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): Olanzapine, oral
Medicine (ATC): N05AH03
Indication (ICD10 code): F31.1, F31.2, F31.7, Bipolar I Disorder (BD-I) treatment and prevention of mania, 3rd line treatment as a safe and effective alternative to lithium and valproate.
Patient population: Adults
Prevalence of condition: Worldwide prevalence of BD-I 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: Risperidone, oral (acute treatment); lithium and/or valproate (acute and maintenance treatment). Olanzapine + fluoxetine is current standard of care for acute treatment of depression.
Efficacy estimates: (preferably NNT)
Acute mania, NNT 6 (Butler et al., 2018)[1]
Prevention of mania, NNT 5 (RCT events as reported in Miura 2014)[2]
Primary outcome:

- *Acute treatment of mania*: Response rate (>50% reduction in YMRS) *and* significant mean difference in change of mania scale score, both at 3 weeks
  - vs placebo (Butler, 2018, 5 RCTs N=1199): NNT 6; pooled result random effects model OR 1.99 (95% CI 1.29 to 3.08); Mean difference in change of YMRS 4.9 (95%CI 2.34, 7.45)
  - vs valproate (Butler, 2018): Non-significant
- *Maintenance treatment:* Relapse of mania/ hypomania
  - vs placebo (Miura, 2014): Risk Ratio 0·35 (95%CI 0·25 to 0·50) on network meta-analysis; NNT 5
  - vs lithium (Lindstrom, 2017)[3]: Risk Ratio 0.59 (95% CI 0.39 to 0.89); NNT 11
  - vs valproate (Lindstrom, 2017): Non-significant, Risk Ratio 1.26 (95% CI 0.35 to 4.58) NNT -121
  - vs risperidone LAI (RCT events in Miura, 2014; log-rank in Butler, 2018): NNT 7 for any mood episode, NNT 70 for mania, NNT 10 for depression; Post-hoc Log-rank favors olanzapine p=0.001 for any mood episode.

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

LAI=long-acting injection; YMRS=young mania rating scale

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
As the treatment of acute episodes in BD-I is often continued into maintenance care, it should be informed by evidence for prevention of relapse and side effect burden in long-term treatment. Lithium is proposed as 1st line treatment in acute manic episodes and prevention of mania.[4,5] However, an alternative medicine is needed where laboratory facilities are not accessible and reliable, for non-responders, poor tolerability, if the risk of teratogenicity and neonatal adverse effects are unacceptable, and if the risk of toxicity or non-adherence preclude its use.

Valproate, current standard of care in maintenance treatment of BD, is 2nd line option in treatment and prevention of mania. However, its evidence of efficacy is largely from its use as an active control in RCTs and from observational studies. Network meta-analysis shows efficacy vs placebo in prevention of any mood episode but not mania or depression.[2] There is a need for a 3rd line option for non-responders, poor tolerability to valproate, and for women in the reproductive age-group.

Olanzapine, in combination with fluoxetine, is current standard of care for acute depression. However, it has a stronger evidence base for treatment and prevention of mania than for depression.[1] The adverse effects of olanzapine differ from those of lithium, making it a viable alternative in patients with renal dysfunction or at risk of lithium toxicity. Weight gain is the predominant adverse effect of olanzapine, and possibly hypertension and Type2 Diabetes.[6] A population cohort study in the UK found olanzapine to be associated with >15% weight gain HR 1.84 (95% CI 1.47–2.30; $p < 0.001$) and with hypertension HR 1.41 (95% CI 1.06–1.87; $p = 0.017$) but not with Type2DM during maintenance treatment.[7]

Olanzapine is not classified as a teratogen and has been used safely for prevention of relapse in pregnancy.[8] A risk of gestational diabetes has been documented but may be related to confounding factors and risks inherent to bipolar disorder rather than olanzapine.[9] As with other SGAs in pregnancy, it has been associated with transient neurodevelopmental delay in children exposed in utero (resolved by 12 months).[10]

5. Purpose/Objective

To review the evidence of olanzapine in the treatment and prevention of mania in BD
- P: Patients with bipolar disorder
- **I**: Olanzapine
- **C**: Lithium/ valproate
- **O**: Response rate (>50% reduction in symptoms) and mean difference in change of mania symptom scores; time to recurrence and relapse rate

6. Methods

Search strategy:

- As described in the attached overview of BD.
    - Evidence for this review taken from Butler et al (2018),[1] Miura et al. (2014),[2] Lindstrom et al. (2017),[3] and Kessing et al (2017).[4]

