South African National Department of Health
Medicine Review
Component: Tertiary

TITLE: Aripiprazole for management of schizophrenia in patients with a poor response to olanzapine and where clozapine is not an option due to metabolic adverse effects.

Date: May 2024

Medicine (ATC): Aripiprazole (N05AX12)
Indication (ICD10): Schizophrenia (F20 – F29)
Patient population: Patients with schizophrenia who have poor response to olanzapine and where clozapine cannot be used due to metabolic effects.
Prevalence: An estimated 1% of South Africans suffer from schizophrenia (all cases)
Level of Care: Tertiary and Quaternary Hospital Level
Prescriber level: Psychiatrist
Current Standard of Care/ Comparator(s): amisulpride

Key findings

- Amisulpride is currently recommended as a third-line schizophrenia treatment in patients where metabolic adverse events are of concern and for patients with persistent negative symptoms.
- Aripiprazole is approved as a third-line agent in children and adolescents with obesity or adverse metabolic effects from other antipsychotics.
- On evaluation of utilisation and cost, it was found that amisulpride costs and expenditure far exceed other agents used in the second and third-line management of schizophrenia, including aripiprazole.
- A search for systematic reviews, meta-analyses and network meta-analyses was undertaken to assess efficacy and tolerability of aripiprazole as a possible step before amisulpride.
- Aripiprazole is generally comparable in terms of global status, mental status, relapse and study discontinuation. [2-5]
  - Global status: No significant differences found between aripiprazole as compared to risperidone (RR 1.08, 95% CI 0.96 to 1.21, i^2=0%, p=0.20, (n = 6381, 80 RCTs, low quality evidence) and olanzapine RR 1.06, 95% CI 0.96 to 1.17, i^2=0%, P=0.28, (n = 1739, 11 RCTs, very low-quality evidence).
  - Mental Status: Approximately 40% reduction in overall symptoms in acute treatment. Although aripiprazole generally ranked lower on the NMA forest plots than olanzapine, amisulpride and risperidone, confidence intervals overlapped for overall change in symptoms, positive, negative, and depressive symptom changes in acute and long-term treatment. (Moderate certainty)
  - Leaving study early: Significantly better than placebo in acute and long-term treatment on NMA, with overlapping confidence intervals between antipsychotics. On meta-analysis, no significant difference compared to risperidone but significantly more people left the study early for any reason as compared to olanzapine. (Moderate certainty)
  - Relapse: Point estimate of 76% reduction in relapse rate versus placebo, with no differences between aripiprazole and amisulpride, olanzapine, or risperidone. (Moderate certainty)
- In terms of metabolic adverse effects, aripiprazole appears to have the better side effect profile as compared to amisulpride, risperidone and olanzapine.[6-4, 6]
  - Aripiprazole associated with more akathisia and sedation than placebo but found to be neutral for metabolic and other adverse events assessed. (Moderate certainty)

TERTIARY AND QUATERNARY EXPERT REVIEW COMMITTEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
					X (aripiprazole)
It is recommended that aripiprazole be added to the Essential Medicines List (EML) as a third-line option for the management of schizophrenia, for patients where weight gain and/or metabolic symptoms are of concern (e.g. BMI >30, Type 2 Diabetes). *Rationale: Aripiprazole demonstrates a similar efficacy when compared with other antipsychotics and is significantly less costly than amisulpride (the currently recommended 3rd-line agent). It was found that amisulpride costs currently far exceed those of other 2nd, 3rd, and 4th line agents thus aripiprazole should be added as a step before amisulpride is considered. Aripiprazole has a favourable safety profile particularly in terms of metabolic adverse effects.* *Level of Evidence: I (meta-analysis and network meta-analyses of RCTs of high to low quality; although risk of bias is unclear for most RCTs, results tended to be consistent between analyses)*					

(Refer to appendix 1 for the evidence to decision framework)

BACKGROUND

The Tertiary Expert Review Committee identified medicines previously excluded from the EML where price was listed as a review indicator. Quetiapine, as a third-line treatment option for the management of schizophrenia, is one such example and has been tabled for review on account of significant price decreases since the original EML decision. In undertaking this review, an assessment of all approved agents in this setting was undertaken. Table 1 below indicates the previous reviews completed and associated recommendations.

Within the broader context of reviewing suitable third-line options for the management of schizophrenia, the specific aim of this review was to determine whether aripiprazole could be used as a third line treatment of schizophrenia spectrum disorders as an alternative to amisulpride if olanzapine was ineffective and/or metabolic adverse effects were a concern.

Table 1: Tertiary recommendations

	NEMLC OUTCOMES	REVIEW INDICATORS
Quetiapine for Third-line Schizophrenia *15 September 2016*	**Not Approved** Amisulpride Approved for this indication.	Price
Amisulpride for Psychosis. *03 December 2009*	**Approved** for use as an appropriate alternative to existing agents in patients with negative symptoms failing first and second generation antipsychotics.	Efficacy or safety new information
Aripiprazole for Schizophrenia in children. *29 November 2013*	**Approved** for use as a third-line agent in children with psychotic disorders who are intolerant to typical and atypical antipsychotic agents with: • Obesity, defined as BMI ≥ 30 or age appropriate measures, **or** • Excessive weight gain, if associated with metabolic syndrome in adherent patients on other atypical antipsychotics, not responsive to other	New evidence of efficacy in children and adolescents

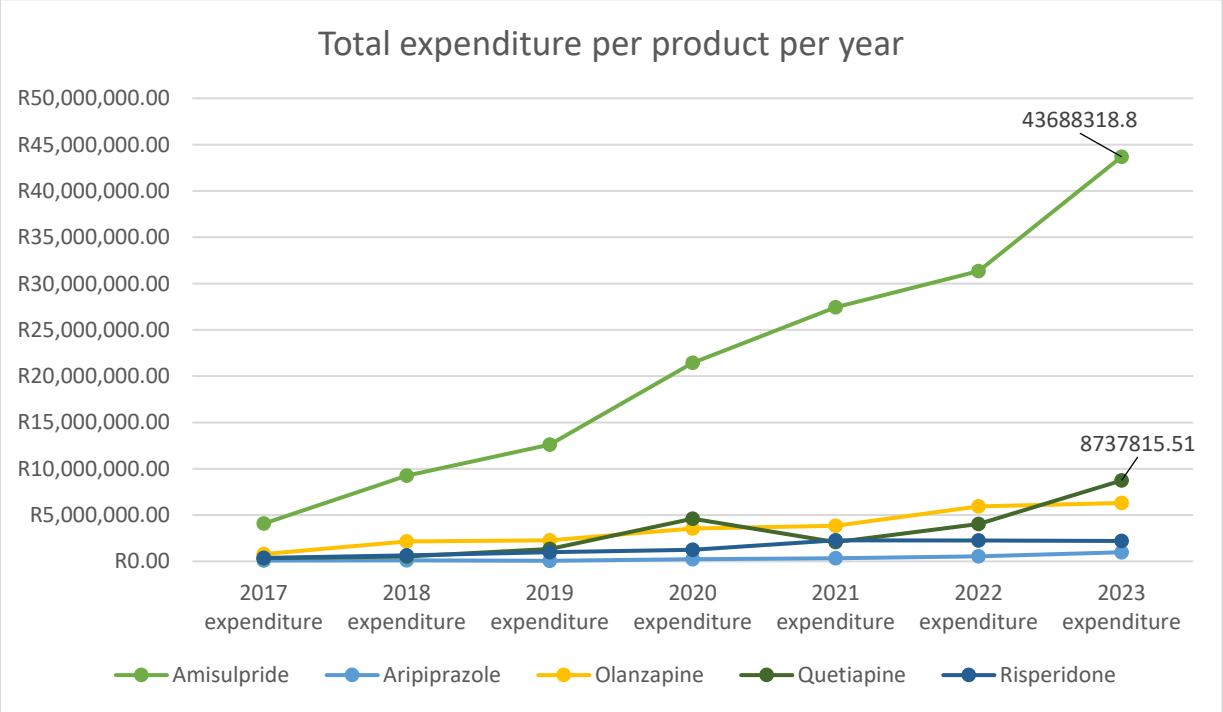
	interventions (e.g. dietary management and/or physical exercise). Aripiprazole be initiated, in these cases, in consultation with or, where available, by a subspecialist (i.e. child and adolescent psychiatrist)	

The utilisation of amisulpride, aripiprazole, quetiapine, risperidone and olanzapine was investigated over the past 5 years. See table 2 and figure 1 below showing the total expenditure per product per year over the last 5 years.

Table 2: Total expenditure per product per year (last 5 years)

	Amisulpride	Aripiprazole	Olanzapine	Quetiapine	Risperidone
2017 expenditure	R4,082,677.50	R90,292.07	R789,712.81	R344,854.60	R376,117.00
2018 expenditure	R9,257,223.20	R119,206.72	R2,147,779.23	R523,295.44	R647,161.00
2019 expenditure	R12,605,714.40	R68,027.70	R2,278,034.45	R1,336,065.25	R1,000,203.00
2020 expenditure	R21,437,517.80	R233,889.99	R3,551,060.09	R4,601,676.03	R1,259,920.00
2021 expenditure	R27,437,437.10	R332,572.99	R3,847,584.06	R2,079,266.56	R2,274,024.00
2022 expenditure	R31,339,456.80	R546,066.49	R5,938,265.98	R4,030,990.55	R2,262,710.00
2023 expenditure	R43,688,318.80	R986,195.33	R6,308,106.28	R8,737,815.51	R2,204,942.00

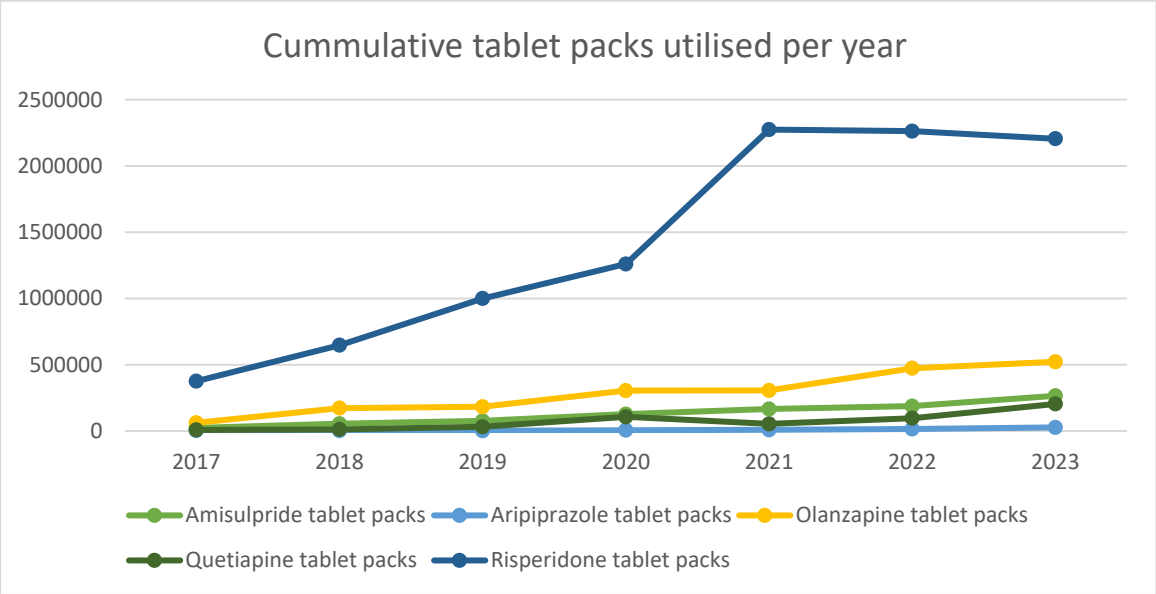
Figure 1: Graphical representation of total expenditure per product per year (last 5 years)



As is represented by the above table and graph, the expenditure of amisulpride far exceeds any of the other lines of care, with the expenditure for 2023 reaching **over R43 million**.

