South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Mental Healthcare conditions

1. Executive Summary

Date: 13 June 2019
Medicine (INN): Olanzapine, oral
Medicine (ATC): N05AH03
Indication (ICD10 code): Schizophrenia and related disorders F20.0-20.9; F22.0-22.9; F25.0-25.9
Patient population: Adults
Prevalence of condition: Worldwide prevalence of Schizophrenia is approximately 1%
Level of Care: Secondary level of care (District and Regional Hospital level)
Prescriber Level: Specialist and Medical Officer under specialist guidance
Current standard of Care: 1st/ 2nd line, haloperidol, risperidone or chlorpromazine with addition of orphenadrine for neuroleptic induced parkinsonism; 2nd/ 3rd line, clozapine for poor response or amisulpiride at tertiary level for negative symptoms
Efficacy estimates: (preferably NNT):
Vs risperidone, NNT 25 (Odds ratio 0.78 (95% CI 0.62 to 0.98)) for discontinuation due to inefficacy (Komossa et al., 2010)[1]
Primary outcome:

- Change in PANSS rating scale score, standard mean difference [SMD] (95% CI)
  - vs placebo: SMD -0.59 (-0.65 to -0.53) (Leucht et al., 2013, network analysis)[2]
  - vs haloperidol: SMD –0.17 (–0.24 to –0.10) (Leucht et al., 2013, pairwise analysis)[2]
  - vs risperidone: SMD -1.94 (-3.31 to -0.58) (Komossa et al., 2010);[1] SMD -0.30 (-0.56 to -0.04) for negative symptoms and SMD -0.32 (-0.57 to -0.06) for positive symptoms in patients with prominent negative s(Krause et al., 2018)[3]
  - vs clozapine: not significant (Komossa et al., 2010)[1]
  - vs amisulpiride: not significant (Komossa et al., 2010)[1]

Motivator/reviewer name(s): Dr L. Robertson, Dr H Dawood
PTC affiliation: Gauteng Provincial PTC, Sedibeng District PTC

PANSS=Positive and negative Syndrome Scale

2. Name of author(s)/motivator(s)

Primary reviewer: Dr Lesley Robertson
Secondary reviewer(s): Dr Halima Dawood

3. Author affiliation and conflict of interest details

- Dr Lesley Robertson: Affiliated to the University of the Witwatersrand, the South African Society of Psychiatrists, Adult Hospital Level Committee member (2017-2020). Conflict of interests: Dr Reddys: Annual congress attendance and accommodation, 2014 – 2019; AstraZeneca: Lunch 25 July 2017; Sanofi: Lunch 21 March 2018; Lundbeck: Lunch 29 January 2019.
  Note: Dr Lesley Robertson recused from the final decision-making process regarding a recommendation.
- Dr Halima Dawood: Greys hospital, KZN Department of health; Caprisa, UKZN; Member of the Adult Hospital Level Committee; potentially significant conflict of interest (MSD: ECMID 2018 - Conference attendance; ACTA study - DSMB member (crypto meningitis); Adcock Ingram - HIV discussion with general practitioners).

4. Introduction/Background

Schizophrenia is a heterogenous condition, requiring individualised treatment according to predominant symptoms, response to medication, tolerability, and mental and physical comorbidities.[4] The current standard of care for acute psychotic episodes in schizophrenia includes haloperidol, risperidone, and chlorpromazine. The addition of orphenadrine is recommended for neuroleptic induced parkinsonism, and propranolol for akathisia. Clozapine is recommended for treatment resistance.

While clozapine is still the most efficacious antipsychotic in the treatment of schizophrenia, it requires regular monitoring for neutropenia, which is costly and inconvenient. Olanzapine is structurally similar to clozapine with affinity to dopaminergic, serotonergic, muscarinic, adrenergic and histaminergic binding sites. Expert opinion[4] suggests that olanzapine may be more effective than other antipsychotic medicines (except clozapine), based on the significantly lower discontinuation rates with olanzapine vs other antipsychotics in the CATIE trial and the results of recent meta-analyses.