- To ensure no recent studies on alternative medicines as monotherapy in maintenance treatment of bipolar disorder were missed, a second Pubmed search was conducted on 04/05/2019 using search terms “lithium, carbamazepine, lamotrigine, valproate, clozapine, olanzapine, quetiapine, risperidone, antidepressants” AND “bipolar disorder” AND “maintenance OR long-term OR relapse OR recurrence OR hospitalisation” for any papers published in English since 01/01/2017 (see Appendix III, additional searches).
    - One observational study which was not included in Kessing et al (2017) was identified: (Joas et al., 2017).[11] This study evaluated treatment of individuals with bipolar disorder in Swedish registries (N= 35 022), using a model of analysis which assessed within-individual efficacy comparing time-on and time-off the respective treatments, addressing some confounders inherent to naturalistic data. Six medicines in monotherapy were studied: lithium, valproate, carbamazepine, olanzapine, and quetiapine.

- To establish whether oral risperidone would be equivalent to the LAI in maintenance treatment of BD, two searches were conducted (results are discussed below under section 7. Alternative agents):
    - Pubmed search for pharmacokinetic or comparison studies between risperidone LAI and oral risperidone, with no publication type or date restrictions (details are in Appendix III). Google scholar was also used to identify any comparison studies. Two studies in schizophrenia were identified (*Mannaert et al., 2005* and *Chue et al., 2005*).[12, 13] No studies relevant to BD were identified.

- Reference lists of the maintenance trials of risperidone LAI as monotherapy in BD (*Quiroz et al., 2010* and *Vieta et al., 2012*)[14, 15] were searched for any studies of oral risperidone in prevention of relapse in BD. Two systematic reviews were identified (*Rendell et al., 2006* and *Derry et al., 2007*).[16, 17]

Evidence synthesis:

Acute treatment of mania

- Vs placebo, RCT evidence: Butler et al. (2018)[1]
  Response rate: OR 1.99 (95% CI 1.29, 3.08) pooled result (5 RCTs, N=1199), random effects model, NNT 6.
  Change of YMRS: Mean Difference 4.9 (95%CI 2.34, 7.45), pooled result, random effects model.
  Withdrawal due to adverse events: OR 1.12 (95% CI 0.41, 3.09), pooled result (5 RCTs, n=1236), random effects model, NNH 56.
- Vs valproate, RCT evidence: Butler et al (2018)[1]
  Response rate: non-significant (2 RCTs, N=635, results not pooled); NNT 19 from combined events
  Change of YMRS: MD 1.68 (95%CI -0.59, 3.95), pooled result (3 RCTs, N=750), random effects model.
  Withdrawal due to adverse events: OR 1.55 (95% CI 0.65, 3.73), pooled result (4 RCTs, N=747), random effects model, NNH 28.

Maintenance treatment

- Vs placebo, lithium, and valproate: see Table 1 for evidence from RCTs and network meta-analysis
- Vs lithium: see Table 1 for RCT evidence and Table 2 for observational study evidence
- Within-individual efficacy: see Table 2 for observational study evidence

7. Alternative agents

- Lithium and valproate are proposed as 1st and 2nd line agents. These are discussed in the BD overview, in the background above, and in the motivation for lithium.

Acute treatment of mania, RCT evidence: Butler et al. (2018)[1]

- Carbamazepine: 2 RCTs, grade of evidence not sufficient to draw a conclusion
  - vs placebo, *Weisler 2006*, n=443: Response to treatment, NNT 4; Change in YMRS, difference of 6 points (95% CI not provided). However, NNH 14 for any adverse event and NNH 20 for severe rash.
  - vs valproate, *Vasudev 2000*, n=30: Response to treatment, NNT -5 (NNT favours valproate although statistically non-significant). However, NNH 2 for any adverse event and NNH 6 for tremor.
- Quetiapine: 5 RCTs (N=1007) with a sufficient grade of evidence to draw a conclusion
  - vs placebo, combined events, NNT 6; however, change in YMRS not significant, MD 4.92 (95% CI 0.31, 9.53). Requires a higher dose for treatment of mania compared with depression (mean dose 600mg vs 300mg); NNH -100 for any adverse event.
- Risperidone, oral: 2 RCTs (N=584) with a sufficient grade of evidence to draw a conclusion
  - vs placebo, combined events, NNT 4; change in YMRS, MD 5.70 (95% CI 2.33, 9.07); NNH 100 for any adverse event.

