, Incoherence
Haloperidol vs. Sulpiride	indirect	very low	Study limitations, Serious Imprecision
Haloperidol vs. Thioridazine	mixed	very low	Study limitations, Serious Imprecision
Haloperidol vs. Thiothixene	indirect	very low	Study limitations, Serious Imprecision
Haloperidol vs. Trifluoperazine	mixed	very low	Study limitations, Imprecision, Heterogeneity, Incoherence
Haloperidol vs. Ziprasidone	mixed	very low	Study limitations, Imprecision, Heterogeneity, Incoherence
Haloperidol vs. Zotepine	mixed	very low	Imprecision, Heterogeneity, Serious Incoherence
Haloperidol vs. Zuclopenthixol	mixed	very low	Study limitations, Serious Imprecision
Iloperidone vs. Levomepromazine	indirect	low	Serious Imprecision
Iloperidone vs. Loxapine	indirect	very low	Study limitations, Serious Imprecision
Iloperidone vs. Lurasidone	indirect	low	Serious Imprecision
Iloperidone vs. Molindone	indirect	very low	Study limitations, Serious Imprecision
Iloperidone vs. Olanzapine	indirect	low	Study limitations, Heterogeneity
Iloperidone vs. Paliperidone	indirect	low	Imprecision, Heterogeneity
Iloperidone vs. Penfluridol	indirect	very low	Study limitations, Serious Imprecision
Iloperidone vs. Perazine	indirect	low	Serious Imprecision
Iloperidone vs. Perphenazine	indirect	moderate	Imprecision

Comparison	Nature of evidence	Confidence level	Downgrading
Iloperidone vs. Pimozide	indirect	very low	Study limitations, Serious Imprecision
Iloperidone vs. Placebo	mixed	moderate	Publication Bias
Iloperidone vs. Quetiapine	indirect	low	Imprecision, Heterogeneity
Iloperidone vs. Risperidone	mixed	moderate	Imprecision
Iloperidone vs. Sertindole	indirect	low	Serious Imprecision
Iloperidone vs. Sulpiride	indirect	very low	Study limitations, Serious Imprecision
Iloperidone vs. Thioridazine	indirect	very low	Study limitations, Imprecision, Heterogeneity
Iloperidone vs. Thiothixene	indirect	very low	Study limitations, Imprecision, Heterogeneity
Iloperidone vs. Trifluoperazine	indirect	very low	Study limitations, Serious Imprecision
Iloperidone vs. Ziprasidone	mixed	very low	Study limitations, Imprecision, Heterogeneity, Incoherence
Iloperidone vs. Zotepine	indirect	moderate	Imprecision
Iloperidone vs. Zuclopenthixol	indirect	very low	Study limitations, Imprecision, Heterogeneity
Levomepromazine vs. Loxapine	indirect	low	Serious Imprecision
Levomepromazine vs. Lurasidone	indirect	low	Serious Imprecision
Levomepromazine vs. Molindone	indirect	low	Serious Imprecision
Levomepromazine vs. Olanzapine	indirect	low	Imprecision, Heterogeneity
Levomepromazine vs. Paliperidone	indirect	low	Serious Imprecision
Levomepromazine vs. Penfluridol	indirect	very low	Study limitations, Serious Imprecision
Levomepromazine vs. Perazine	indirect	low	Serious Imprecision