In comparison to other medicines on the EML for schizophrenia, at lowest target doses according to Leucht et al.[2], olanzapine is more costly than haloperidol and risperidone but cheaper than chlorpromazine and clozapine (Table 1). However, if orphenadrine is added to haloperidol or risperidone to mitigate extra-pyramidal side effects, then olanzapine is less expensive or roughly equivalent in cost, even if metformin is added for olanzapine-induced obesity or hyperglycaemia.

Table 1. Cost comparison of olanzapine vs standard care antipsychotics and medicines for adverse effects

Contract circular RT289-2019 prices (average weighted prices used as required [5]		**Dosing (Leucht et al., 2013)[2]**
Antipsychotics	**Cost/month (30 d)**	
Haloperidol 5mg tablet, 28 tablets	R 8.92 – R 17.83	5 – 10mg / day
Risperidone 2mg tablet, 28 tablets	R 10.96	4 mg/day
Risperidone 3mg, 28 tablets	R 13.61	6 mg/day
Chlorpromazine 100mg tablet, 84 tablets	R 85.05 – R 170.11	300 – 600 mg/day
Olanzapine 10mg tablet, 28 tablets	R 24.03 – R 48.06	10 – 20mg/day
Clozapine 100mg tablet, 84 tablets	R 83.66 – R 209.14	200 – 500 mg/ day
Amisulpiride 200mg tablet, 28 tablets (TQEML only)	R 199.24 – R 398.49	400 – 800 mg/day
Medicines for neuroleptic induced adverse effects	**Cost/month**	**Dosing (Total daily dose, Adult Hospital STGs)**
Orphenadrine 50mg tablet, 56 tablets	R 36.97 – 55.46	100 – 150 mg/day
Propranolol 10mg tablet, 84 tablets	R 8.22	20 mg/ day
Propranolol 40mg tablet, 84 tablets	R 6.67 –40.02	40 – 240mg/ day
Metformin 500mg tablet, 56 tablets	R 8.66	1000mg/ day

5. Purpose/Objective

To review the evidence for olanzapine in the treatment and prevention of psychosis in schizophrenia

- P: Patients with schizophrenia and related disorders

- **I**: Olanzapine

- **C**: other antipsychotics on the NEML for schizophrenia: haloperidol, chlorpromazine, risperidone, clozapine, amisulpiride (TQEML)

- **O**: efficacy: improvement in rating scale; discontinuation due to inefficacy; tolerability: adverse events

6. Methods

Search strategy:

To obtain recent evidence, Pubmed and Cochrane databases were searched on 21/05/2019 for systematic reviews and meta-analyses in English published in the preceding 10 years (since 24/05/2009) using search terms olanzapine AND schizophrenia. The full search strategy and results are attached in Appendix I (Pubmed) and II (Cochrane).

The following studies were included for decision-making:

Author and Title	**Comments**	**Funding source**
Leucht et al., 2013[2] Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis	Indirect and direct comparisons AMSTAR 10/11 No list of excluded studies	None
Komossa et al. 2010[1] Olanzapine versus other atypical antipsychotics for Schizophrenia	Cochrane review Direct comparisons with other SGAs for efficacy and tolerability AMSTAR 11/11	Bundesministerium für Bildung und Forschung, Nr FKZ: 01 KG 0606, GZ:GF-GFKG01100506, Germany
Krause et al., 2018[3] Antipsychotic drugs for patients with schizophrenia and predominant or prominent negative symptoms: a systematic review and meta-analysis	Direct comparisons regarding effect on negative symptoms AMSTAR 10/11 No list of excluded studies	Bundesministerium für Bildung und Forschung, BMBF, Grant Number FKZ 01KG1508 (German Federal Ministry of Education and Research)

Two other Cochrane reviews identified were *Jayaram et al., 2006 Risperidone versus olanzapine for schizophrenia*[6] and *Duggan et al., 2005 Olanzapine for schizophrenia*.[7] These were not included as their findings have been updated by Leucht et al., 2013, Krause et al., 2018, and Komossa et al., 2010.