Figure 2 is a graphical representation of cumulative packs used per year over the last 5 years.

Figure 2: Graphical representation of cumulative packs used per year over the last 5 years



COST PER PATIENT PER YEAR (BASED ON COMPARATIVE DOSING)

Table 3 below shows the comparative cost of the various second- and third-line medications, based on a consensus-based target dose range and on the most affordable strength and pack size as of February 2024. Notably, aripiprazole is almost eight times less costly than amisulpride and has a lower pill burden (2 tablets once a day vs 2 tablets twice a day at the higher dose).

Table 3: Comparative cost per patient per year at lower and higher target doses

Medicine Pack short Description	Price*	Dose#	Cost per day	Cost per month	Cost per year
Amisulpride; 200mg; Tablet; 30 Tablets	R186.50	400mg/day	R12.43	R348.13	**R4,538.17**
		800mg/day	R24.87	R696.27	**R9,076.33**
Quetiapine; 200mg; Tablet; 60 Tablets	R48.83	400mg/day	R1.63	R45.57	**R594.10**
Quetiapine; 300mg; Tablet; 60 Tablets (2) Quetiapine; 200mg; Tablet; 60 Tablets (1)	R67.33	800mg/day	R3.06	R85.63	**R1,116.23**
Aripiprazole; 15mg; Tablet; 30 Tablets	R47.43	15mg/day	R1.58	R44.27	**R577.07**
		30mg/day	R3.16	R88.54	**R1,154.13**
Olanzapine; 10mg; Tablet; 28 Tablets	R14.39	10mg/day	R0.51	R14.39	**R187.58**
		20mg/day	R1,03	R28.78	**R375.17**
Risperidone; 2mg; Tablet; 30 Tablets	R5.59	4mg/day	R0.37	R10.43	**R136.02**
Risperidone; 3mg; Tablet; 30 Tablets	R7.38	6mg/day	R0.49	R13.78	**R179.58**

**Master Health Product List: February 2024*

#International Consensus Study of Antipsychotic Dosing[1]

Table 4 represents the change in price over time since the original EML decisions pertaining to amisulpride and quetiapine.

Table 4: Price changes over time.

Medicine Pack short Description	Previous September 2016*	Current February 2024	% change
Quetiapine; 100mg; Tablet; 90 Tablets	R101.57	R45.43	-55%
Quetiapine; 200mg; Tablet; 60 Tablets	R119.12	R48.83	-59%
Quetiapine; 25mg; Tablet; 100 Tablets	R50.16	R26.21	-48%
Quetiapine; 300mg; Tablet; 60 Tablets	R190.94	R67.33	-65%
Amisulpride; 200mg; Tablet; 30 Tablets	R279.20	R186.50	-33%
Amisulpride; 50mg; Tablet; 30 Tablets	R125.82	R92.90	-26%
Aripiprazole; 10mg; Tablet; 30 Tablets	R798.99	R30.84	-96%
Aripiprazole; 15mg; Tablet; 30 Tablets	R798.99	R47.43	-94%
Aripiprazole; 5mg; Tablet; 30 Tablets	R684.00	R35.27	-95%
Olanzapine; 10mg; Tablet; 28 Tablets	R30.94	R14.39	-53%
Olanzapine; 2.5mg; Tablet; 28 Tablets	R18.24	R11.10	-39%
Olanzapine; 5mg; Tablet; 28 Tablets	R24.73	R9.49	-62%
Risperidone; 0.5mg; Tablet; 30 Tablets	R8.21	4.92	-40%
Risperidone; 1mg; Tablet; 30 Tablets	R4.79	5.66	+18%
Risperidone; 2mg; Tablet; 30 Tablets	R5.59	5.89	+5%
Risperidone; 3mg; Tablet; 30 Tablets	R7.70	7.38	-4%

**Aripiprazole pricing from March 2017*

PROPOSED APPROACH

Due to the high price of amisulpride, it was proposed that investigation should be undertaken to evaluate the most appropriate agent for third-line treatment of schizophrenia spectrum disorders where there is concern of metabolic adverse effects from other atypical antipsychotics. Since aripiprazole is already included on the EML for children and adolescents, and that it has become more affordable over the past few years, it was proposed that aripiprazole be considered for adults in the third-line schizophrenia setting.

Purpose/Objective i.e. PICO

-P *(patient/population):* Patients with Schizophrenia who have failed third-line therapy (olanzapine) or where weight gain and other metabolic effects may be a concern (e.g. BMI >30, Type 2 Diabetes)

-I *(intervention):* Aripiprazole

-C *(comparator): Amisulpride*/olanzapine/risperidone

-O *(outcome):*

- Global state: Clinical Global Impression (CGI)
- Mental state: positive and negative syndrome scale (PANSS)
- Leaving study early
- Relapse
- Adverse effects

-S *(study type):* Systematic review and meta-analyses/network meta-analyses

METHODS

Search Strategy

A rapid literature search was conducted in PubMed, and Cochrane Library (See Appendix 2). Abstract and title screening, as well as full text review, was undertaken initially by JR and then assessed by LR.

RESULTS

After removal of three duplicates, a total of 83 studies were identified (see search summary in appendix 2). From these, four network meta-analysis (NMA) and one systematic review were included. The 78 excluded studies are listed in Appendix 3. AMSTAR 2 assessments were undertaken on all selected NMAs in duplicate by JR and KM. Details of the five included studies are summarized in Table 5.

Table 5: Summary of included studies.

Citation	Study design	Population (n)	Treatment	Quality and internal validity (AMSTAR 2)
Huhn et.al. 2019[2]	Systematic Review and NMA of placebo controlled and head-to-head published and unpublished RCTs. Evaluated effects of acute treatment (up to 13 weeks)	402 RCTs with 53 463 participants (adults with acute symptoms of multi-episode schizophrenia or related disorders). Note: 6 RCTs (n=2 329) also used by Khanna et al. 4 RCTs (n=476) also used by Zhao et al.	32 antipsychotics including amisulpride, aripiprazole	Moderate (no full list of excluded studies). Note: overall ROB of included studies unclear
Khanna et.al. 2014[3]	Cochrane systematic review and meta-analysis of published and unpublished RCTs. Evaluated effects of acute treatment (duration varied, mostly up to 12 weeks)	174 RCTs involving 17244 participants. Note: 6 RCTs (n=2 329) also used by Huhn et al	Aripiprazole Versus: clozapine; quetiapine; risperidone; ziprasidone; olanzapine	High Note: overall ROB of included studies unclear. Directions of effects were assessed which risk of bias were a concern to assess if direction of effect changed.
Leucht et.al. 2023[4]	Systematic Review and NMA of published and unpublished RCTs. Evaluated effects of long-term (at least 6 months) treatment.	45 with 11 238 participants (adults with initially acute symptoms of schizophrenia or related disorders). Note: 2 RCTs (n=753) also used by Zhao et al. 22 RCTs (n= 8474) also used by Burschinski et al.	24 antipsychotics including amisulpride, aripiprazole and placebo (olanzapine used as reference)	Low (no full list of excluded studies, did not describe included study outcomes, did not report funding of studies).
Zhao et.al. 2016[5]	Systematic review and network meta-analysis of published RCTs. Evaluated relapse in short and long-term treatment (mean study duration 48 weeks (range 4–156 weeks))	56 RCTs with 10177 participants (adults with schizophrenia or related disorders who are initially clinically stable on antipsychotic monotherapy). Note: 4 RCTs (n=476) also used by Huhn et al. 2 RCTs (n=753) also used by Leucht et al.	18 antipsychotics including: amisulpride, aripiprazole, risperidone, and olanzapine.	High Note: Risk of selection bias at treatment initiation unclear in about 75% of RCTs.
Burschinski et.al. 2023[6]	Network meta-analysis of published and unpublished RCTs. Evaluated metabolic adverse effects in mid- to long-term treatment (> 3months and > 6 months, respectively).	137 RCTs with 35007 participants with schizophrenia or related disorders. Note: 22 RCTs (n= 8474) also used by Leucht et al.	31 antipsychotics including: amisulpride, aripiprazole, risperidone, and olanzapine	High Note: Some concerns and high ROB in 75% and 25% of RCTs, res mainly related to missing outcome data and high dropout rates in long-term studies.

Quality and internal validity

AMSTAR 2 assessments were undertaken for all reviews in duplicate (JR and KM):

- *Huhn et.al. was found to be Moderate Quality (excluded studies not outlined).*
- *Leucht et.al. was found to be Low Quality (no full list of excluded studies, did not describe included study outcomes, did not report funding of studies).*
- *Burschinski et.al. was found to be High Quality.*
- *Khanna et.al. was found to be High Quality.*
- *Zhao et.al. was found to be High Quality.*

EFFICACY AND SAFETY IN SCHIZOPHRENIA

GLOBAL STATE

Khanna et. al. 2014[3] reported global state of aripiprazole versus risperidone and olanzapine (but not amisulpride). Global state was defined as no clinically important response which, in turn, was defined by each individual study.

- No significant differences for global state compared to risperidone, relative risk 1.08, 95% CI 0.96 to 1.21, i^2=0%, p=0.20, (n = 6381, 80 RCTs, low quality evidence).
- No significant differences for global state compared to olanzapine, relative risk 1.06, 95% CI 0.96 to 1.17, i^2=0%, P=0.28, (n = 1739, 11 RCTs, very low-quality evidence).

MENTAL STATUS

Huhn et.al. 2019[2] reported findings of overall change in symptoms; positive and negative symptoms; and depressive symptoms versus placebo as follows:

Table 6. Efficacy versus placebo (Huhn et al.)