Comparison	Nature of evidence	Confidence level	Downgrading
Levomepromazine vs. Perphenazine	indirect	low	Imprecision, Heterogeneity
Levomepromazine vs. Pimozide	indirect	very low	Study limitations, Serious Imprecision
Levomepromazine vs. Placebo	indirect	low	Publication Bias, Imprecision
Levomepromazine vs. Quetiapine	indirect	low	Serious Imprecision
Levomepromazine vs. Risperidone	mixed	very low	Imprecision, Heterogeneity, Serious Incoherence
Levomepromazine vs. Sertindole	indirect	low	Serious Imprecision
Levomepromazine vs. Sulpiride	indirect	low	Serious Imprecision
Levomepromazine vs. Thioridazine	indirect	low	Serious Imprecision
Levomepromazine vs. Thiothixene	indirect	very low	Study limitations, Serious Imprecision
Levomepromazine vs. Trifluoperazine	indirect	low	Serious Imprecision
Levomepromazine vs. Ziprasidone	indirect	low	Serious Imprecision
Levomepromazine vs. Zotepine	indirect	low	Imprecision, Heterogeneity
Levomepromazine vs. Zuclopenthixol	indirect	low	Serious Imprecision
Loxapine vs. Lurasidone	indirect	low	Serious Imprecision
Loxapine vs. Molindone	indirect	very low	Study limitations, Serious Imprecision
Loxapine vs. Olanzapine	indirect	very low	Study limitations, Imprecision, Heterogeneity

Comparison	Nature of evidence	Confidence level	Downgrading
Loxapine vs. Paliperidone	indirect	very low	Study limitations, Serious Imprecision
Loxapine vs. Penfluridol	indirect	very low	Study limitations, Serious Imprecision
Loxapine vs. Perazine	indirect	very low	Study limitations, Serious Imprecision
Loxapine vs. Perphenazine	indirect	low	Serious Imprecision
Loxapine vs. Pimozide	indirect	very low	Study limitations, Serious Imprecision
Loxapine vs. Placebo	mixed	low	Study limitations, Publication Bias
Loxapine vs. Quetiapine	indirect	very low	Study limitations, Serious Imprecision
Loxapine vs. Risperidone	indirect	very low	Study limitations, Imprecision, Heterogeneity
Loxapine vs. Sertindole	indirect	very low	Study limitations, Serious Imprecision
Loxapine vs. Sulpiride	indirect	very low	Study limitations, Serious Imprecision
Loxapine vs. Thioridazine	mixed	very low	Study limitations, Serious Imprecision
Loxapine vs. Thiothixene	mixed	very low	Study limitations, Serious Imprecision, Incoherence
Loxapine vs. Trifluoperazine	mixed	very low	Study limitations, Imprecision, Heterogeneity, Incoherence
Loxapine vs. Ziprasidone	indirect	very low	Study limitations, Serious Imprecision
Loxapine vs. Zotepine	indirect	low	Serious Imprecision
Loxapine vs. Zuclopenthixol	indirect	very low	Study limitations, Serious Imprecision
Lurasidone vs. Molindone	indirect	low	Serious Imprecision
Lurasidone vs. Olanzapine	mixed	low	Imprecision, Incoherence
Lurasidone vs. Paliperidone	indirect	low	Imprecision, Heterogeneity
Lurasidone vs. Penfluridol	indirect	very low	Study limitations, Serious Imprecision
Lurasidone vs. Perazine	indirect	low	Serious Imprecision
Lurasidone vs. Perphenazine	indirect	low	Imprecision, Heterogeneity

Comparison	Nature of evidence	Confidence level	Downgrading
Lurasidone vs. Pimozide	indirect	very low	Study limitations, Serious Imprecision
Lurasidone vs. Placebo	mixed	low	Publication Bias, Incoherence
Lurasidone vs. Quetiapine	mixed	low	Imprecision, Heterogeneity
Lurasidone vs. Risperidone	indirect	moderate	Imprecision
Lurasidone vs. Sertindole	indirect	low	Serious Imprecision
Lurasidone vs. Sulpiride	indirect	low	Serious Imprecision
Lurasidone vs. Thioridazine	indirect	low	Serious Imprecision
Lurasidone vs. Thiothixene	indirect	very low	Study limitations, Serious Imprecision
Lurasidone vs. Trifluoperazine	indirect	low	Serious Imprecision
Lurasidone vs. Ziprasidone	indirect	low	Serious Imprecision
Lurasidone vs. Zotepine	indirect	low	Imprecision, Heterogeneity
Lurasidone vs. Zuclopenthixol	indirect	low	Serious Imprecision
Molindone vs. Olanzapine	indirect	very low	Study limitations, Serious Imprecision
Molindone vs. Paliperidone	indirect	low	Serious Imprecision
Molindone vs. Penfluridol	indirect	very low	Study limitations, Serious Imprecision
Molindone vs. Perazine	indirect	very low	Study limitations, Serious Imprecision
Molindone vs. Perphenazine	indirect	low	Serious Imprecision
Molindone vs. Pimozide	indirect	very low	Study limitations, Serious Imprecision
Molindone vs. Placebo	mixed	very low	Study limitations, Publication Bias, Imprecision
Molindone vs. Quetiapine	indirect	very low	Study limitations, Serious Imprecision
Molindone vs. Risperidone	indirect	very low	Study limitations, Serious Imprecision
Molindone vs. Sertindole	indirect	very low	Study limitations, Serious Imprecision