Evidence synthesis:

1. Leucht et al., 2013[2]

Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis

Network Meta-analysis: AMSTAR 10/11 (No list of excluded studies)
Included 212 trials (n=43 049); evaluated effects of acute treatment (note, did not evaluate effect on negative symptoms or on depression)

Outcome measures
Efficacy: Change in rating scale (PANSS or BPRS)
Acceptability: All-cause discontinuation
Tolerability: Weight gain, EPSE, Prolactin increase, QTc prolongation, Sedation

Results

<u>Efficacy vs other antipsychotic, on network analysis</u>
<u>Standardised mean difference, SMD (95% CI) in rating scale change</u>

Olanzapine superior to haloperidol and chlorpromazine;
clozapine superior to olanzapine

Vs chlorpromazine: **–0·18 (–0·34 to –0·02)**
Vs haloperidol: **–0·11 (–0·18 to –0·05)**
Vs risperidone: –0·03 (–0·10 to 0·04) NS
Vs amisulpiride: 0·07 (–0·05 to 0·19) NS
Vs clozapine**: 0·29 (0·14 to 0·44)**

<u>Efficacy vs other antipsychotics on pairwise analysis</u>
<u>Standardised mean difference, SMD (95% CI) in rating scale change</u>

Olanzapine superior to haloperidol (no RCTs with chlorpromazine)

Vs haloperidol (11 RCTs, n=3202): **–0.17 (–0.24 to –0.10)**
Vs risperidone (10 RCTs, n=1786): –0.05 (–0.14 to 0.05) NS
Vs amisulpiride (5RCTs, n=662): 0.03 (–0.33 to 0.38) NS
Vs clozapine (2 RCTs, n=104): –0.08 (–0.46 to 0.31) NS

<u>Efficacy vs placebo on network analysis, SMD (95% CI) in rating scale change</u>