Maintenance treatment, prevention of mania

- Carbamazepine (see separate motivation for all results):
  - vs placebo: network meta-analysis, non-significant, risk ratio 0.68 (95% CI 0.44, 1.06) for prevention of any mood episode. Not included in analysis for mood subtypes.
  - vs lithium: NNT -8 (favors lithium, events from 1 RCT, Hartong et al., n=53).
  - within-individual analysis: hazard ratio 0.50 (95% CI 0.29–0.86), observational study, n=1253
- Quetiapine (mean dose 600mg, see separate motivation for all results)
  - vs placebo: NNT 10 (combined events, 2 RCTs, N=1757); network meta-analysis, risk ratio 0.61 (95% CI 0.42 – 0.92).
  - vs lithium: non-significant, HR 0.780 (95% CI 0.527, 1.14), 1 RCT, N=1172.
  - within-individual analysis: hazard ratio (95 % CI 0.58–0.93), observational study, n=4191.
- Risperidone LAI: (see Table 3 for evidence of efficacy LAI from RCTs and network meta-analysis).
  - Vs placebo: NNT 4 (combined events, 2 RCTs, n=567); network meta-analysis, risk ratio 0·42 (95% CI 0·28–0·64).
  - Vs olanzapine: NNT -70 (1 RCT, n=260). However, NNT -7 for prevention of any mood episode (post-hoc log-rank favors olanzapine p=0.001) and NNT -10 for prevention of depression.

- Observational studies: No evidence of risperidone use: Kessing et al. (2017)[4] included "risperidone" in their search terms but none of the included studies studied risperidone (oral or LAI) specifically. Joas et al. (2017)[11] did not include risperidone among the medications studied for effect in bipolar disorder.

- Risperidone, oral: All RCTs included in systematic reviews and meta-analyses by Butler (2018), Lindstrom (2017), and Miura (2014) for maintenance treatment are of risperidone LAI. It is not clear if oral risperidone would be equivalent to the LAI formulation in terms of efficacy and tolerability. Results of the additional searches described are as follows:
  - *Mannaert et al., 2005*:[12] extrapolation of single dose risperidone LAI and oral risperidone pharmacokinetic profiles to steady-state. A 1mg dose of oral risperidone administered to 12 healthy volunteers and a 50mg dose of risperidone LAI to 26 people with schizophrenia. The simulated pharmacokinetic profile used to mimic chronic treatment over 16 weeks revealed lower peak plasma concentrations and less fluctuation with risperidone LAI vs oral risperidone.
  - *Chue et al., 2005*:[13] Double-blind, non-inferiority study of Risperidone LAI vs oral risperidone in maintenance over 12 weeks in schizophrenia (N=640). Equivalent efficacy on Positive and Negative Syndrome Scale as well as equivalent safety and tolerability. No assessment of mood outcomes.
  - *Rendell et al., 2006*:[16] Cochrane systematic review of randomised trials of risperidone vs placebo or other treatments for the prevention or attenuation of mood episodes in BD. No trials identified for inclusion.
  - *Derry et al., 2007:*[17] A systematic review of randomised trials of atypical antipsychotics in acute and maintenance treatment of BD. No trials using risperidone for >6 weeks duration identified.

8. Interpretation of the evidence and comments

Olanzapine has RCT evidence of efficacy vs placebo in the treatment of acute mania, NNT=6.

It may be continued into maintenance treatment for prevention of mania, with efficacy vs placebo from RCTs (NNT 5) and network meta-analysis. From one RCT, it is superior to risperidone LAI for prevention of any mood episode (NNT 7).

Observational studies reveal efficacy in prevention of any mood episode, mania, and depression which is equivalent to lithium in some patients. While olanzapine may prevent depression in selected patients in observational studies, the evidence for this from RCTs and network meta-analysis is not consistent. The two possible alternatives to olanzapine are oral risperidone and quetiapine.

Oral risperidone has evidence of efficacy in the acute treatment of mania. However, it is not possible to recommend oral risperidone for maintenance treatment. Firstly, no RCT or observational studies of oral risperidone in maintenance treatment of BD could be identified for this review. Secondly, the RCTs of risperidone LAI may not be applicable to oral risperidone. The two studies comparing risperidone LAI and oral risperidone do not give an adequate indication of equivalent efficacy and tolerability in BD. Thirdly, the evidence for risperidone LAI in maintenance treatment is very weak. Extracted data from RCTs was inadequate for analysis of mood subtypes by Butler et al (2018), prevention of any mood episode was inferior to olanzapine in one head to head study, and there is an absence of observational evidence of efficacy. Thus, the evidence on network meta-analysis is poorly supported by direct RCT and observational evidence. Finally, risperidone LAI has no evidence of efficacy in treatment or prevention of depression, implying that adjunctive medication will be required in almost all BD patients on risperidone as maintenance treatment.