	Amisulpride	Aripiprazole	Olanzapine	Risperidone
Overall change in symptoms SMD (95%CI)	-0.73 (-0.89 to -0.58) N=705 Moderate certainty	-0.41 (-0.50 to -0.32) N = 1926 Low certainty	-0.56 (-0.62 to-0.50) N = 5602 Moderate certainty	-0.55 (-0.62 to -0.48) N= 3827 High certainty
Positive symptoms SMD (95% CI)	-0.69 (-0.86 to -0.52) N=626 Moderate certainty	-0.38 (-0.48 to-0.28) N=1451 Low certainty	-0.53 (-0.60 to -0.46) N=4227 Moderate certainty	-0.61(-0.68 to-0.54) N = 3351 Moderate certainty
Negative symptoms SMD (95% CI)	-0.50 (-0.64 to-0.37) N=691 Moderate certainty	-0.33 (-0.41 to-0.24) N=1353 Low certainty	-0.45 (-0.51 to-0.39) N = 4224 Moderate certainty	-0.37 (-0.43 to-0.31) N = 3435 Moderate certainty
Depressive symptoms SMD (95% CI)	-0.44 (-0.60 to -0.28) N=663 High certainty	-0.24 (-0.34 to-0.13) N=1996 Moderate certainty	-0.37 (-0.46 to -0.29) N = 2753 High certainty	-0.23 (-0.34 to -0.11) N = 1566 Moderate certainty

Standard mean difference: SMD

Favours antipsychotic	*Favours placebo*	*Neutral*

Amisulpride, aripiprazole, olanzapine and risperidone were all shown to be superior to placebo in terms of overall change in symptoms, positive symptoms, negative symptoms, and depressive symptoms. Amisulpride ranked higher than aripiprazole on NMA of acute overall symptom reduction as well as positive, negative, and depressive symptoms, however for most outcomes there was some overlap in confidence intervals, and certainty varied.

Long-term (at least 6 months) treatment

Leucht et.al. 2023 evaluated long term efficacy following treatment of acute illness, using olanzapine as the reference in the NMA. The findings for overall change in symptoms, positive and negative symptoms, and depressive symptoms are presented in Table 7 (confidence in evidence with CINeMA as reported by Leucht et al.) While aripiprazole was slightly less efficacious than olanzapine for overall change and positive symptoms, there was no difference for negative and depressive symptoms.

Table 7. Efficacy vs olanzapine (Leucht et al.)

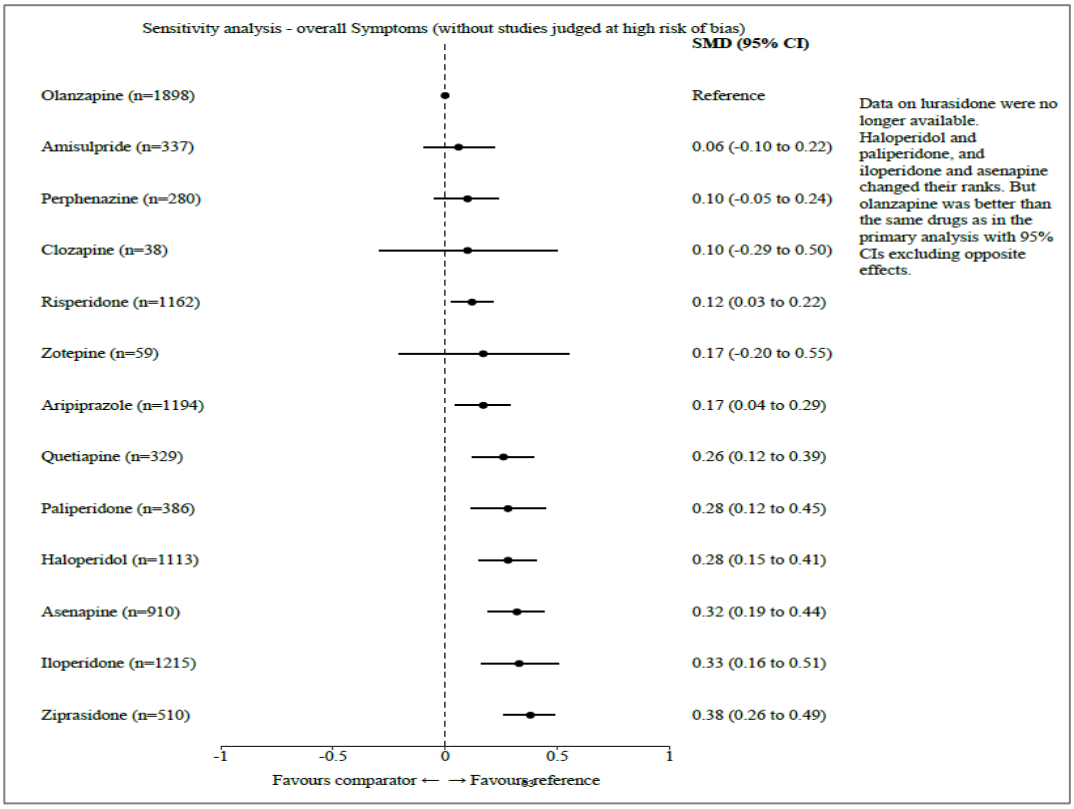
	Amisulpride	**Aripiprazole**	**Risperidone**	**Olanzapine**
Overall change in symptoms SMD (95%CI)	0.06 (-0.10 to 0.22) N = 337 Low confidence	0.16 (0.04-0.28) N=1194 Moderate confidence	0.12 (0.03 to 0.21) N = 1162 Moderate confidence	Reference N=1940
Positive symptoms SMD (95%CI)	0.05 (-0.12 to 0.21) N = 307	0.18 (0.05-0.31) N = 1138	0.08 (-0.06 to 0.21) N = 847	Reference
Negative symptoms SMD (95%CI)	0.08 (-0.14 – 0.19) N = 307	0.13 (0.00 to 0.26) N = 1138	0.21 (0.07 to 0.34) N = 847	Reference
Depressive symptoms SMD (95%CI)	0.12 (-0.06 to 0.29) N = 307	0.04 (-0.14 to 0.23) N = 989	0.10 (-0.02 to 0.21) N = 1038	Reference

SMD=Standard mean differences

Favours alternative antipsychotic	*Favours olanzapine*	*Neutral*

A sensitivity analysis for the primary outcome (overall change in symptoms) with removal of studies judged to have a high-risk of bias did not alter the results for amisulpride, aripiprazole, and risperidone versus olanzapine (Figure 3).

Figure 3. Forest plot for change in overall symptoms excluding high risk of bias studies (Leucht et.al.2023) compared to olanzapine.



Note: mental state data from Khanna et.al. not extracted, as GRADED as very low quality, with various measures used.

LEAVING STUDY EARLY

Acute treatment

Khanna et. al. 2016 reported on leaving the study early for any reason up to 12 week follow up for aripiprazole versus risperidone and olanzapine but not versus amisulpride.

- Vs risperidone: no significant difference, relative risk 1.02, 95% CI 0.79 to 1.32, i^2=0%, P=0.98, (n = 1239, 12 RCTs, very low-quality evidence).
- Vs olanzapine: significantly more people receiving aripiprazole left the study early for any reason, relative risk 1.15 CI 1.05 to 1.25, i^2=28%, P=0.52, (n = 316, 2 RCTs, very low-quality evidence).

Huhn et al. 2023 reported on all-cause discontinuation, finding all four antipsychotics were superior to placebo (Table 8; level of certainty in the evidence as reported by Huhn et al.).

Table 8. All-cause discontinuation in acute treatment vs placebo (Huhn et al.)

	Amisulpride	**Aripiprazole**	**Olanzapine**	**Risperidone**
All-cause discontinuation RR (95%CI)	0·67 (0·55 to 0·78) N=732 Moderate certainty	0·80 (0·73 to 0·86) N = 1742 High certainty	0·69 (0·65 to 0·74) N = 5373 High certainty	0·82 (0·80 to 0·85) N= 3970 High certainty

RR=relative risk

Favours antipsychotic	*Favours placebo*	*Neutral*

Long-term treatment

Leucht et.al. 2023 found no difference in all-cause discontinuation after at least 6 months follow-up following acute treatment for either amisulpride or aripiprazole versus olanzapine (Table 9).

Table 9. All cause discontinuation in long-term treatment vs olanzapine (Leucht et al.)

	Aripiprazole	**Amisulpride**	**Risperidone**	**Olanzapine**
All-cause discontinuation RR (95% CI)	1.12 (0.98 to 1.27) N = 1245	1.08 (0.89 to 1.28) N = 341	1.26 (1.14 to1.38) N = 1237	Reference N=2011

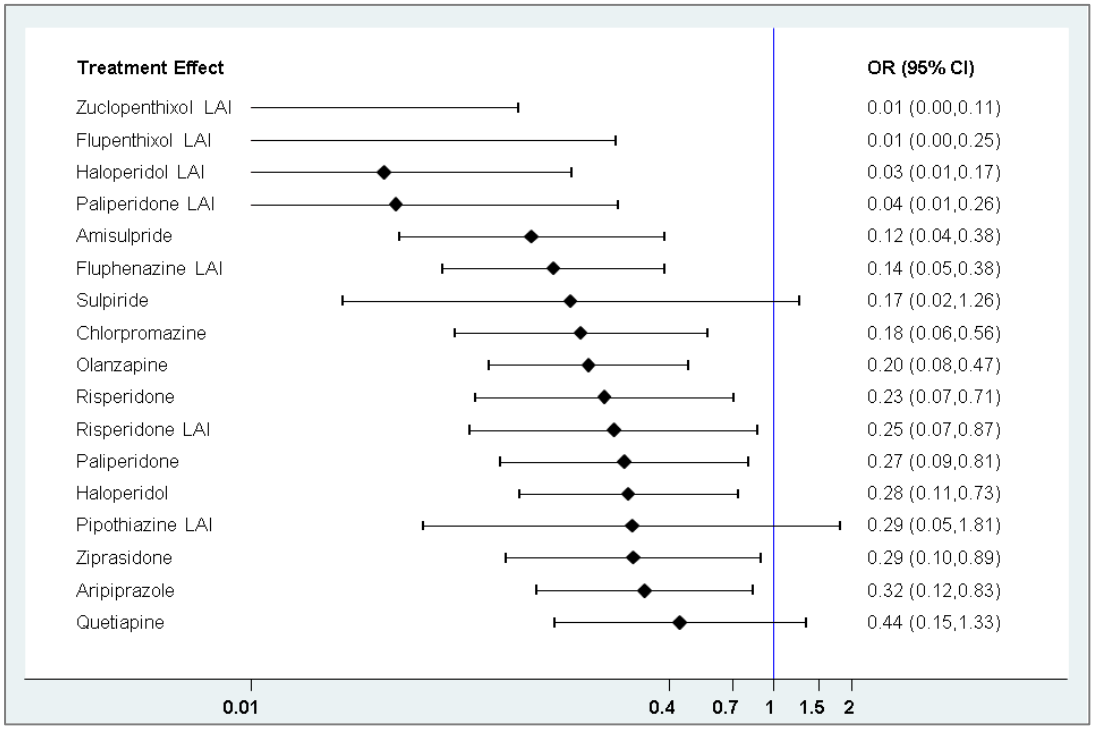
RR=relative risk

CINeMA assessed as generally moderate to low.