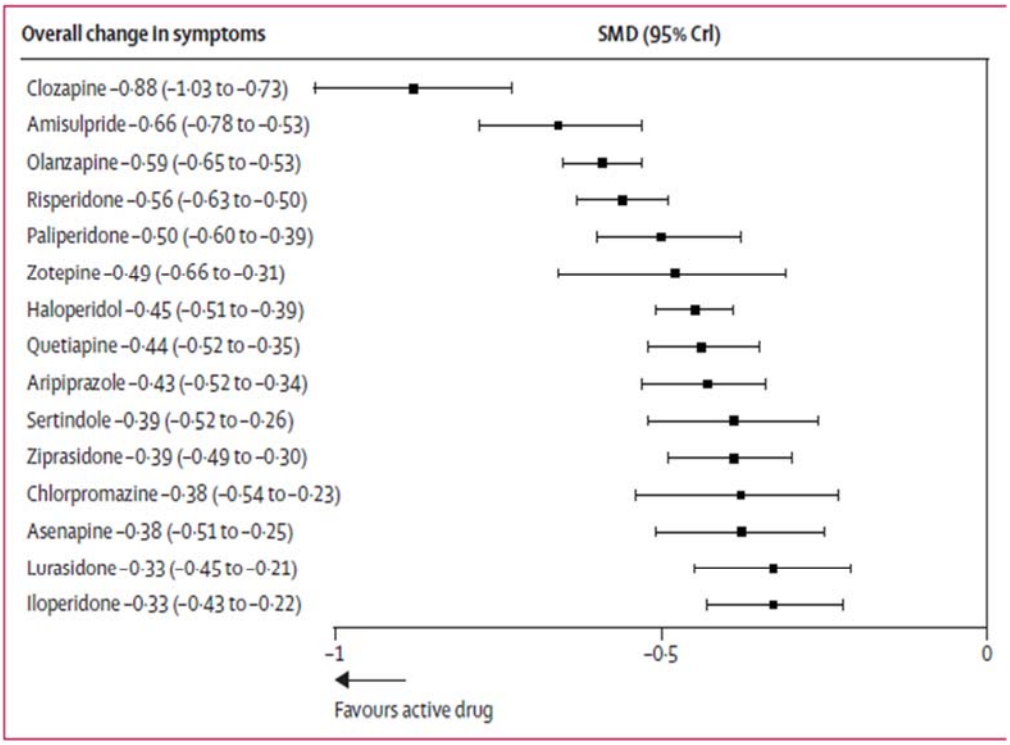

***Figure 3*: Forest plot for efficacy of antipsychotics drugs compared with placebo**
Treatments are ranked according to their surface under the cumulative ranking (SUCRA) values (appendix p 98).
SMD=standardised mean difference. CrI=credible interval.