The evidence for quetiapine in the treatment of acute mania and prevention of mania indicates it is less efficacious than olanzapine. At the high doses required for treatment and prevention of mania, it is also likely to be more costly.

In conclusion, olanzapine is the preferred 3rd line agent for treatment and prevention of mania in BD-I, notwithstanding its adverse effects.

Table 1. Olanzapine – efficacy estimates, maintenance treatment (Miura et al. 2014, Butler et al. 2018, Lindstrom et al. 2017)

Intervention vs control	Mood state	Eligible RCTs	NNT	NNH	Butler et al., 2018[1] Time to recurrence	Lindstrom et al., 2017[3] Relapse rate Pooled data - random effects model	Miura et al., 2014[2] Network meta-analysis Risk ratio (95% CI)
Olanzapine vs placebo	Any mood episode	*Tohen et al. 2006* N=361, all BD-I manic or mixed episode	3	-13	Favours Olz HR 2.67 (95% CI 2.03, 3.50), p<0.001	Pooled data favours Olz RR 0.52 (95% CI 0.38, 0.71)	0.50 (0.39 – 0.63)
		Vieta et al. 2012 n=266, all BD-I with manic or mixed episode	3	-43	Log-rank (by region) favors Olz p<0.001		
		Berwaerts et al. 2012	Events not reported		Favours Olz post hoc, p<0.001	Not included	
		Events combined	**3**	**-18**	-	-	
	Mania/ hypomania	*Tohen et al. 2006*	5		Favours Olz HR 3.90 (95% CI 2.40, 6.33), p<0.001	Pooled data favours Olz RR 0.37 (95% CI 0.27, 0.51)	0.35 (0.25 – 0.50)
		Vieta et al. 2012	5		Not analysed		
		Berwaerts et al. 2012	Events not reported		Favours Olz post hoc p<0.001	Not included	
		Events combined	**5**		-	-	
	Depression	*Tohen et al. 2006*	11		Favours Olz HR 2.10, (95% CI 1.46, 3.02), p<0.001	Pooled data NS: RR 1.44 (95% CI 0.92, 2.24)	0.80 (0.57 – 1.12)
		Vieta et al. 2012	13		Not analysed		
		Events combined	18		-	-	
Olanzapine vs lithium	Any mood episode	*Tohen et al 2005* N=431, all BD-I with manic or mixed episode*	11	-15	Log rank Not Significant p=0.07	Pooled data with *Tohen 2003* NS RR 0.80 (95% CI 0.63, 1.03)	Not applicable
	Mania/ hypomania	*Tohen et al 2005**	10		Not analysed	Pooled data with *Tohen 2003* NS RR 0.67 (95% CI 0.39, 1.15)	
	Depression	*Tohen et al 2005**	-320		Not analysed	Pooled data with *Tohen 2003* NS RR 1.44 (95% CI 0.92, 2.24)	
Olanzapine vs valproate	Any mood episode	*Tohen et al 2003* N=251, all BD-I with manic or mixed episode	-113	Events not reported	Log rank Not Significant	Results of pooled data with *Tohen 2005* as above	
	Mania/ hypomania	*Tohen et al 2003*	-121		Not analysed		
	Depression	*Tohen et al 2003*	-61		Not analysed		

NNT=number needed to treat; NS=not significant; Olz=olanzapine; RCT=randomised controlled trial; RR=risk ratio

*Re-analysis by Tohen et al (2016) revealed more time in subsyndromal depression in olanzapine arm vs lithium

Table 2. Olanzapine – evidence from observational studies

Paper	Comments
Kessing et al., 2017[4] Systematic review of observational studies of maintenance treatment of lithium vs other mood stabilisers	Olanzapine use specifically noted in 3 of the 9 monotherapy studies. Equivalent to lithium in two of these studies: o Re-hospitalisation rate, hazard ratio [HR (95% CI)] 0.90 (0.77-1.06), in one nationwide study of BD-I patients (N=2927) discharged from hospital following a manic episode. o Relapse rate among BD outpatients (N=554), NNT 100 although lithium superior to olanzapine (p<0.05).
Joas et al., 2017[11] Observational study of Swedish registry-linked data: within-individual analysis for hospitalisation rates	Olanzapine (n=6466) effective in prevention of mania, HR 0.56 (0.46–0.67), any mood episode HR 0.77 (0.72–0.83), and, slightly less so, for depression HR 0.80 (0.68–0.93)

