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

MEDICINE REVIEW

1. Executive Summary

Date: 14 March 2019
Medicine (INN): Clozapine
Medicine (ATC): N05AH02
Indication (ICD10 code): Bipolar Disorder, treatment and prevention of relapse into any episode in treatment resistant patients, defined as a failure of two trials of dissimilar treatments in adequate dosage and duration (F31.0-.9)
Patient population: Adults
Prevalence of condition: Worldwide prevalence 2-3%
Level of Care: Secondary level of care (District and Regional Hospital level)
Prescriber Level: Specialist
Current standard of Care: Lithium and/or valproate or lamotrigine and/or risperidone or olanzapine or quetiapine
Efficacy estimates: (preferably NNT) Not available
Primary outcome: Improvement in symptoms, reduced hospitalisation
Motivator/reviewer name(s): Dr L. Robertson
PTC affiliation: Gauteng Provincial PTC, Sedibeng District PTC

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

Dr Lesley Robertson

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 was recused from the final decision-making process regarding a recommendation.

4. Introduction/Background

BD is a chronic relapsing illness with severe behavioural disturbance, with its onset in youth and persisting throughout life.[1-3] It requires treatment of acute episodes and prevention of relapse. Lithium is the treatment of choice but may not be well-tolerated and may not be adequately efficacious. There is a limited range of other effective medications, either as alternatives or as adjunctive to lithium.

Treatment resistance has been defined as a failure to respond to two trials of dissimilar treatments in adequate dosage and duration.[3] A small percentage, possibly <2%, of BD patients could be expected to be resistant to current treatment with agents on the NEML.

5. Purpose/Objective

To review the evidence of clozapine in the management of treatment-resistant BD (TRBD)
- **P:** Patients with bipolar disorder
- **I**: Clozapine
- **C**: Lithium/ valproate/ alternative antipsychotic
- **O**: Reduction in symptoms and prevention of relapse into any episode

6. Methods

Search strategy:
As described in attached overview of BD

Evidence synthesis:

a) **Butler et al. (2018).[1] Treatment for Bipolar Disorder in Adults: A Systematic Review**
No eligible studies for clozapine or TRBD

b) **Miura et al. (2014)[2] Network meta-analysis of 33 RCTs (N=6846) for maintenance treatment**
No eligible studies for clozapine or TRBD

c) **Li et al. (2015) Clozapine for treatment-resistant bipolar disorder: a systematic review**
Systematic review of 'all types of trials.' Comprehensive search of Pubmed, Embase, Cochrane Library, Cochrane Controlled Trials Register, Chinese databases and citations yielded 15 trials with 1044 participants.

Table 1. Efficacy in treatment-resistant BD

RCTS	Retrospective studies	Open-label prospective trials
1999 **N=38 (26 with BD, 12 with SAD)** Clozapine vs TAU: Significant improvement in clozapine group in all measures except depression, plus reduced total medicine usage over one year No difference in physical symptoms/ adverse effects.	**1991** **N=78 poorly responsive to existing treatment (14 with psychotic BD, 25 with SAD, 39 with schizophrenia)** Positive response rates better for those with BD: 43% of BD, 15-20% of SAD, 10% of schizophrenia	**5 long-term trials, conducted between 1994 to 2003, N=403 (147 with BD, 137 SAD, 105 schizophrenia, 14 unipolar depression), trial duration ranged from 16 – 60 months** Overall results: Reduction in hospitalisation (2 trials, N=24) Improvement in symptoms and psychosocial functioning (all trials) BD and SAD showed greater improvements than schizophrenia **5 short-term trials, between 1994 and 2005, N=86 (all TRBD, 5 children and adolescents), trial duration from 2 – 13months.** Overall results indicate improvement in symptoms in over half of participants
2010 **N=71 with TRBD** Clozapine + lithium significantly better than clozapine + valproate ($p<0.05$) No difference in adverse effects	**2006** **N=51 with TRBD treated with add-on clozapine > 6months** Reduced total number and hospitalisations/ year. Hospitalisations reduced for manic, hypomanic and depressive episodes	
	2012 **2-year mirror-image pharmaco-epidemiological database study** **N=326 BD on clozapine (1.5% of total sample)** Clozapine vs pre-clozapine periods: Mean hospital admissions reduced from 3.2 to 2 Mean bed-days reduced from 179 to 35 Reduced co-psychotropic prescription from 4.5 DDD to 3.9 DDD Reduced intentional self-harm hospital visits from 8% to 3%	

TAU=treatment as usual; SAD=schizoaffective disorder

Adverse effects were similar to those found in schizophrenia trials. Reported severe adverse effects were leucopenia (2%), agranulocytosis (0.3%) and seizures (0.5%). Clinically significant side effects included sedation (12%), constipation (5%), sialorrhea (5%), weight gain (4%), and body aches and pains (2%). Although adverse effects may have been under-reported, there were no cases where discontinuation of clozapine was necessary.

7. Alternative agents

None: The adverse effect profile of clozapine means that it is not used unless there is evidence of treatment resistance to two adequate trials of established medication.

Interpretation of the evidence and comments

There is very limited evidence (LoE III) from RCTs with small samples, retrospective studies, and prospective open-label studies, that clozapine may be effective and safe in TRBD.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident: [ ] Not confident: [X] Uncertain: [ ]	Systematic review of low quality RCTs and observational studies.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms: [ ] Harms outweigh benefits: [ ] Benefits = harms or Uncertain: [ ]	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes: [ ] No: [X]	
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/ month (30 d): **Medicine** | **Price (ZAR)** Clozapine 100 to 400 mg daily | 35.14 to 140.54 *Contract circular RT289-2019 (Accessed June 2019) **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 this evidence review, the Adult Hospital Level Committee recommends that clozapine be recommended for treatment refractory bipolar disorder.

Rationale: Limited evidence of efficacy suggest that clozapine is safe and efficacious for treatment resistant bipolar disorder.

Level of Evidence: II Systematic review of low quality RCTs and observational studies

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
	X	

VEN status:

Vital	Essential	Necessary
	X	

NEMLC MEETING OF 11 JULY 2019:

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

Monitoring and evaluation considerations

Research priorities

References:

1. Butler M, Urosevic S, Desai P, Sponheim SR, Popp J, Nelson VA, et al. Treatment for Bipolar Disorder in Adults: A Systematic Review. AHRQ Comparative Effectiveness Reviews. Rockville (MD)2018,
2. Miura T, Noma H, Furukawa TA, Mitsuyasu H, Tanaka S, Stockton S, et al. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. Lancet Psychiatry. 2014;1(5):351-9.10.1016/S2215-0366(14)70314-1
3. Li XB, Tang YL, Wang CY, de Leon J. Clozapine for treatment-resistant bipolar disorder: a systematic review. Bipolar disorders. 2015;17(3):235-47.10.1111/bdi.12272