Acceptability and tolerability vs placebo

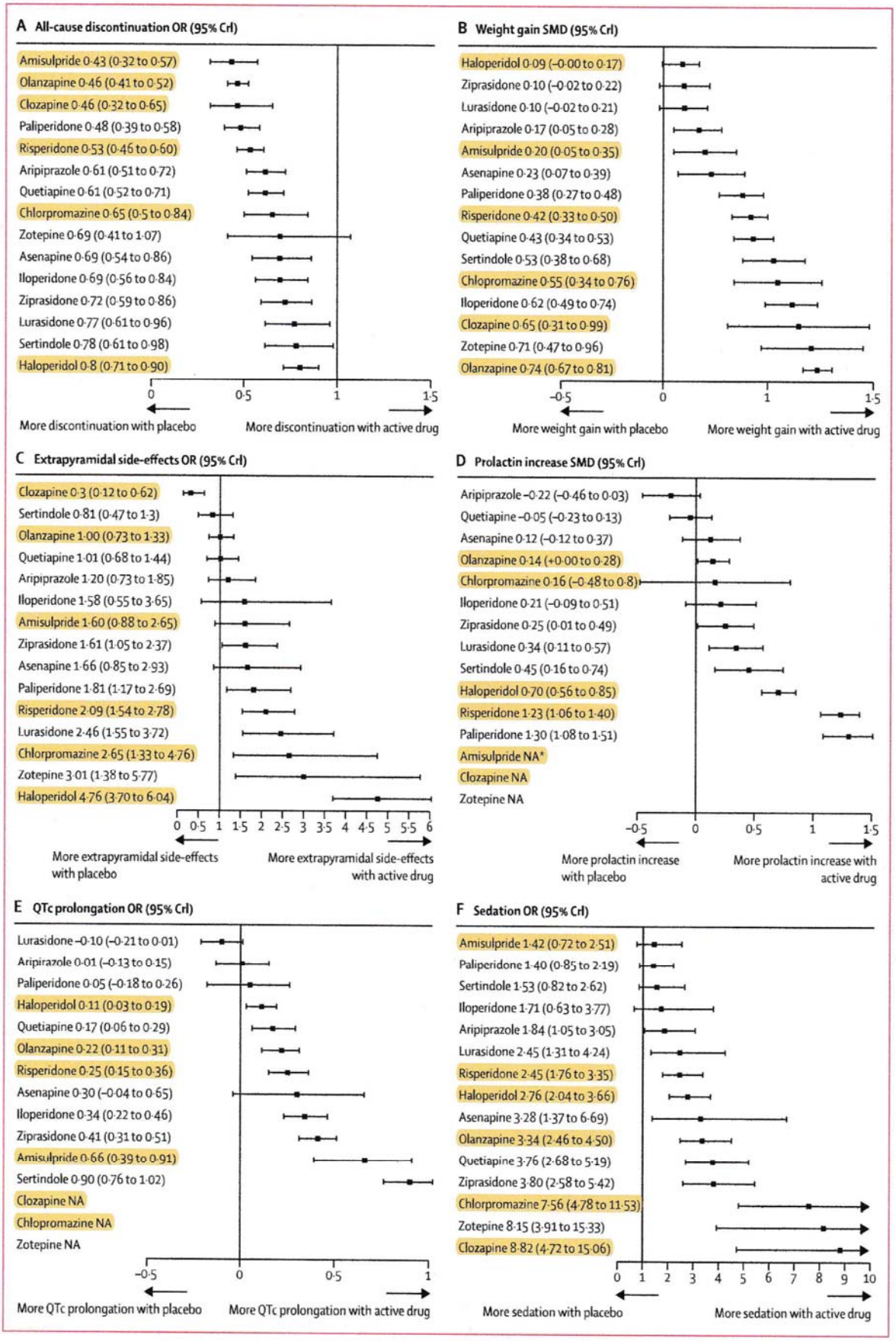

Figure 4: **Forest plots for effect sizes of antipsychotic drugs compared with placebo for secondary outcomes**
Results are shown for all-cause discontinuation (A), weight gain (B), extrapyramidal side-effects (C), prolactin increase (D), QTc prolongation (E), and sedation (F). Treatments are ranked according to their surface under the cumulative ranking (SUCRA) values (appendix pp 97–104). Extrapyramidal side-effects are defined by at least one use of antiparkinson drugs. OR=odds ratio. CrI=credible interval. SMD=standardised mean difference. *In one small study,[43] amisulpride (mean 473 mg per day) produced less prolactin increase than haloperidol (mean 28 mg per day), but prolactin concentrations were highly imbalanced at baseline, so we excluded this result (inclusion of this study in the analysis did not affect the ranking of the other drugs).

2. Komossa et al. 2010[1]
Olanzapine versus other atypical antipsychotics for Schizophrenia

Cochrane Review: AMSTAR 11/11

Included 50 trials (n=9476) with 6 comparisons. For this review, comparisons between olanzapine and risperidone, clozapine and amisulpiride (on TQEML for treatment resistant negative symptoms) are reported on.

Outcome measures

Efficacy: Improvement in general mental state on PANSS score; drop-outs due to inefficacy

Tolerability: Adverse effects of EPSE, Prolactin increase weight gain, glucose, cholesterol, seizures, low white blood cell count

Efficacy: improvement in PANSS score weighted mean difference [WMD] (95% CI)	**Efficacy: drop-outs due to inefficacy Risk ratio [RR] (95% CI)**
Vs risperidone (15RCTs, n=2390): **-1.94 (-3.31 to -0.58)**	Vs risperidone (14RCTs, n=2744): **0.78 (0.62 to 0.98), NNT 25**
Vs clozapine (7RCTs, n=618): -1.97(-4.66 to 0.71) NS	Vs clozapine (10RCTs, n=1674): 1.38 (0.77 to 2.47) NS
Vs amisulpiride (3RCTs, n=701): WMD -1.57 (-6.09, 2.94) NS	Vs amisulpiride (4RCTs, n=724): 0.84 (0.50 to 1.40) NS