Comparison	Nature of evidence	Confidence level	Downgrading
Molindone vs. Sulpiride	indirect	very low	Study limitations, Serious Imprecision
Molindone vs. Thioridazine	indirect	very low	Study limitations, Serious Imprecision
Molindone vs. Thiothixene	indirect	very low	Study limitations, Serious Imprecision
Molindone vs. Trifluoperazine	mixed	very low	Study limitations, Serious Imprecision
Molindone vs. Ziprasidone	indirect	very low	Study limitations, Serious Imprecision
Molindone vs. Zotepine	indirect	low	Serious Imprecision
Molindone vs. Zuclopenthixol	indirect	very low	Study limitations, Serious Imprecision
Olanzapine vs. Paliperidone	mixed	low	Imprecision, Heterogeneity
Olanzapine vs. Penfluridol	indirect	very low	Study limitations, Serious Imprecision
Olanzapine vs. Perazine	indirect	low	Serious Imprecision
Olanzapine vs. Perphenazine	mixed	low	Serious Imprecision
Olanzapine vs. Pimozide	indirect	very low	Study limitations, Serious Imprecision
Olanzapine vs. Placebo	mixed	moderate	Study limitations
Olanzapine vs. Quetiapine	mixed	low	Imprecision, Heterogeneity
Olanzapine vs. Risperidone	mixed	very low	Serious Heterogeneity, Serious Incoherence
Olanzapine vs. Sertindole	mixed	low	Imprecision, Heterogeneity
Olanzapine vs. Sulpiride	indirect	very low	Study limitations, Serious Imprecision
Olanzapine vs. Thioridazine	indirect	very low	Study limitations, Serious Imprecision
Olanzapine vs. Thiothixene	indirect	very low	Study limitations, Serious Imprecision
Olanzapine vs. Trifluoperazine	indirect	low	Study limitations, Imprecision
Olanzapine vs. Ziprasidone	mixed	very low	Study limitations, Imprecision, Heterogeneity
Olanzapine vs. Zotepine	indirect	low	Serious Imprecision

