South African National Department of Health
Brief Report of Rapid Review
Component: Tertiary

TITLE: Quetiapine for 3rd Line Schizophrenia management

Date: May 2024

Also see review document: **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.**

Medicine (ATC): Quetiapine (N05AH04)
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
Level of Care: Tertiary and Quaternary Hospital Level
Prescriber level: Psychiatrist
Current Standard of Care/ Comparator(s): amisulpride

Key findings

- Quetiapine is currently not an EML approved medicine for the third-line management of schizophrenia, with price as a review indicator. Its associated price has since decreased resulting in this re-evaluation.
- Amisulpride is currently the recommended third-line treatment option in this setting where metabolic adverse events are of concern, and for patients with persistent negative symptoms.
- A network meta-analysis found similar outcomes in terms of mental status for quetiapine, aripiprazole and amisulpride with overlapping confidence intervals when comparing agents.[2]
- In terms of metabolic adverse effects, both quetiapine and amisulpride were inferior to aripiprazole, particularly in the context of metabolic adverse effects.[3]
- Quetiapine is similarly priced to aripiprazole on a per patient basis, however, aripiprazole is preferred ahead of quetiapine on account of the more favourable metabolic adverse event profile. The cost of amisulpride far exceeds the cost of both these agents.

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				

It is recommended that the decision to exclude quetiapine from the Essential Medicines List (EML) for the third-line management of schizophrenia be upheld.

Rationale: Even though quetiapine is similarly priced to aripiprazole, aripiprazole has similar efficacy and a more favourable side effect profile.

Level of Evidence: I (network meta-analyses of RCTs) – high to moderate quality

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

BACKGROUND

Quetiapine was identified as a possible item for re-evaluation and inclusion on the Tertiary/Quaternary EML as a third-line management option for refractory schizophrenia due to its significant decrease in price. An assessment of the approved agents for this setting was undertaken. Table 1 below indicates the previous reviews completed and associated recommendations:

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 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)	New evidence of efficacy in children and adolescents

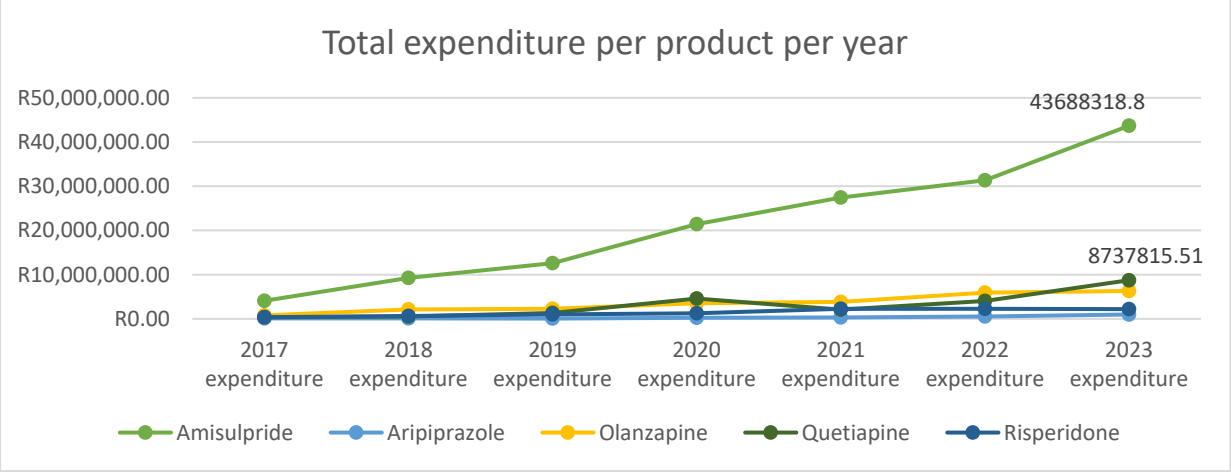
UTILISATION OF AMISULPRIDE, ARIPIPRAZOLE, QUETIAPINE

The utilisation of amisulpride, aripiprazole and quetiapine 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)



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, quetiapine and aripiprazole are approximately eight times less costly than amisulpride.

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*

Purpose/Objective i.e. PICO

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

-I *(intervention):* Quetiapine

-C *(comparator):* Amisulpride and Aripiprazole

-O *(outcome):*

- Mental state: positive and negative syndrome scale (PANSS)
- 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

See *'aripiprazole_May 2024 review' document for search results.* Two network meta-analyses (NMA) were included specifically for quetiapine compared to aripiprazole (Table 5): one evaluating the efficacy and tolerability of oral antipsychotics in acute treatment (Huhn et.al.) and one evaluating metabolic adverse events during mid- to long-term treatment of schizophrenia. A list of excluded studies is available in *'aripiprazole_May 2024 review'*. AMSTAR 2 assessments were undertaken on all selected NMAs.

Table 5: Summary of included studies.