Favours alternative antipsychotic	*Favours olanzapine*	*Neutral*

Zhao et al. 2016 found that those stabilised on amisulpride, aripiprazole, olanzapine, or risperidone were less likely to withdraw from the study due to inefficacy than those receiving placebo, with overlapping confidence intervals (Figure 4).

Figure 4. Forest plot: Study withdrawal due to inefficacy vs placebo (Zhao et al.)

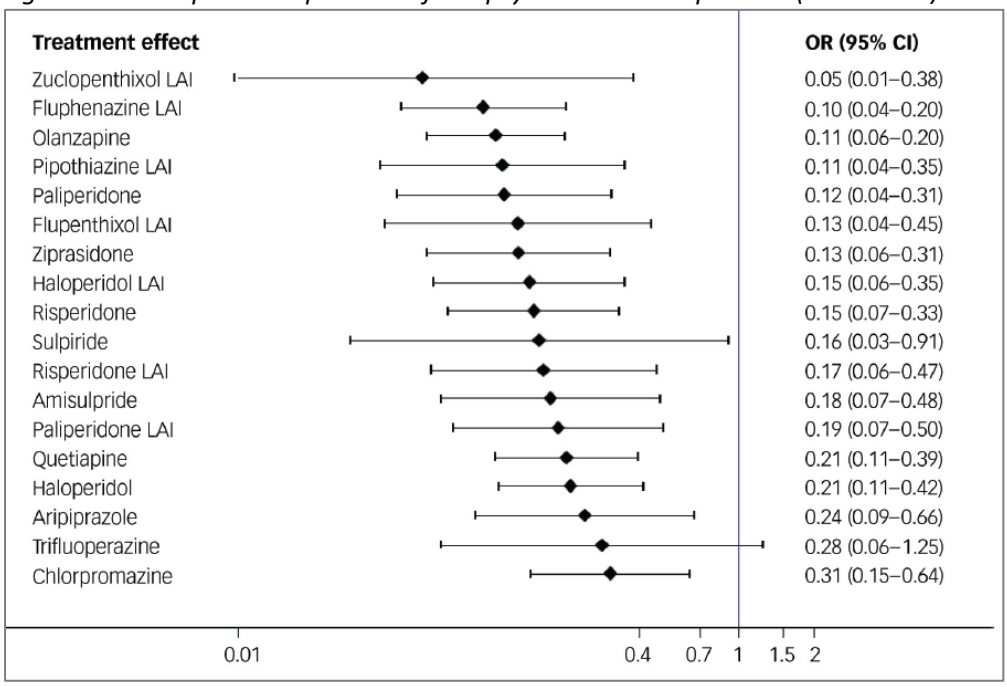


OR=odds ratio

RELAPSE

Zhao et. al. 2016 evaluated relapse prevention in clinically stable adults as its primary outcome of interest. All evaluated antipsychotics except one (trifluoperazine) were found to be better than placebo (Figure 5).

Figure 5. Forest plot: relapse rate of antipsychotics versus placebo (Zhao et al.)

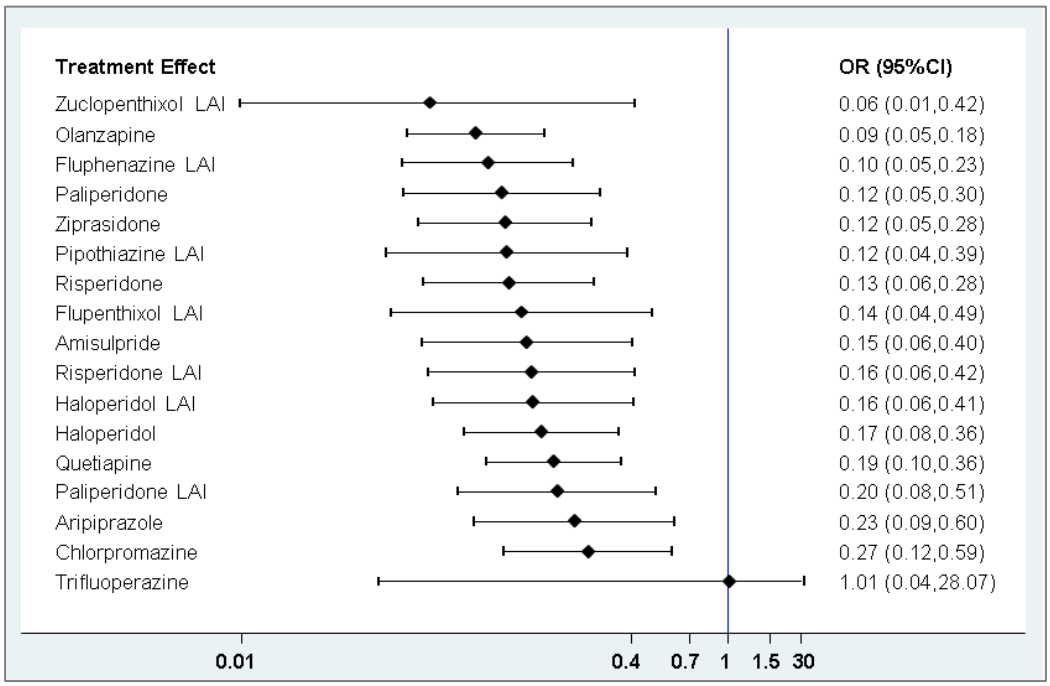


Zhao et al. found no significant differences between aripiprazole and amisulpride, risperidone or olanzapine:

- Aripiprazole compared to amisulpride, OR 0.73 (95% CI 0.19 to 2.86).
- Aripiprazole compared to olanzapine, OR 0.54 (95% CI 0.17 to 1.72).
- Aripiprazole compared to risperidone, OR 0.76 (95% CI 0.21 to 2.82).

A sensitivity analysis excluding trials of less than 6 months duration similarly found all four antipsychotics reduced relapse rates with overlapping confidence intervals (Figure 6).

Figure 6. Forest plot: relapse rate versus placebo excluding trials of <6 months duration (Zhao et al.)



ADVERSE EFFECTS

Amisulpride was previously included on the Tertiary and Quaternary EML as a third-line option for patients where weight gain or metabolic side effects were of concern. Thus, an additional agent would need to be either neutral or beneficial in terms of metabolic adverse events. The findings for amisulpride, risperidone and olanzapine are included below for comparison purposes.

Weight gain

Acute treatment

Huhn et al. found aripiprazole was not associated with weight gain versus placebo (Table 10, certainty of evidence as reported by the Huhn et al.).

Table 10. Weight gain in acute treatment versus placebo (Huhn et al.)

	Amisulpride	**Aripiprazole**	**Risperidone**	**Olanzapine**
Weight Gain MD in kg (95% CI)	0·84 (0·14 to 1·53) N=592 Moderate certainty	0·48, (–0·05 to 1·01) N=1199 Low certainty	1·44 (1·05 to 1·83) N = 2521 High certainty	2·78 (2·44 to 3·13) N = 4198 High certainty

MD: mean difference

Favours antipsychotic	*Favours placebo*	*Neutral*

Khanna et al. found that significantly more people receiving olanzapine than aripiprazole gained weight, RR 0.25, 95%CI 0.15 to 0.43 (n = 1538, 9 RCTs, very low-quality evidence).

Mid-term (>3months) and long-term treatment (>6months)

In their NMA, Burschinski et al 2023 found aripiprazole was weight neutral, whereas amisulpride, risperidone, and olanzapine were all associated with weight gain (Table 11; confidence in the evidence as reported by the Burschinksi et al).

Table 11. Weight gain with mid- to long-term treatment versus placebo (Burschinski et al.)

	Amisulpride	**Aripiprazole**	**Risperidone**	**Olanzapine**
Weight Gain MD in kg (95% CI)	1.43 (0.45 to 2.41) N=1000 Moderate confidence	0.41 (-0.40 to 1.28) N=2218 Low confidence	1.87 (1.12 to 2.65) N = 3388) Moderate confidence	3.82 (3.15 to 4.50) N = 6156 Moderate confidence

MD: mean difference

Favours antipsychotic	*Favours placebo*	*Neutral*

Compared to olanzapine, Leucht et al. (2023) found less weight gain in long-term treatment with aripiprazole (MD -3.07, 95% CI -4.81 to -1.34, n=285), risperidone (MD -2.27, 95% CI -3.70 to -1.03, n=647) and amisulpride (MD -2.30, 95% CI -3.35 to -1.25, n=181); certainty in the evidence not reported.

Fasting glucose, cholesterol and triglycerides

Acute treatment

Not reported on by Huhn et al. or Khanna et al.

Mid- to long-term treatment (>3months to >6months, respectively)

Burschinski et al. (2023) found aripiprazole did not differ from placebo for any of the measures (Table 12, overall confidence in the evidence not reported).

Table 12. Metabolic adverse effects with mid- long-term treatment versus placebo (Burschinski et al.)

	Amisulpride	**Aripiprazole**	**Risperidone**	**Olanzapine**
Fasting Glucose MD in mg/kg (95%CI)	1.85 (-1.89 to 5.64) N=234	0.35 (-2.40 to 3.28) N=617	3.51 (0.21 to 7.21) N = 1159	5.07 (2.44 to 7.98) N = 2702
Total cholesterol MD in mg/dl (95% CI)	9.77 (-6.96 to 26.68) N=53	-0.75 (-4.90 to 3.21) N=1202	3.62 (-0.93 to 8.28) N = 1767	12.65 (8.73 to 16.51) N = 3779
LDL cholesterol MD in mg/dl (95% CI)	9.72 (-6.90 to 26.88) N=52	-1.92 (-5.64 to1.96) N=1086	4.02 (-0.91 to 9.04) N = 1052	8.09 (4.32 to 11.89) N = 2386
HDL cholesterol MD in mg/dl (95% CI)	-5.24 (-8.94 to -2.05) N=53	0.71 (-0.76 to 1.98) N=1190	-1.20 (-2.45 to 0.15) N = 1373	-2.59 (-3.71 to -1.44) N = 2772
Triglycerides MD in mg/dl (95% CI)	38.98 (12.66 to 66.49) N=53	-1.07 (-12.26 to 9.87) N=1174	2.88 (-10.54 to 16.07) N = 1665	31.66 (20.32 to 42.84) N = 3315

MD: mean difference

Favours antipsychotic	*Favours placebo*	*Neutral*

Other adverse effects

Acute treatment

Huhn et al. found that aripiprazole had lower prolactin levels versus placebo and differ from placebo in antiparkinsonian medication use or QTc prolongation (Table 13; level of certainty in the evidence as reported by the Huhn et al).

Table 13. Adverse effects in acute treatment versus placebo (Huhn et al.)