Comparison	Nature of evidence	Confidence level	Downgrading
Olanzapine vs. Zuclopenthixol	indirect	very low	Study limitations, Serious Imprecision
Paliperidone vs. Penfluridol	indirect	very low	Study limitations, Serious Imprecision
Paliperidone vs. Perazine	indirect	low	Serious Imprecision
Paliperidone vs. Perphenazine	indirect	low	Serious Imprecision
Paliperidone vs. Pimozide	indirect	very low	Study limitations, Serious Imprecision
Paliperidone vs. Placebo	mixed	high	
Paliperidone vs. Quetiapine	indirect	low	Imprecision, Heterogeneity
Paliperidone vs. Risperidone	indirect	low	Imprecision, Heterogeneity
Paliperidone vs. Sertindole	indirect	low	Imprecision, Heterogeneity
Paliperidone vs. Sulpiride	indirect	low	Serious Imprecision
Paliperidone vs. Thioridazine	indirect	very low	Study limitations, Serious Imprecision
Paliperidone vs. Thiothixene	indirect	very low	Study limitations, Serious Imprecision
Paliperidone vs. Trifluoperazine	indirect	very low	Study limitations, Imprecision, Heterogeneity
Paliperidone vs. Ziprasidone	indirect	low	Imprecision, Heterogeneity
Paliperidone vs. Zotepine	indirect	low	Serious Imprecision
Paliperidone vs. Zuclopenthixol	indirect	low	Serious Imprecision
Penfluridol vs. Perazine	indirect	very low	Study limitations, Serious Imprecision
Penfluridol vs. Perphenazine	indirect	very low	Study limitations, Serious Imprecision
Penfluridol vs. Pimozide	indirect	very low	Study limitations, Serious Imprecision
Penfluridol vs. Placebo	indirect	very low	Study limitations, Publication Bias, Serious Imprecision
Penfluridol vs. Quetiapine	indirect	very low	Study limitations, Serious Imprecision
Penfluridol vs. Risperidone	indirect	very low	Study limitations, Serious Imprecision

Comparison	Nature of evidence	Confidence level	Downgrading
Penfluridol vs. Sertindole	indirect	very low	Study limitations, Serious Imprecision
Penfluridol vs. Sulpiride	indirect	very low	Study limitations, Serious Imprecision
Penfluridol vs. Thioridazine	indirect	very low	Study limitations, Serious Imprecision
Penfluridol vs. Thiothixene	indirect	very low	Study limitations, Serious Imprecision
Penfluridol vs. Trifluoperazine	indirect	very low	Study limitations, Serious Imprecision
Penfluridol vs. Ziprasidone	indirect	very low	Study limitations, Serious Imprecision
Penfluridol vs. Zotepine	indirect	very low	Study limitations, Serious Imprecision
Penfluridol vs. Zuclopenthixol	indirect	very low	Study limitations, Serious Imprecision
Perazine vs. Perphenazine	indirect	low	Serious Imprecision
Perazine vs. Pimozide	indirect	very low	Study limitations, Serious Imprecision
Perazine vs. Placebo	indirect	low	Publication Bias, Imprecision
Perazine vs. Quetiapine	indirect	low	Serious Imprecision
Perazine vs. Risperidone	indirect	low	Serious Imprecision
Perazine vs. Sertindole	indirect	low	Serious Imprecision
Perazine vs. Sulpiride	indirect	low	Serious Imprecision
Perazine vs. Thioridazine	indirect	very low	Study limitations, Serious Imprecision
Perazine vs. Thiothixene	indirect	very low	Study limitations, Serious Imprecision
Perazine vs. Trifluoperazine	indirect	very low	Study limitations, Serious Imprecision
Perazine vs. Ziprasidone	indirect	low	Serious Imprecision
Perazine vs. Zotepine	mixed	very low	Study limitations, Serious Imprecision
Perazine vs. Zuclopenthixol	indirect	low	Serious Imprecision
Perphenazine vs. Pimozide	indirect	very low	Study limitations, Serious Imprecision