Adverse effects

Comparator	EPSE (use of antiparkinson medicine), Risk ratio (95% CI)	Prolactin change in ng/ml, WMD (95% CI)
Vs risperidone	13 RCTs (n=2599): **0.78 (0.65 to 0.95), NNH -20**	6 RCTs (n=1291): **-22.84ng/ml (-27.98 to -17.69)**
Vs clozapine	6 RCTs (n=561): 1.14 (0.60 to 2.19) NS	1 RCT (n=120): 0.57 (0.09 to 1.05) NS
Vs amisulpiride	1 RCT (n=377): 0.66 (0.37 to 1.17) NS	Amenorrhoea, galactorrhoea, sexual dysfunction all NS
	Weight gain, change in kg, WMD (95% CI)	Weight gain, Risk ratio (95% CI)
Vs risperidone	13 RCTs (n=2116): **2.61kg (1.48 to 3.74)**	11 RCTs (n=2594): **1.81 (1.39 to 2.35) NNH 8**
Vs clozapine	7 RCTs (n=581): 0.04 kg (-0.97 to 1.06) NS	7 RCTs (n=1600): 1.13 (0.70 to 1.81) NS
Vs amisulpiride	3 RCTs, (n=672): **2.11 kg (1.29 to 2.94)**	3 RCTs, (n=672): **1.83 (1.34 to 2.50); NNH 8**
	Glucose, change in mg/dl, WMD (95% CI)	Cholesterol, change in mg/dl, WMD, 95% CI
Vs risperidone	7 RCTs (n=1201):**7.58mg/dl (3.93 to 11.23)**	7 RCTs (n=1391):**10.36mg/dl (6.28 to 14.43)**
Vs clozapine	3 RCTs (n=89): -2.62mg/dl (-16.34 to 11.09) NS	3 RCTs (n=89): 1.16mg/dl (-17.52 to 19.85) NS
Vs amisulpiride	2 RCTs (n=406): **7.30mg/dl (6.99 to 7.62)**	1 RCT (n=85): 3.42mg/dl (-5.48 to 12.32) NS
	Seizures, Risk ratio (95% CI)	Significantly low WCC, Risk ratio (95% CI)
Vs risperidone	4 RCTs (n=671): 3.82 (0.43 to 34.35) NS	3 RCTs (n=484): 1.00 (0.09 to 10.59) NS
Vs clozapine	4 RCTs (n=1097): **0.15 (0.04 to 0.58), NNH -38**	4 RCTs (n=1264): **0.18 (0.08 to 0.41), NNH -18**
Vs amisulpiride	1 RCTs (n=210): 1.51 (0.06 to 36.61) NS	1 RCT (n=210): 2.52 (0.12 to 51.74) NS

3. Krause et al., 2018[3]

Antipsychotic drugs for patients with schizophrenia and predominant or prominent negative symptoms: a systematic review and meta-analysis

Systematic review and pairwise meta-analysis: AMSTAR 10/11 (no list of excluded studies)

Included 21 trials (n=3451); evaluated effects of acute treatment

Outcome measures

Efficacy: mean change from baseline to endpoint in negative symptoms of schizophrenia as measured by negative subscales

Results

Subgroup with predominant negative symptoms (little or no positive symptoms), change in rating scale standardised mean difference [SMD] (95% CI)

RCTs	Negative symptoms	Depression	Positive symptoms
Vs placebo (1 RCT, n=104)	SMD 0.03 (-0.38 to 0.44)	SMD -0.23 (-0.64 to 0.18)	SMD -0.32 (-0.73 to 0.09)
Vs haloperidol (1 RCT, n=35)	**SMD -0.75 (-1.44 to -0.06)**	SMD -0.33 (-1.00 to 0.34)	SMD -0.45 (-1.12 to 0.23)
Vs amisulpiride (1 RCT, n=140)	SMD 0.06 (-0.27 to 0.39)	SMD -0.08 (-0.41 to 0.26)	SMD -0.19 (-0.52 to 0.14)

Subgroup with prominent negative symptoms (also have positive symptoms), change in rating scale standardised mean difference [SMD] (95% CI)

RCTs	Negative symptoms	Depression	Positive symptoms
Vs risperidone (1 RCT, n=235)	**SMD -0.30 (-0.56 to -0.04)**	Not estimable	**SMD -0.32 (-0.57 to -0.06)**

7. Alternative agents

Amisulpiride (TQEML) – for poor response of negative symptoms in patients with predominant negative symptoms

Clozapine – for poor response or tolerability to olanzapine or amisulpiride

8. Interpretation of the evidence and comments

On network analysis, it has evidence of superior efficacy to haloperidol and chlorpromazine. Only clozapine is more efficacious than olanzapine. In direct comparisons it has evidence of superiority to haloperidol in general (Leucht et al., 2013) and in patients with predominant negative symptoms (single small RCT in Krause et al., 2018). There are no direct comparisons between olanzapine and chlorpromazine. Although no significant difference is found between olanzapine and risperidone on network analysis, direct comparisons in Krause et al. and Komossa et al suggest olanzapine may be more effective in selected patients.