	Amisulpride	**Aripiprazole**	**Olanzapine**	**Risperidone**
Antiparkinson medication use RR (95% CI)	1·46 (0·96 to 2·04) N=517 Low certainty	1·32 (0·90 to 1·82) N=678 Low certainty	1·02 (0·79 to 1·30) N=3012 Low certainty	1·80 (1·40 to 2·38) N=2174 Low certainty
Akathisia RR (95% CI)	2·50 (1·21 to 4·34) N=271 Moderate certainty	1·95 (1·30 to 2·74) N=1116 Low certainty	0·99 (0·70 to 1·34) N=2956 Very low certainty	2·73 (2·00 to 3·98) N=2104 Low certainty
Prolactin levels MD in ng/ml (95%CI)	26·87 (15·63 to 38·19) N=58 Low certainty	-7·10 (-11·17 to -3·09) N=1076 Very low certainty	4·47 (1·60 to 7·38) N= 2411 Very low certainty	37·98 (34·64 to 41·38) N=1761 Moderate certainty
QTc prolongation MD in ms (95%CI)	14·10 (7·71 to 20·45) N=110 High certainty	–0·43 (–3·62 to 2·77) N=603 Low certainty	4·29 (1·91 to 6·68) N=1895 Moderate certainty	4·77 (2·68 to 6·87) N=1295 High certainty
Sedation RR (95% CI)	1·56 (0·91 to 2·23) N=314 Moderate certainty	1·46 (1·11 to 1·83) N=935 Low certainty	2·17 (1·93 to 2·40) N=3730 Moderate certainty	2·03 (1·67 to 2·51) N=2824 Moderate certainty

MD=mean difference; RR=risk ratio

Favours antipsychotic	*Favours placebo*	*Neutral*

Khanna et al. found aripiprazole had fewer extra-pyramidal adverse effects than risperidone, relative risk 0.39, 95% CI 0.31 to 0.50 (n = 2605, 31 RCTs, low quality evidence).

Long-term treatment (at least 6 months)

Leucht et. al. 2023 found that aripiprazole had fewer adverse effects than olanzapine (Table 14).

Table 14. Adverse effects in long-term treatment versus olanzapine (Leucht et al.)

	Aripiprazole	**Amisulpride**	**Risperidone**	**Olanzapine**
Antiparkinson medication use OR (95% CI)	0.69 (0.51 to 0.95) N = 1146	1.37 (0.89 to 2.12) N = 341	1.69 (1.31 to 2.19) N = 1227	Reference
Akathisia OR (95% CI	1.10 (0.77 to 1.57) N = 1245	0.95 (0.52 to 1.77) N = 152	1.35 (0.96 to 1.91) N = 1227	Reference
Prolactin levels MD (95% CI)	-8.89 (-14.87 to -2.91) N = 285	No data	30.50 (19.36 to 41.65) N = 536	Reference
QTc prolongation MD (95% CI)	No data	5.00 (-1.81 to 11.81) N = 110	-0.12 (-3.94 to 3.69) N = 710	Reference
Sedation OR (95% CI)	0.53 (0.34 to 0.84) N = 1245	0.81 (0.43 to 1.55) N = 341	0.94 (0.73 to 1.22) N = 1227	Reference

MD: mean difference, OR: odds ratio

Favours comparator	*Favours olanzapine*	*Neutral*

COSTS

As noted above, aripiprazole is less costly than amisulpride although more expensive than olanzapine. (*Refer to table 3: Comparative cost per patient per year).*

DISCUSSION

The aim of this review was to determine whether aripiprazole could be used in the third line treatment of schizophrenia spectrum disorders as an alternative to amisulpride if olanzapine is not effective and/or metabolic adverse effects are a concern. The relative efficacy and adverse effects of amisulpride, aripiprazole, olanzapine, and risperidone in acute (≤ 3 months), medium (> 3months and ≤ 6 months), and long-term (> 6 months) treatment has been demonstrated using five network meta-analyses and systematic reviews to capture the outcomes and the various treatment durations.

All four antipsychotics were superior to placebo in acute treatment of overall symptoms, positive, negative, and depressive symptoms. However, aripiprazole may not be as efficacious as olanzapine in acute (Khanna et al; Huhn et al.) and long-term (Leucht et al.) improvement of overall symptoms. Possible differences between aripiprazole and amisulpride are less clear. While amisulpride ranked higher than aripiprazole on NMA of acute overall symptom reduction (Huhn et al) and amisulpride was similar to olanzapine in long-term treatment (Leucht et al.), the confidence in these findings was assessed as low to moderate. Additionally, all four antipsychotics had similar efficacy in relapse prevention, and none were associated with increased study withdrawal due to inefficacy among participants stabilised on treatment (Zhao et al.).

Of note, aripiprazole had a favourable adverse effect profile in terms of metabolic and other adverse events. Aripiprazole may be weight neutral versus placebo in acute (Huhn et al.) and mid- to long-term treatment (Burschinski et al.). Consistent with its weight neutral profile, aripiprazole was not associated with increased glucose, cholesterol, or triglycerides in mid- to long-term treatment.

While there was an unclear risk of bias for most of the RCTs included, the results are consistent between reviews. Therefore, it appears that aripiprazole is generally comparable in efficacy to amisulpride, olanzapine, and risperidone, with some possible differences in acute overall symptom reduction. In terms of adverse events, aripiprazole appears to have fewer metabolic and other adverse events than amisulpride, risperidone, or olanzapine.

CONCLUSION

On evaluation of antipsychotics in the third-line management of schizophrenia, it was found that the cost and expenditure on the currently recommended agent, amisulpride, far exceeded that of any other antipsychotic. It was thus determined that an alternative agent should be added to the schizophrenia algorithm for patients who may be experiencing or who are at risk of metabolic adverse events from other agents, prior to use of amisulpride. It is further recommended that amisulpride be maintained on the EML but reserved for patients with a poor response to previous lines of therapy and/or persistent negative symptoms.

It is therefore proposed that aripiprazole be added to the management algorithm for schizophrenia, for patients experiencing or at risk of metabolic adverse events from olanzapine, prior to consideration of amisulpride. See management algorithm.

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Declaration of interests:

- Lesley Robertson. Lesley Robertson, Department of Psychiatry, University of the Witwatersrand: no interests to declare.
- Jane Riddin (Essential Drugs Programme) has no interests to declare.
- Kim MacQuilkan (GH-SCTA) has no interests to declare.
- Roger Wiseman (Liberty Health (Pty) Ltd, South Africa) has no interests to declare.
- Marc Blockman (Department of Clinical Pharmacology, Groote Schuur Hospital, Cape Town, Western Cape, South Africa and the Department of Medicine, University of Cape Town, Cape Town, Western Cape, South Africa). Has no interests to declare.

Appendix 1: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High: ☐ Moderate: ☐ Low: ☒ Very low: ☒	*Global status* Meta-analysis (Khanna et al) ranked high quality (AMSTAR 2). However, included RCTs had overall unclear ROB. Aripiprazole vs risperidone – low quality evidence Aripiprazole vs olanzapine – very low quality
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large: ☐ Moderate: ☐ Small: ☐ None: ☒	*Global status* No significant differences found between aripiprazole as compared to risperidone and olanzapine.
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High: ☐ Moderate: ☒ Low: ☐ Very low: ☐	*Mental status* Network Meta-analysis (Huhn et al.; Leucht et al.) of moderate and low quality, respectively (AMSTAR 2). Unclear ROB for most of the RCTs included in all analyses. Certainty generally low to moderate.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large: ☐ Moderate: ☐ Small: ☒ None: ☐	*Mental status* Approximately 40% reduction in overall symptoms in acute treatment. Although aripiprazole generally ranked lower on the NMA forest plots than olanzapine, amisulpride and risperidone, confidence intervals overlapped when compared against each other for overall change in symptoms, positive, negative, and depressive symptom changes in acute and long-term treatment.

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☒ Low ☐ Very low ☐	*Leaving study early* Meta-analysis (Khanna et al.) of high but NMAs (Huhn et al.; Leucht et al.; Zhao et al.) of moderate, low and high quality, respectively (AMSTAR 2). Unclear ROB for most of the RCTs included in all analyses. Certainty indicated as high to moderate (Khanna et al.; Huhn et al), and moderate to low (Leucht et al).
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☐ Small ☒ None ☐	*Leaving study early* • Significantly better than placebo in acute and long-term treatment on NMA, with overlapping confidence intervals between antipsychotics. • On meta-analysis, no significant difference compared to risperidone but significantly more people left the study early for any reason as compared to olanzapine.
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☒ Low ☐ Very low ☐	*Relapse* Systematic review and NMA (Zhao et al.) ranked high quality (AMSTAR 2). However, unclear randomization, allocation concealment, and blinding in most included RCTs.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☒ Small ☐ None ☐	*Relapse* Point estimate of 76% reduction in relapse rate versus placebo, with no differences between aripiprazole and amisulpride, olanzapine, or risperidone.
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☒ Low ☐ Very low ☐	*Adverse events* Studies included were ranked low to high (AMSTAR 2) with some concerns/ unclear ROB in most included RCTs. Moderate to very low certainty.

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge ☐ Moderate ☐ Small ☒ None ☐	Adverse events Aripiprazole associated with more akathisa and sedation than placebo but found to be neutral for metabolic and other adverse events assessed.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☒ Favours control ☐ Intervention = Control *or* Uncertain ☐	Desirable effects consistently better than placebo, with overlapping confidence intervals compared to other antipsychotics for most outcomes. Very few undesirable harms, particularly with regards to metabolic effects.
FEASABILITY	**Is implementation of this recommendation feasible?** Yes ☒ No ☐ Uncertain ☐	
RESOURCE USE	**How large are the resource requirements?** More intensive ☐ Less intensive ☒ Uncertain ☐	See costing tables at start of report. Aripiprazole will be less cost intensive than amisulpride
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor ☐ Major ☐ Uncertain ☒ **Is the option acceptable to key stakeholders?** Yes ☐ No ☐ Uncertain ☒	
EQUITY	**Would there be an impact on health inequity?** Yes ☐ No ☒ Uncertain ☐	

Appendix 2: Search Strategy

PubMed

Search	Query	Search Details	Results
#3	Relapse prevention	("schizophrenia"[Title/Abstract] AND "relapse prevention"[Title/Abstract] AND "antipsychotic"[Title/Abstract]) AND (meta-analysis[Filter] OR systematicreview[Filter])	28
#2	Metabolic side effects and schizophrenia and network meta-analysis	"metabolic side effects"[Title/Abstract] AND "schizophrenia"[Title/Abstract] AND "network meta analysis"[Title/Abstract]	4
#1	antipsychotics and schizophrenia and network meta-analysis	"schizophrenia"[Title/Abstract] AND "antipsychotics"[Title/Abstract] AND "network meta analysis"[Title/Abstract] AND "efficacy"[Title/Abstract]	34

Cochrane Library

search	**Query**	**Results**
#1	MeSH descriptor: [Quetiapine Fumarate] explode all trees	870
#2	MeSH descriptor: [Amisulpride] explode all trees	236
#3	MeSH descriptor: [Aripiprazole] explode all trees	755
#4	MeSH descriptor: [Schizophrenia] explode all trees	9853
#5	#1 AND #2 AND #3 AND #4	4
#6	#5 PLUS Cochrane review limit	3
#7	#4 AND (#1 OR #2 OR #3)	698
#8	#7 PLUS Cochrane review limit	20