Comparison	Nature of evidence	Confidence level	Downgrading
Perphenazine vs. Placebo	mixed	moderate	Publication Bias
Perphenazine vs. Quetiapine	mixed	very low	Imprecision, Heterogeneity, Incoherence
Perphenazine vs. Risperidone	mixed	low	Serious Imprecision
Perphenazine vs. Sertindole	indirect	low	Imprecision, Heterogeneity
Perphenazine vs. Sulpiride	indirect	low	Serious Imprecision
Perphenazine vs. Thioridazine	indirect	very low	Study limitations, Serious Imprecision
Perphenazine vs. Thiothixene	indirect	very low	Study limitations, Serious Imprecision
Perphenazine vs. Trifluoperazine	indirect	very low	Study limitations, Imprecision, Heterogeneity
Perphenazine vs. Ziprasidone	mixed	low	Imprecision, Heterogeneity
Perphenazine vs. Zotepine	indirect	low	Serious Imprecision
Perphenazine vs. Zuclopenthixol	mixed	very low	Study limitations, Serious Imprecision
Pimozide vs. Placebo	indirect	very low	Study limitations, Publication Bias, Serious Imprecision
Pimozide vs. Quetiapine	indirect	very low	Study limitations, Serious Imprecision
Pimozide vs. Risperidone	indirect	very low	Study limitations, Serious Imprecision
Pimozide vs. Sertindole	indirect	very low	Study limitations, Serious Imprecision
Pimozide vs. Sulpiride	indirect	very low	Study limitations, Serious Imprecision
Pimozide vs. Thioridazine	indirect	very low	Study limitations, Serious Imprecision
Pimozide vs. Thiothixene	indirect	very low	Study limitations, Serious Imprecision
Pimozide vs. Trifluoperazine	indirect	very low	Study limitations, Serious Imprecision
Pimozide vs. Ziprasidone	indirect	very low	Study limitations, Serious Imprecision
Pimozide vs. Zotepine	indirect	very low	Study limitations, Serious Imprecision
Pimozide vs. Zuclopenthixol	indirect	very low	Study limitations, Serious Imprecision

Comparison	Nature of evidence	Confidence level	Downgrading
Placebo vs. Quetiapine	mixed	moderate	Publication Bias
Placebo vs. Risperidone	mixed	high	
Placebo vs. Sertindole	mixed	low	Study limitations, Publication Bias
Placebo vs. Sulpiride	indirect	low	Study limitations, Publication Bias
Placebo vs. Thioridazine	mixed	very low	Study limitations, Publication Bias, Incoherence
Placebo vs. Thiothixene	mixed	very low	Study limitations, Publication Bias, Serious Incoherence
Placebo vs. Trifluoperazine	mixed	very low	Study limitations, Publication Bias, Imprecision, Heterogeneity
Placebo vs. Ziprasidone	mixed	low	Study limitations, Publication Bias
Placebo vs. Zotepine	mixed	moderate	Publication Bias
Placebo vs. Zuclopenthixol	indirect	low	Study limitations, Publication Bias
Quetiapine vs. Risperidone	mixed	low	Imprecision, Heterogeneity
Quetiapine vs. Sertindole	indirect	low	Serious Imprecision
Quetiapine vs. Sulpiride	indirect	very low	Study limitations, Serious Imprecision
Quetiapine vs. Thioridazine	indirect	very low	Study limitations, Serious Imprecision
Quetiapine vs. Thiothixene	indirect	very low	Study limitations, Serious Imprecision
Quetiapine vs. Trifluoperazine	indirect	very low	Study limitations, Serious Imprecision
Quetiapine vs. Ziprasidone	mixed	low	Serious Imprecision
Quetiapine vs. Zotepine	indirect	low	Imprecision, Heterogeneity
Quetiapine vs. Zuclopenthixol	indirect	very low	Study limitations, Serious Imprecision
Risperidone vs. Sertindole	mixed	very low	Imprecision, Heterogeneity, Incoherence
Risperidone vs. Sulpiride	indirect	very low	Study limitations, Serious Imprecision
Risperidone vs. Thioridazine	indirect	very low	Study limitations, Serious Imprecision