Table 3. Risperidone long-acting injection– efficacy estimates, maintenance treatment (Miura et al. 2014, Butler et al. 2018, Lindstrom et al. 2017)

Intervention vs control	Mood state	Eligible RCTs	NNT	NNH	Butler et al., 2018[1] Time to recurrence	Lindstrom et al., 2017[3] Relapse rate Pooled data - random effects model	Miura et al., 2014[2] Network meta-analysis Risk ratio (95% CI)
Risperidone LAI vs placebo	Any mood episode	*Quiroz et al. 2010* N=303, all BD-I manic or mixed episode	4	1/0	Log-rank Favours Risp LAI HR 0.40 (95% CI 0.27, 0.59) p=0.001	Pooled data favours Risp LAI RR 0.61 (95% CI 0.47, 0.80)	0·64 (0·48–0·85)
		Vieta et al. 2012 n=264, all BD-I with manic or mixed episode	6	43	Log-rank (by region) Favours Risp LAI p=0.03		
		Events combined	**5**		-		
	Mania/ hypomania	*Quiroz et al. 2010*	3		Not analysed	Pooled data favours Risp LAI RR 0.42 (95% CI 0.28, 0.62)	0·42 (0·28–0·64)
		Vieta et al. 2012	5		Not analysed		
		Events combined	**4**		-		
	Depression	*Quiroz et al. 2010*	-26		Not analysed	Pooled data NS RR 1.21 (95% CI 0.81, 1.80)	1·32 (0·84–2·09)
		Vieta et al. 2012	-53		Not analysed		
		Events combined	**-35**				
Risperidone LAI vs olanzapine	Any mood episode	*Vieta et al. 2012* n=260, all BD-I manic or mixed episode	-7	Events not reported	Post-hoc Log-rank Favours Olanzapine p=0.001	Not analysed	Not applicable
	Mania/ hypomania	*Vieta et al. 2012*	-70		Not analysed	Not analysed	
	Depression	*Vieta et al. 2012*	-10		Not analysed	Not analysed	

NNT=number needed to treat; NS=not significant; Risp LAI=Risperidone long-acting injection; RCT=randomised controlled trial; RR=risk ratio

EVIDENCE TO DECISION FRAMEWORK

<table>
<tr><th></th><th>JUDGEMENT</th><th>SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>QUALITY OF EVIDENCE</td><td>What is the overall confidence in the evidence of effectiveness?

Confident [X] Not confident [ ] Uncertain [ ]</td><td>Network meta-analyses; Systematic review of RCTs of low to moderate quality.</td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable effects?

Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]</td><td></td></tr>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available:
Yes [ ] No [X]
List the members of the group.</td><td></td></tr>
<tr><td>VALUES & PREFERENCES / ACCEPTABILITY</td><td>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 [ ]</td><td></td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?

More intensive [ ] Less intensive [ ] Uncertain [x]</td><td>Cost of medicines/ course month (30 d):
<table><tr><th>Medicine</th><th>Price (ZAR)</th></tr><tr><td>Olanzapine, oral 5-20mg at night</td><td>20.34 to 48.06*</td></tr></table>* Contract circular RT289-2019 (Accessed June 2019)
Additional resources: n/a</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?

Yes [ ] No [X] Uncertain [ ]</td><td></td></tr>
<tr><td>FEASIBILITY</td><td>Is the implementation of this recommendation feasible?
Yes [X] No [ ] Uncertain [ ]</td><td></td></tr>
</table>

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
	☐	☐	☐	☒	☐

Recommendation

Based on the evidence review, the Adult Hospital Level Committee recommends that olanzapine be used in the following scenario(s):

- Third line option, following non-response or poor tolerability of lithium as 1st line, valproate as 2nd line.

Rationale: Evidence of efficacy for acute treatment of depressive episodes of bipolar disorder and prevention of relapse of mania or hypomania. Alternative option to lithium and valproate where there are teratogenic concerns.

Level of Evidence: II Systematic review of RCTs of low to moderate quality.

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

Acceptability of olanzapine amongst prescribers and patients.

Research priorities

References:

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