Search summary

	Findings
Pubmed (efficacy)	34
Pubmed (metabolic adverse effects)	4
Pubmed (relapse)	28
Cochrane	20
Duplicates removed	-3
Total summary	83

Appendix 3: excluded studies

	Study – Efficacy Search	Inclusion/Exclusion
1	Comprehensive evaluation of 45 augmentation drugs for schizophrenia: a network meta-analysis. Etchecopar-Etchart D, Yon DK, Wojciechowski P, Aballea S, Toumi M, Boyer L, Fond G.EClinicalMedicine. 2024 Feb 7;69:102473. doi: 10.1016/j.eclinm.2024.102473. eCollection 2024 Mar.PMID: 38356727	Exclude – does not meet PICO
2	Efficacy of pharmacological agents for the management of treatment-resistant schizophrenia: a network meta-analysis. Mishra A, Maiti R, Mishra BR, Srinivasan A.Expert Rev Clin Pharmacol. 2024 Mar;17(3):293-302. doi: 10.1080/17512433.2024.2310715. Epub 2024 Jan 26.PMID: 38269529 Review.	Exclude – does not meet PICO
3	Efficacy and effectiveness of antipsychotics in schizophrenia: network meta-analyses combining evidence from randomised controlled trials and real-world data. Efthimiou O, Taipale H, Radua J, Schneider-Thoma J, Pinzón-Espinosa J, Ortuño M, Vinkers CH, Mittendorfer-Rutz E, Cardoner N, Tanskanen A, Fusar-Poli P, Cipriani A, Vieta E, Leucht S, Tiihonen J, Luykx JJ.Lancet Psychiatry. 2024 Feb;11(2):102-111. doi: 10.1016/S2215-0366(23)00366-8. Epub 2024 Jan 9.PMID: 38215784	Exclude – did not include amisulpride in analysis
4	Efficacy and feasibility of aerobic exercise interventions as an adjunctive treatment for patients with schizophrenia: a meta-Analysis. Guo J, Liu K, Liao Y, Qin Y, Yue W.Schizophrenia (Heidelb). 2024 Jan 2;10(1):2. doi: 10.1038/s41537-023-00426-0.PMID: 38167923	Exclude – does not meet PICO
5	Comparative efficacy and tolerability of pharmacological interventions for acute bipolar depression in adults: a systematic review and network meta-analysis. Yildiz A, Siafis S, Mavridis D, Vieta E, Leucht S.Lancet Psychiatry. 2023 Sep;10(9):693-705. doi: 10.1016/S2215-0366(23)00199-2.PMID: 37595997	Exclude – does not meet PICO
6	A network meta-analysis of efficacy, acceptability, and tolerability of antipsychotics in treatment-resistant schizophrenia. Dong S, Schneider-Thoma J, Bighelli I, Siafis S, Wang D, Burschinski A, Schestag K, Samara M, Leucht S.Eur Arch Psychiatry Clin Neurosci. 2023 Aug 1. doi: 10.1007/s00406-023-01654-2. Online ahead of print.PMID: 37526675	Exclude – did not include aripiprazole in analysis
7	Comparison of antipsychotic dose equivalents for acute bipolar mania and schizophrenia. Yu CL, Carvalho AF, Thompson T, Tsai TC, Tseng PT, Hsu CW, Hsu TW, Liang CS.BMJ Ment Health. 2023 Feb;26(1):e300546. doi: 10.1136/bmjment-2022-300546. Epub 2023 Feb 7.PMID: 36789916	Exclude – does not meet PICO
8	Pharmacological and nonpharmacological augmentation treatments for clozapine-resistant schizophrenia: A systematic review and network meta-analysis with normalized entropy assessment. Yeh TC, Correll CU, Yang FC, Chen MH, Tseng PT, Hsu CW, Carvalho AF, Stubbs B, Thompson T, Chu CS, Yu CL, Il Shin J, Yang SN, Tu YK, Liang CS.Asian J Psychiatr. 2023 Jan;79:103375. doi: 10.1016/j.ajp.2022.103375. Epub 2022 Nov 26.PMID: 36470132	Exclude – does not meet PICO
9	Evidence-based Shared-Decision-Making Assistant (SDM-assistant) for choosing antipsychotics: protocol of a cluster-randomized trial in hospitalized patients with schizophrenia. Siafis S, Bursch N, Müller K, Schmid L, Schuster F, Waibel J, Huynh T, Matthes F, Rodolico A, Brieger P, Bühner M, Heres S, Leucht S, Hamann J.BMC Psychiatry. 2022 Jun 17;22(1):406. doi: 10.1186/s12888-022-04036-5.PMID: 35715740	Exclude – does not meet PICO
10	Comparative efficacy and tolerability of 32 oral and long-acting injectable antipsychotics for the maintenance treatment of adults with schizophrenia: a systematic review and network meta-analysis. Schneider-Thoma J, Chalkou K, Dörries C, Bighelli I, Ceraso A, Huhn M, Siafis S, Davis JM, Cipriani A, Furukawa TA, Salanti G, Leucht S.Lancet. 2022 Feb 26;399(10327):824-836. doi: 10.1016/S0140-6736(21)01997-8.PMID: 35219395	Exclude – does not meet PICO – does not evaluate amisulpride

11	Psychosocial and psychological interventions for relapse prevention in schizophrenia: a systematic review and network meta-analysis. Bighelli I, Rodolico A, García-Mieres H, Pitschel-Walz G, Hansen WP, Schneider-Thoma J, Siafis S, Wu H, Wang D, Salanti G, Furukawa TA, Barbui C, Leucht S.Lancet Psychiatry. 2021 Nov;8(11):969-980. doi: 10.1016/S2215-0366(21)00243-1. Epub 2021 Oct 12.PMID: 34653393	Exclude – does not meet PICO
12	Efficacy and safety of antipsychotic treatments for schizophrenia: A systematic review and network meta-analysis of randomized trials in Japan. Kishi T, Ikuta T, Sakuma K, Okuya M, Iwata N.J Psychiatr Res. 2021 Jun;138:444-452. doi: 10.1016/j.jpsychires.2021.04.032. Epub 2021 Apr 30.PMID: 33964682	Exclude – limited population
13	A network meta-analysis of the dose-response effects of lurasidone on acute schizophrenia. Srisurapanont M, Suttajit S, Likhitsathian S, Maneeton B, Maneeton N.Sci Rep. 2021 Mar 10;11(1):5571. doi: 10.1038/s41598-021-84836-z.PMID: 33692392	Exclude – does not meet PICO
14	Short-acting intramuscular second-generation antipsychotic drugs for acutely agitated patients with schizophrenia spectrum disorders. A systematic review and network meta-analysis. Paris G, Bighelli I, Deste G, Siafis S, Schneider-Thoma J, Zhu Y, Davis JM, Vita A, Leucht S.Schizophr Res. 2021 Mar;229:3-11. doi: 10.1016/j.schres.2021.01.021. Epub 2021 Feb 17.PMID: 33607608 Review.	Exclude – does not meet PICO
15	Lurasidone compared to other atypical antipsychotic monotherapies for adolescent schizophrenia: a systematic literature review and network meta-analysis. Arango C, Ng-Mak D, Finn E, Byrne A, Loebel A.Eur Child Adolesc Psychiatry. 2020 Sep;29(9):1195-1205. doi: 10.1007/s00787-019-01425-2. Epub 2019 Nov 22.PMID: 31758359	Exclude – does not meet PICO
16	Extensions of the probabilistic ranking metrics of competing treatments in network meta-analysis to reflect clinically important relative differences on many outcomes. Mavridis D, Porcher R, Nikolakopoulou A, Salanti G, Ravaud P.Biom J. 2020 Mar;62(2):375-385. doi: 10.1002/bimj.201900026. Epub 2019 Oct 29.PMID: 31661561	Exclude – does not meet PICO
17	Ziprasidone, haloperidol and clonazepam intramuscular administration in the treatment of agitation symptoms in Chinese patients with schizophrenia: A network meta-analysis. Su L, Lu Z, Shi S, Xu Y.Gen Psychiatr. 2018 Nov 10;31(2):e000016. doi: 10.1136/gpsych-2018-000016. eCollection 2018.PMID: 30582129	Exclude – does not meet PICO
18	Psychological interventions to reduce positive symptoms in schizophrenia: systematic review and network meta-analysis. Bighelli I, Salanti G, Huhn M, Schneider-Thoma J, Krause M, Reitmeir C, Wallis S, Schwermann F, Pitschel-Walz G, Barbui C, Furukawa TA, Leucht S.World Psychiatry. 2018 Oct;17(3):316-329. doi: 10.1002/wps.20577.PMID: 30192101	Exclude – does not meet PICO
19	Efficacy and metabolic effects of lurasidone versus brexpiprazole in schizophrenia: a network meta-analysis. Ng-Mak D, Tongbram V, Ndirangu K, Rajagopalan K, Loebel A.J Comp Eff Res. 2018 Aug;7(8):737-748. doi: 10.2217/cer-2018-0016. Epub 2018 Apr 26.PMID: 29697278	Exclude – does not meet PICO
20	Efficacy, acceptability, and tolerability of antipsychotics in children and adolescents with schizophrenia: A network meta-analysis. Krause M, Zhu Y, Huhn M, Schneider-Thoma J, Bighelli I, Chaimani A, Leucht S.Eur Neuropsychopharmacol. 2018 Jun;28(6):659-674. doi: 10.1016/j.euroneuro.2018.03.008. Epub 2018 May 24.PMID: 29802039 Review.	Exclude – does not meet PICO
21	Efficacy and safety of aripiprazole lauroxil once-monthly versus aripiprazole once-monthly long-acting injectable formulations in patients with acute symptoms of schizophrenia: an indirect comparison of two double-blind placebo-controlled studies.	Exclude – does not meet PICO