The choice of treatment also depends on adverse effects. Olanzapine has a low risk of extra-pyramidal side effects. It would thus be more cost-effective than adding an anticholinergic medicine, if the metabolic risks of olanzapine are acceptable.

Clozapine carries the same metabolic risk as olanzapine, has the additional risk of agranulocytosis, and may convey a higher risk of seizures.

Olanzapine is thus proposed as a cost-effective option in the treatment algorithm for schizophrenia for poor response or tolerability to haloperidol, risperidone, and/or chlorpromazine. Its use would be prior to a trial of clozapine (for treatment resistance in general) or amisulpiride (for treatment resistant negative symptoms).

References

1. Komossa K, Rummel-Kluge C, Hunger H, Schwarz S, Schmidt F, Lewis R, et al. Sertindole versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev. 2007;(3). DOI: 10.1002/14651858.CD006654.pub2.
2. Leucht S, Cipriani A, Spineli L, Mavridis D, Örey D, Richter F, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: A multiple-treatments meta-analysis. Lancet. 2013;382(9896):951–62. DOI: 10.1016/S0140-6736(13)60733-3
3. Krause M, Zhu Y, Huhn M, Schneider-Thoma J, Bighelli I, Nikolakopoulou A, et al. Antipsychotic drugs for patients with schizophrenia and predominant or prominent negative symptoms: a systematic review and meta-analysis. Eur Arch Psychiatry Clin Neurosci [Internet]. 2018;268(7):625–39. DOI: 10.1007/s00406-018-0869-3
4. Smith RC, Leucht S, Davis JM. Maximizing response to first-line antipsychotics in schizophrenia: a review focused on finding from meta-analysis. Psychopharmacology (Berl). 2019;236(2):545–59. DOI: 10.1007/s00213-018-5133-z
5. National Department of Health. Contract circular RT289-2019
6. Jayaram M, Hosalli P. Risperidone versus olanzapine for schizophrenia. Cochrane Database Syst Rev. 2005;(2). DOI: 10.1002/14651858.CD005237.pub2.
7. Duggan L, Fenton M, Dardennes R, El-Dosoky A, Indran S. Olanzapine for schizophrenia. Cochrane Database Syst Rev. 2003;(2). DOI: 10.1002/14651858.CD001359.pub2.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [X] Not confident [ ] Uncertain [ ]	Network meta-analyses; Systematic reviews of RCTs of low to moderate quality (disease-oriented outcomes).
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [ ] No [X] List the members of the group.	
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	
RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [ ] Uncertain [x]	Cost of medicines: See table 1 above. **Additional resources:** n/a
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [X] Uncertain [ ]	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes [X] No [ ] Uncertain [ ]	

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☐	X	☐

Recommendation

Based on the evidence review, the Adult Hospital Level Committee recommends that olanzapine be used as 2nd or 3rd line treatment according to clinical judgement following haloperidol, risperidone and /or chlorpromazine in patients with schizophrenia, prior to consideration of clozapine (for treatment resistance in general) or amisulpiride (for treatment resistant negative symptoms).

Rationale: Evidence suggests that olanzapine is more efficacious than haloperidol and chlorpromazine; and more efficacious than risperidone in select patients. Choice of treatment is also dependant on adverse effects – extra-pyramidal effects greater with haloperidol; metabolic risk associated with clozapine and olanzapine and clozapine has the additional risk of agranulocytosis, and may convey a higher risk of seizures. **Level of Evidence: II, network meta-analysis and systematic reviews of RCTs of low-moderate quality.**

NEMLC MEETING OF 11 JULY 2019:

NEMLC accepted the proposal as recommended by the Adult Hospital Level Committee (see above).

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
	X	

VEN status:

Vital	Essential	Necessary
	X	

Monitoring and evaluation considerations

Research priorities