Comparison	Nature of evidence	Confidence level	Downgrading
Risperidone vs. Thiothixene	indirect	very low	Study limitations, Serious Imprecision
Risperidone vs. Trifluoperazine	indirect	low	Study limitations, Imprecision
Risperidone vs. Ziprasidone	mixed	very low	Imprecision, Heterogeneity, Incoherence
Risperidone vs. Zotepine	indirect	low	Serious Imprecision
Risperidone vs. Zuclopenthixol	mixed	very low	Study limitations, Serious Imprecision
Sertindole vs. Sulpiride	indirect	very low	Study limitations, Serious Imprecision
Sertindole vs. Thioridazine	indirect	very low	Study limitations, Serious Imprecision
Sertindole vs. Thiothixene	indirect	very low	Study limitations, Serious Imprecision
Sertindole vs. Trifluoperazine	indirect	very low	Study limitations, Serious Imprecision
Sertindole vs. Ziprasidone	indirect	very low	Study limitations, Serious Imprecision
Sertindole vs. Zotepine	indirect	low	Imprecision, Heterogeneity
Sertindole vs. Zuclopenthixol	indirect	very low	Study limitations, Serious Imprecision
Sulpiride vs. Thioridazine	mixed	very low	Study limitations, Serious Imprecision
Sulpiride vs. Thiothixene	indirect	very low	Study limitations, Serious Imprecision
Sulpiride vs. Trifluoperazine	mixed	very low	Study limitations, Serious Imprecision
Sulpiride vs. Ziprasidone	indirect	very low	Study limitations, Serious Imprecision
Sulpiride vs. Zotepine	indirect	low	Serious Imprecision
Sulpiride vs. Zuclopenthixol	indirect	low	Serious Imprecision
Thioridazine vs. Thiothixene	mixed	very low	Study limitations, Serious Imprecision, Serious Incoherence
Thioridazine vs. Trifluoperazine	indirect	very low	Study limitations, Imprecision, Heterogeneity
Thioridazine vs. Ziprasidone	indirect	very low	Study limitations, Serious Imprecision
Thioridazine vs. Zotepine	indirect	very low	Study limitations, Serious Imprecision

Comparison	Nature of evidence	Confidence level	Downgrading
Thioridazine vs. Zuclopenthixol	indirect	very low	Study limitations, Serious Imprecision
Thiothixene vs. Trifluoperazine	indirect	very low	Study limitations, Imprecision, Heterogeneity
Thiothixene vs. Ziprasidone	indirect	very low	Study limitations, Serious Imprecision
Thiothixene vs. Zotepine	indirect	very low	Study limitations, Serious Imprecision
Thiothixene vs. Zuclopenthixol	indirect	very low	Study limitations, Serious Imprecision
Trifluoperazine vs. Ziprasidone	indirect	very low	Study limitations, Serious Imprecision
Trifluoperazine vs. Zotepine	indirect	moderate	Imprecision
Trifluoperazine vs. Zuclopenthixol	indirect	very low	Study limitations, Serious Imprecision
Ziprasidone vs. Zotepine	indirect	low	Imprecision, Heterogeneity
Ziprasidone vs. Zuclopenthixol	indirect	very low	Study limitations, Serious Imprecision
Zotepine vs. Zuclopenthixol	indirect	low	Serious Imprecision

Tabelle 15.3: CINeMA ratings for all comparisons of the primary outcome

In this table we present the evidence levels for all comparisons of the primary outcome "overall change in symptoms". Comparison: names of the antipsychotics compared. Nature of evidence: mixed=combination of direct and indirect evidence, indirect=only indirect evidence available. Confidence level: high, moderate, low, very low. Downgrading: CINeMA items responsible for downgrading. CINeMA (Confidence in Network Meta-analysis).

Outcome: all-cause discontinuation

For this outcome the CINeMA assessment was performed and reported in the manuscript (see Figure 7 of this application), however reasons for downgrading are not reported in the manuscript nor in the Supplementary material of Huhn et al., 2019

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In their NMA, Schneider-Thoma performed the CINeMA assessment for all primary and secondary outcomes and reported the final judgment in the main manuscript. However, reasons for downgrading are not reported in the manuscript nor in the Supplementary material, where the authors state: “As there were more than 2000 comparisons to rate (406 for the primary outcome), it was not possible to judge each comparison individually and the described generic approach was applied” (Schneider-Thoma et al., 2022, Supplementary material, p. 271). As the CINeMA appraisal requires the original database to be carried out, it was not possible to report here the reasons for downgrading.