	Cameron C, Zummo J, Desai D, Drake C, Hutton B, Kotb A, Weiden PJ.Curr Med Res Opin. 2018 Apr;34(4):725-733. doi: 10.1080/03007995.2017.1410471. Epub 2018 Jan 10.PMID: 29179595	
22	Efficacy, acceptability and tolerability of 8 atypical antipsychotics in Chinese patients with acute schizophrenia: A network meta-analysis. Bai Z, Wang G, Cai S, Ding X, Liu W, Huang D, Shen W, Zhang J, Chen K, Yang Y, Zhang L, Zhao X, Ouyang Q, Zhao J, Lu H, Hao W.Schizophr Res. 2017 Jul;185:73-79. doi: 10.1016/j.schres.2017.01.002. Epub 2017 Jan 17.PMID: 28108226 Review.	Exclude – does not meet PICO
23	Comparative efficacy and safety of antipsychotics in the treatment of schizophrenia: a network meta-analysis in a Japanese population. Kishi T, Ikuta T, Matsunaga S, Matsuda Y, Oya K, Iwata N.Neuropsychiatr Dis Treat. 2017 May 11;13:1281-1302. doi: 10.2147/NDT.S134340. eCollection 2017.PMID: 28553116	Exclude – does not meet PICO
24	Acute Antipsychotic Treatment of Children and Adolescents With Schizophrenia-Spectrum Disorders: A Systematic Review and Network Meta-Analysis. Pagsberg AK, Tarp S, Glintborg D, Stenstrøm AD, Fink-Jensen A, Correll CU, Christensen R.J Am Acad Child Adolesc Psychiatry. 2017 Mar;56(3):191-202. doi: 10.1016/j.jaac.2016.12.013. Epub 2016 Dec 29.PMID: 28219485 Review.	Exclude – does not meet PICO
25	Antipsychotic Drugs in Schizophrenia: Relative Effects in Patients With and Without Treatment Resistance. Andrade C.J Clin Psychiatry. 2016 Dec;77(12):e1656-e1660. doi: 10.4088/JCP.16f11328.PMID: 28086018	Exclude – does not meet PICO
26	Efficacy, Acceptability, and Tolerability of Antipsychotics in Treatment-Resistant Schizophrenia: A Network Meta-analysis. Samara MT, Dold M, Gianatsi M, Nikolakopoulou A, Helfer B, Salanti G, Leucht S.JAMA Psychiatry. 2016 Mar;73(3):199-210. doi: 10.1001/jamapsychiatry.2015.2955.PMID: 26842482	Exclude – does not include aripiprazole and amisulpride
27	Comparative cost-effectiveness of 11 oral antipsychotics for relapse prevention in schizophrenia within Singapore using effectiveness estimates from a network meta-analysis. Lin L, Zhao YJ, Zhou HJ, Khoo AL, Teng M, Soh LB, Lim BP, Sim K.Int Clin Psychopharmacol. 2016 Mar;31(2):84-92. doi: 10.1097/YIC.0000000000000111.PMID: 26619182	Exclude – does not meet PICO
28	A Systematic Review and Network Meta-Analysis to Assess the Relative Efficacy of Antipsychotics for the Treatment of Positive and Negative Symptoms in Early-Onset Schizophrenia. Harvey RC, James AC, Shields GE.CNS Drugs. 2016 Jan;30(1):27-39. doi: 10.1007/s40263-015-0308-1.PMID: 26801655 Review.	Exclude – does not meet PICO
29	Publication bias and small-study effects magnified effectiveness of antipsychotics but their relative ranking remained invariant. Mavridis D, Efthimiou O, Leucht S, Salanti G.J Clin Epidemiol. 2016 Jan;69:161-9. doi: 10.1016/j.jclinepi.2015.05.027. Epub 2015 Jun 5.PMID: 26210055	Exclude – does not meet PICO
30	Meta-analyses of the efficacy of asenapine for acute schizophrenia: comparisons with placebo and other antipsychotics. Szegedi A, Verweij P, van Duijnhoven W, Mackle M, Cazorla P, Fennema H.J Clin Psychiatry. 2012 Dec;73(12):1533-40. doi: 10.4088/JCP.11r07596.PMID: 23290326	Exclude – does not meet PICO

Study – metabolic side effects search		Inclusion/Exclusion
1	Metabolic side effects of antipsychotic drugs in individuals with schizophrenia during medium- to long-term treatment: protocol for a systematic review and network meta-analysis of randomized controlled trials. Schneider-Thoma J, Kapfhammer A, Wang D, Bighelli I, Siafis S, Wu H, Hansen WP, Davis JM, Salanti G, Leucht S.Syst Rev. 2021 Aug 2;10(1):214. doi: 10.1186/s13643-021-01760-z.PMID: 34340713	Excluded – newer NMA included

2	Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. Pillinger T, McCutcheon RA, Vano L, Mizuno Y, Arumuham A, Hindley G, Beck K, Natesan S, Efthimiou O, Cipriani A, Howes OD.Lancet Psychiatry. 2020 Jan;7(1):64-77. doi: 10.1016/S2215-0366(19)30416-X. Epub 2019 Dec 17.PMID: 31860457	Excluded – newer NMA included
3	The metabolic side effects of 12 antipsychotic drugs used for the treatment of schizophrenia on glucose: a network meta-analysis. Zhang Y, Liu Y, Su Y, You Y, Ma Y, Yang G, Song Y, Liu X, Wang M, Zhang L, Kou C.BMC Psychiatry. 2017 Nov 21;17(1):373. doi: 10.1186/s12888-017-1539-0.PMID: 29162032	Excluded – newer NMA included

Study – Relapse prevention		Inclusion/Exclusion
1	Comparative efficacy and tolerability of 32 oral and long-acting injectable antipsychotics for the maintenance treatment of adults with schizophrenia: a systematic review and network meta-analysis. Schneider-Thoma J, Chalkou K, Dörries C, Bighelli I, Ceraso A, Huhn M, Siafis S, Davis JM, Cipriani A, Furukawa TA, Salanti G, Leucht S.Lancet. 2022 Feb 26;399(10327):824-836. doi: 10.1016/S0140-6736(21)01997-8.PMID: 35219395	Duplicate - exclude
2	Examination of Dosing of Antipsychotic Drugs for Relapse Prevention in Patients With Stable Schizophrenia: A Meta-analysis. Leucht S, Bauer S, Siafis S, Hamza T, Wu H, Schneider-Thoma J, Salanti G, Davis JM.JAMA Psychiatry. 2021 Nov 1;78(11):1238-1248. doi: 10.1001/jamapsychiatry.2021.2130.PMID: 34406325	Exclude – does not meet PICO
3	The response of subgroups of patients with schizophrenia to different antipsychotic drugs: a systematic review and meta-analysis. Leucht S, Chaimani A, Krause M, Schneider-Thoma J, Wang D, Dong S, Samara M, Peter N, Huhn M, Priller J, Davis JM.Lancet Psychiatry. 2022 Nov;9(11):884-893. doi: 10.1016/S2215-0366(22)00304-2. Epub 2022 Oct 10.PMID: 36228647	Exclude – does not meet PICO
4	Maintenance treatment with antipsychotic drugs for schizophrenia. Ceraso A, Lin JJ, Schneider-Thoma J, Siafis S, Tardy M, Komossa K, Heres S, Kissling W, Davis JM, Leucht S.Cochrane Database Syst Rev. 2020 Aug 11;8(8):CD008016. doi: 10.1002/14651858.CD008016.pub3.PMID: 32840872	Exclude – does not meet PICO
5	Efficacy and effectiveness of antipsychotics in schizophrenia: network meta-analyses combining evidence from randomised controlled trials and real-world data. Efthimiou O, Taipale H, Radua J, Schneider-Thoma J, Pinzón-Espinosa J, Ortuño M, Vinkers CH, Mittendorfer-Rutz E, Cardoner N, Tanskanen A, Fusar-Poli P, Cipriani A, Vieta E, Leucht S, Tiihonen J, Luykx JJ.Lancet Psychiatry. 2024 Feb;11(2):102-111. doi: 10.1016/S2215-0366(23)00366-8. Epub 2024 Jan 9.PMID: 38215784	Exclude – does not meet PICO
6	Maintenance Treatment With Antipsychotic Drugs in Schizophrenia: A Cochrane Systematic Review and Meta-analysis. Ceraso A, Lin JJ, Schneider-Thoma J, Siafis S, Heres S, Kissling W, Davis JM, Leucht S.Schizophr Bull. 2022 Jun 21;48(4):738-740. doi: 10.1093/schbul/sbac041.PMID: 35556140	Exclude – does not meet PICO
7	Relapse prevention in schizophrenia with new-generation antipsychotics: a systematic review and exploratory meta-analysis of randomized, controlled trials. Leucht S, Barnes TR, Kissling W, Engel RR, Correll C, Kane JM.Am J Psychiatry. 2003 Jul;160(7):1209-22. doi: 10.1176/appi.ajp.160.7.1209.PMID: 12832232 Review.	Exclude – Does not include aripiprazole (Zhao et.al. included)
8	Eicosapentaenoic acid interventions in schizophrenia: meta-analysis of randomized, placebo-controlled studies. Fusar-Poli P, Berger G.J Clin Psychopharmacol. 2012 Apr;32(2):179-85. doi: 10.1097/JCP.0b013e318248b7bb.PMID: 22367656 Review.	Exclude – does not meet PICO
9	Continuing, reducing, switching, or stopping antipsychotics in individuals with schizophrenia-spectrum disorders who are clinically stable: a systematic review and network meta-analysis.	Exclude – does not meet PICO

	Ostuzzi G, Vita G, Bertolini F, Tedeschi F, De Luca B, Gastaldon C, Nosé M, Papola D, Purgato M, Del Giovane C, Correll CU, Barbui C.Lancet Psychiatry. 2022 Aug;9(8):614-624. doi: 10.1016/S2215-0366(22)00158-4. Epub 2022 Jun 23.PMID: 35753323	
10	Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. Leucht S, Tardy M, Komossa K, Heres S, Kissling W, Salanti G, Davis JM.Lancet. 2012 Jun 2;379(9831):2063-71. doi: 10.1016/S0140-6736(12)60239-6. Epub 2012 May 3.PMID: 22560607	Exclude – does not meet PICO
11	Standard versus reduced dose of antipsychotics for relapse prevention in multi-episode schizophrenia: a systematic review and meta-analysis of randomised controlled trials. Højlund M, Kemp AF, Haddad PM, Neill JC, Correll CU.Lancet Psychiatry. 2021 Jun;8(6):471-486. doi: 10.1016/S2215-0366(21)00078-X.PMID: 34023019	Exclude – does not meet PICO
12	Efficacy and safety of second-generation long-acting injections in schizophrenia: a meta-analysis of randomized-controlled trials. Fusar-Poli P, Kempton MJ, Rosenheck RA.Int Clin Psychopharmacol. 2013 Mar;28(2):57-66. doi: 10.1097/YIC.0b013e32835b091f.PMID: 23165366 Review.	Exclude – does not meet PICO
13	Benzodiazepines for schizophrenia. Volz A, Khorsand V, Gillies D, Leucht S.Cochrane Database Syst Rev. 2007 Jan 24;(1):CD006391. doi: 10.1002/14651858.CD006391.PMID: 17253592 Updated. Review.	Exclude – does not meet PICO
14	Antipsychotic dose reduction compared to dose continuation for people with schizophrenia. Rodolico A, Siafis S, Bighelli I, Samara MT, Hansen WP, Salomone S, Aguglia E, Cutrufelli P, Bauer I, Baeckers L, Leucht S.Cochrane Database Syst Rev. 2022 Nov 24;11(11):CD014384. doi: 10.1002/14651858.CD014384.pub2.PMID: 36420692	Exclude – does not meet PICO
15	Brexpiprazole for schizophrenia and as adjunct for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antipsychotic - what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? Citrome L.Int J Clin Pract. 2015 Sep;69(9):978-97. doi: 10.1111/ijcp.12714. Epub 2015 Aug 6.PMID: 26250067	Exclude – does not meet PICO
16	Long-Acting Injectable Second-Generation Antipsychotics vs Placebo and Their Oral Formulations in Acute Schizophrenia: A Systematic Review and Meta-Analysis of Randomized-Controlled-Trials. Wang D, Schneider-Thoma J, Siafis S, Burschinski A, Dong S, Wu H, Zhu Y, Davis JM, Priller J, Leucht S.Schizophr Bull. 2024 Jan 1;50(1):132-144. doi: 10.1093/schbul/sbad089.PMID: 37350486	Exclude – does not meet PICO
17	Low dose vs standard dose of antipsychotics for relapse prevention in schizophrenia: meta-analysis. Uchida H, Suzuki T, Takeuchi H, Arenovich T, Mamo DC.Schizophr Bull. 2011 Jul;37(4):788-99. doi: 10.1093/schbul/sbp149. Epub 2009 Nov 27.PMID: 19946012	Exclude – does not meet PICO
18	A systematic review of service-user reasons for adherence and nonadherence to neuroleptic medication in psychosis. Wade M, Tai S, Awenat Y, Haddock G.Clin Psychol Rev. 2017 Feb;51:75-95. doi: 10.1016/j.cpr.2016.10.009. Epub 2016 Oct 28.PMID: 27838461 Review.	Exclude – does not meet PICO
19	Long-acting injectable vs oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. Kishimoto T, Robenzadeh A, Leucht C, Leucht S, Watanabe K, Mimura M, Borenstein M, Kane JM, Correll CU.Schizophr Bull. 2014 Jan;40(1):192-213. doi: 10.1093/schbul/sbs150. Epub 2012 Dec 17.PMID: 23256986	Exclude – does not meet PICO
20	Maintenance treatment with antipsychotic drugs for schizophrenia. Leucht S, Tardy M, Komossa K, Heres S, Kissling W, Davis JM. Cochrane Database Syst Rev. 2012 May 16;(5):CD008016. doi: 10.1002/14651858.CD008016.pub2.PMID: 22592725 Updated. Review.	Exclude – does not meet PICO