Citation	Study design	Population (n)	Treatment	Quality (AMSTAR 2)
Huhn et.al. 2019[2]	Systematic Review and NMA of placebo controlled and head-to-head RCTs	402 studies in patients with acute symptoms of schizophrenia or related disorders	32 antipsychotics including amisulpride, aripiprazole and quetiapine	Moderate (excluded studies not outlined).
Burschinski et.al. 2023[3]	Network meta-analysis of randomised controlled trials (RCTs)	137 RCTs with 35007 participants with schizophrenia on long-term antipsychotics	31 antipsychotics including: amisulpride, aripiprazole and quetiapine	High

Quality and internal validity

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

- *Huhn et.al. was found to be Moderate Quality (excluded studies not outlined).*
- *Burschinski et.al. was found to be High Quality.*

EFFICACY IN SCHIZOPHRENIA

The previous review of quetiapine in 2016 (appendix 2) used a network meta-analysis (NMA) by Leucht et al. (2013)[4] to evaluate efficacy in terms of overall change in symptoms. The mean differences (MD) were as follows: amisulpride MD=0.66 (0.53 to 0.78); quetiapine MD = 0.44 (0.35 to 0.52); and aripiprazole MD = 0.43 (0.34 to 0.52).[4]

Updated mean differences versus placebo from the more recent NMA by Huhn et.al. 2019[2] are presented in Table 6. Aripiprazole and quetiapine are similar in efficacy for all mental status outcomes and have overlapping confidence intervals when compared to amisulpride for negative and depressive symptoms.

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

	Amisulpride (95% CI)	Aripiprazole (95% CI)	Quetiapine (95% CI)
Overall change in symptoms *(Standard mean differences)*	-0.73 (-0.89 to -0.58) N=705 Moderate certainty	-0.41 (-0.50 to -0.32) N = 1926 Low certainty	-0.42 (-0.50 to-0.33) N=3002 Moderate certainty
Positive symptoms *(Standard mean differences)*	-0.69 (-0.86 to -0.52) N=626 Moderate certainty	-0.38 (-0.48 to-0.28) N=1451 Low certainty	-0.40 (-0.49 to -0.31) N=2935 Moderate certainty
Negative symptoms *(Standard mean differences)*	-0.50 (-0.64 to-0.37) N=691 Moderate certainty	-0.33 (-0.41 to-0.24) N=1353 Low certainty	-0.31 (-0.38 to-0.24) N=2994 Moderate certainty
Depressive symptoms *(Standard mean differences)*	-0.44 (-0.60 to -0.28) N=663 High certainty	-0.24 (-0.34 to-0.13) N=1996 Low certainty	-0.40 (-0.69 to-0.10) N=150 High certainty

SAFETY – METABOLIC ADVERSE EVENTS

The network meta-analysis (Burschinski et.al.)[3] evaluating metabolic side effects in people with schizophrenia on mid- to long-term treatment found that quetiapine had more adverse effects compared to placebo compared to amisulpride or aripiprazole (Table 7).

Table 7. Metabolic adverse effects versus placebo

	Amisulpride (95% CI)	Aripiprazole (95% CI)	Quetiapine (95% CI)
Weight Gain (MD in kg)	1.43 (0.45 to 2.41) N=1000 Moderate confidence	0.41 (-0.40 to 1.28) N=2218 Low confidence	1.59 (0.79 to 2.42) N=2298 Moderate confidence
Fasting Glucose (MD in mg/kg)	1.85 (-1.89 to 5.64) N=234	0.35 (-2.40 to 3.28) N=617	3.14 (0.09 to 6.33) N=951
Total cholesterol (MD in mg/dl)	9.77 (-6.96 to 26.68) N=53	-0.75 (-4.90 to 3.21) N=1202	8.20 (3.33 to 13.30) N=1494
LDL cholesterol (MD in mg/dl)	9.72 (-6.90 to 26.88) N=52	-1.92 (-5.64 to1.96) n=1086	5.87 (1.33 to 10.51) N=881
HDL cholesterol (MD in mg/dl)	-5.24 (-8.94 to -2.05) N=53	0.71 (-0.76 to 1.98) N=1190	-1.59 (-2.91 to -0.27) N=1225
Triglycerides (MD in mg/dl)	38.98 (12.66 to 66.49) N=53	-1.07 (-12.26 to 9.87) N=1174	21.87 (7.79 to 35.81) N=1574

**all analysis versus placebo*
MD: mean difference
CINeMA added for primary outcome of weight gain

Favours antipsychotic	*Favours placebo*	*Neutral*

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 any other antipsychotics.

Quetiapine and aripiprazole were found to have similar pricing on a per patient basis, however aripiprazole was found to be superior in terms of adverse effect profile as compared to quetiapine, particularly regarding metabolic adverse effects.

It is thus recommended that the 2016 decision to exclude quetiapine from the Tertiary/Quaternary EML be upheld. It is further proposed that aripiprazole (based on the findings of the accompanying aripiprazole review document) be added to the management algorithm for schizophrenia in patients experiencing or at risk of metabolic adverse events from olanzapine, prior to consideration of amisulpride.

See management algorithm.

Reviewers: Jane Riddin, Lesley Robertson, Kim MacQuilkan, Roger Wiseman, Marc Blockman
Acknowledgment:
- Tertiary and Quaternary Expert Review Committee

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	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☒ Very low ☐	AMSTAR 2 - moderate quality. Low to moderate certainty (CiNeMA)
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☐ Small ☒ None ☐	Appear to have general comparative efficacy. No difference compared to each other.
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☒ Very low ☐	AMSTAR 2 – High quality. Low to moderate certainty (CiNeMA)
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge ☐ Moderate ☐ Small ☐ None ☐	Amisulpride and aripiprazole shown to have a better side effect profile in terms of metabolic adverse effects.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☐ Favours control ☐ Intervention = Control *or* Uncertain ☒	
FEASABILITY	**Is implementation of this recommendation feasible?** Yes ☐ No ☐ Uncertain ☒	

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
RESOURCE USE	**How large are the resource requirements?** More intensive: ☐ Less intensive: ☐ Uncertain: ☒	See costing tables at start of report.
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: 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

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[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] 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

[4] Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet. 2013, 382 (9896).