21	Definitions and drivers of relapse in patients with schizophrenia: a systematic literature review. Olivares JM, Sermon J, Hemels M, Schreiner A.Ann Gen Psychiatry. 2013 Oct 23;12(1):32. doi: 10.1186/1744-859X-12-32.PMID: 24148707	Exclude – does not meet PICO
22	Iloperidone for schizophrenia: a review of the efficacy and safety profile for this newly commercialised second-generation antipsychotic. Citrome L.Int J Clin Pract. 2009 Aug;63(8):1237-48. doi: 10.1111/j.1742-1241.2009.02142.x.PMID: 19624791 Review.	Exclude – does not meet PICO
23	A meta-analysis of placebo-controlled trials of omega-3 fatty acid augmentation in schizophrenia: Possible stage-specific effects. Chen AT, Chibnall JT, Nasrallah HA.Ann Clin Psychiatry. 2015 Nov;27(4):289-96.PMID: 26554370	Exclude – does not meet PICO
24	Psychosis relapse during treatment with long-acting injectable antipsychotics in individuals with schizophrenia-spectrum disorders: an individual participant data meta-analysis. Rubio JM, Schoretsanitis G, John M, Tiihonen J, Taipale H, Guinart D, Malhotra AK, Correll CU, Kane JM.Lancet Psychiatry. 2020 Sep;7(9):749-761. doi: 10.1016/S2215-0366(20)30264-9.PMID: 32828165	Exclude – does not meet PICO
25	Antipsychotics for primary alcohol dependence: a systematic review and meta-analysis of placebo-controlled trials. Kishi T, Sevy S, Chekuri R, Correll CU.J Clin Psychiatry. 2013 Jul;74(7):e642-54. doi: 10.4088/JCP.12r08178.PMID: 23945459	Exclude – does not meet PICO
26	One year mirror-image study using paliperidone palmitate for relapse prevention of schizophrenia in four university hospitals in Canada. Vincent PD, Demers MF, Doyon-Kemp V, Duchesneau J, Halme A, Masson V.Schizophr Res. 2017 Jul;185:96-100. doi: 10.1016/j.schres.2017.01.013. Epub 2017 Jan 22.PMID: 28119036	Exclude – does not meet PICO

Study – Cochrane search		Inclusion/Exclusion
1	**Risperidone versus other atypical antipsychotics for schizophrenia** Katja Komossa, Christine Rummel-Kluge, Sandra Schwarz, Franziska Schmid, Heike Hunger, Werner Kissling, Stefan Leucht Review 19 January 2011	Exclude – NMA included
2	**Olanzapine versus other atypical antipsychotics for schizophrenia** Katja Komossa, Christine Rummel-Kluge, Heike Hunger, Franziska Schmid, Sandra Schwarz, Lorna Duggan, Werner Kissling, Stefan Leucht Review 17 March 2010	Exclude – NMA included
3	**Clozapine combined with different antipsychotic drugs for treatment-resistant schizophrenia** Sarah Barber[a], Uwaila Olotu[a], Martina Corsi, Andrea Cipriani Review 23 March 2017	Exclude – NMA included
4	**Risperidone (depot) for schizophrenia** Stephanie Sampson, Prakash Hosalli, Vivek A Furtado, John M Davis Review 14 April 2016	Exclude – NMA included
5	**Antipsychotic switching for people with schizophrenia who have neuroleptic-induced weight or metabolic problems** Anitha Mukundan, Guy Faulkner, Tony Cohn, Gary Remington Review 8 December 2010	Exclude – NMA included

6	**Ziprasidone versus other atypical antipsychotics for schizophrenia** Katja Komossa, Christine Rummel-Kluge, Heike Hunger, Sandra Schwarz, Paranthaman Sethupathi Bhoopathi, Werner Kissling, Stefan Leucht Review 7 October 2009	Exclude – NMA included
7	**Fluphenazine (oral) versus atypical antipsychotics for schizophrenia** James R Sampford, Stephanie Sampson, Bao Guo Li, Sai Zhao, Jun Xia, Vivek A Furtado Review 2 July 2016	Exclude – NMA included
8	**Aripiprazole versus typical antipsychotic drugs for schizophrenia** Jayanti Bhattacharjee, Hany G El-Sayeh Review 16 July 2008	Exclude – NMA included
9	**Atypical antipsychotics for psychosis in adolescents** Ajit Kumar, Soumitra S Datta, Stephen D Wright, Vivek A Furtado, Paul S Russell Review 15 October 2013	Exclude – NMA included
10	**Aripiprazole versus placebo for schizophrenia** Ravindra B Belgamwar, Hany George G El-Sayeh Review 10 August 2011	Exclude – active comparators included (below)
11	**Aripiprazole for schizophrenia** Hany George El-Sayeh, Carla Morganti Review 19 April 2006	Exclude – included above Cochrane vs atypical antipsychotics
12	**Amisulpride versus other atypical antipsychotics for schizophrenia** Katja Komossa, Christine Rummel-Kluge, Heike Hunger, Franziska Schmid, Sandra Schwarz, Joaquim I Silveira da Mota Neto, Werner Kissling, Stefan Leucht Review 20 January 2010	Exclude – NMA included
13	**Amisulpride for schizophrenia** Joaquim I Silveira da Mota Neto, Bernardo GO Soares, Mauricio Silva de Lima Review 22 April 2002	Exclude – NMA included
14	**Cannabis and schizophrenia** Benjamin C McLoughlin[a], Jonathan A Pushpa-Rajah[a], Donna Gillies, John Rathbone, Hannele Variend, Eliana Kalakouti, Katerina Kyprianou Review 14 October 2014	Exclude – Does not meet PICO
15	**Clozapine versus other atypical antipsychotics for schizophrenia** Claudia Asenjo Lobos, Katja Komossa, Christine Rummel-Kluge, Heike Hunger, Franziska Schmid, Sandra Schwarz, Stefan Leucht Review 10 November 2010	Exclude – NMA included
16	**Quetiapine versus other atypical antipsychotics for schizophrenia** Laila Asmal, Srnka J Flegar, Jikun Wang, Christine Rummel-Kluge, Katja Komossa, Stefan Leucht Review 18 November 2013	Exclude – NMA included
17	**Chlorpromazine versus atypical antipsychotic drugs for schizophrenia** Kumar B Saha, Li Bo, Sai Zhao, Jun Xia, Stephanie Sampson, Rashid U Zaman Review 5 April 2016	Exclude – NMA included
18	**Risperidone versus other antipsychotics for people with severe mental illness and co-occurring substance misuse** Henk S Temmingh, Taryn Williams, Nandi Siegfried, Dan J Stein	Exclude – NMA included

	Review 22 January 2018	
19	**Quetiapine versus typical antipsychotic medications for schizophrenia** Sirijit Suttajit, Manit Srisurapanont, Jun Xia, Siritree Suttajit, Benchalak Maneeton, Narong Maneeton Review 31 May 2013	Exclude – NMA included

Appendix 4: Previous review quetiapine (September 2016) and amisulpride (December 2009), and aripiprazole (2013)


Quetiapine_schiz_2016.pdf


Schiz Algorithm 2016.pdf


Amisulpride_review_N_december 2009.p


Amisupiride_summary_N1_December 20(


Aripiprazole submission_4N_07F

References

[1] Gardner DM Murphy AL, O'Donnell H, Centorrino F, Baldessarini RJ. International consensus study of antipsychotic dosing. American Journal of Psychiatry. 2010. 167(6): 686-693.

[2] Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, et.al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet. 2019. 394: 939-951.

[3] Khanna P, Suo T, Komossa K, Ma H, Rummel-Kluge C, El-Sayeh HG, Leucht S, Xia J. Aripiprazole versus other atypical antipsychotics for schizophrenia (Review). Cochrane Database of Systematic Reviews. 2014, issue 1, CD006569.

[4] Leucht S, Schneider-Thoma, Burschinslo A, Peter N, Wang D, Dong S, Huhn M, Nikolakopoulou A, Salanti G, Davis JM. Long-term efficacy of antipsychotic drugs in initially acutely ill adults with schizophrenia: systematic review and network meta-analysis. World Psychiatry. 2023, 22:315-324.

[5] Zhao YJ, Lin L, Teng M, Khoo AL, Soh LB, Furukawa TA, Baldessarini RJ, Lim BP, Sim K. Long-term antipsychotic treatment in schizophrenia:systematic review and network meta-analysis of randomised controlled trials. BJPsych Open, 2016, 2: 59-66.

[6] Burschinski A, Schneider-Thoma J, Chiocchia V, Schestag K, Wang D, Siafis S. Metabolic side effects in persons with schizophrenia during mid- to long term treatment with antipsychitics: a network meta-analysis of randomised controlled trials. World Psychiatry. 2023; 22:116-128