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

MEDICINE REVIEW

1. Executive Summary

Date: 23 May 2019
Medicine (INN): Combination treatment with lithium, valproate, lamotrigine, olanzapine, quetiapine, oral risperidone
Medicine (ATC): N05AN01, N03AG01, N03AX09, N05AH03, N05AX08
Indication (ICD10 code): F31.1 - F31.9 Bipolar Disorder, prevention of any mood episode, mania/hypomania, depression
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 and Medical Officer under specialist consultation
Current standard of Care:
Prevention of mania: lithium and/or valproate (algorithm ambiguous regarding risperidone)
Prevention of depression: unclear, may be continuation of acute depression treatment (fluoxetine and olanzapine and/or lithium/ valproate/ lamotrigine/ carbamazepine)
Efficacy estimates (preferably NNT), Prevention of any mood episode:
Olanzapine + lithium or valproate vs lithium of valproate alone: NNT 5, but time to recurrence non-significant
Quetiapine + lithium or valproate vs lithium or valproate alone: NNT 3, time to recurrence Hazard Ratio 0.32 (0.24–0.42)
Primary outcome:

- Maintenance treatment - relapse of any mood episode
  - Lithium + valproate: no evidence and no rationale to support use
  - Olanzapine + lithium or valproate: NNT 5 (Lindstrom, 2017) but time to recurrence non-significant (Butler, 2018). Superior to lithium in one observational study.
  - Quetiapine + lithium or valproate: NNT 3 (Lindstrom, 2017), time to recurrence superior to monotherapy (see Table 1 for hazard ratios), Butler (2018). Quetiapine + lithium superior to lithium in one small observational study.
- See Table 1 for relapse of mania/hypomania and depression

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

Polypharmacy during maintenance treatment of BD is common, particularly in bipolar depression where it is associated with anti-depressant and benzodiazepine use.[1] While RCT evidence is often not generalisable to the real-world setting, there is no evidence base for adjunctive antidepressants in maintenance treatment. There may however be a place for combination treatment between mood stabilisers and antipsychotics, particularly as relapse rates of 40% on lithium monotherapy and 67% on valproate monotherapy have been documented.[1] To avoid unnecessary polypharmacy and adverse effects, there is a need for clarity regarding whether such combination treatment is warranted, and if so, which combinations of medicines have evidence of efficacy in maintenance treatment.

5. Purpose/Objective

To review the evidence for combination treatment using lithium, anti-epileptics and/or antipsychotics with some evidence of efficacy in monotherapy in prevention of relapse in BD

- P: Patients with bipolar disorder
- **I**: Combinations of lithium, valproate, lamotrigine, olanzapine, quetiapine
- **C**: Monotherapy (lithium, valproate, lamotrigine, olanzapine, quetiapine
- **O**: time to recurrence or relapse rate.

6. Methods

Search strategy:

- As described in the attached overview of BD.
    - Evidence for this review taken from Butler *et al.* (2018),[3] Lindström *et al.* (2017),[4] Miura *et al.* (2014),[5] and Kessing *et al.* (2018).[6]

- To ensure no recent studies of 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 additional study was identified (Valdes et al. 2019),[6] a post hoc analysis of an RCT in which 93 patients were randomised to oral risperidone as adjunctive treatment to lithium or valproate for 0 weeks (n=30), 24 weeks (n=33), and 52 weeks (n=30) after acute treatment of a manic episode.

Evidence synthesis:

- Lithium + valproate
    - Network meta-analysis: Miura et al (2014) found the combination of lithium + valproate superior to placebo for prevention of any mood episode (Risk Ratio 0·52 (95% CI 0·35–0·77)) and mania (RR 0·42 (95% CI 0·23–0·76)), but not for depression (RR 0·70 (95% CI 0·41–1·17)). Tolerability and acceptability did not differ from placebo.
    - Vs lithium: non-significant (1 RCT, n=220); NNH 20 (Table 1).
    - Vs valproate: the combination was superior to valproate alone in prevention of any mood episode and mania; NNH 17 (Table 1).
- Lithium + lamotrigine
    - No eligible RCTs identified by Butler (2018), Miura (2014), or Kessing (2017).
- Lamotrigine + valproate
    - Network meta-analysis: 1 RCT (N=86, lamotrigine + valproate vs lamotrigine monotherapy) was identified by Miura et al. but not included in the overall network analysis for efficacy in prevention of any mood episode (reasons unclear) or in closed-loop network (only one comparator node). Excluded by Butler et al from their systematic review because of > 50% attrition.
- Olanzapine + lithium or valproate
    - Vs lithium or valproate: 1 RCT (N=99) included by Butler et al (2018) and Lindstrom et al (2017). Using extracted data for time to recurrence, Butler et al found no significant difference to monotherapy for prevention of any mood episode (Table 1).
    - Vs lithium: 1 observational study (n=1588) included by Kessing (2017) found the combination of olanzapine + lithium superior to lithium alone, HR 0.83 (95% CI 0.70–0.98).
- Quetiapine + lithium or valproate
    - Vs lithium or valproate: 2 RCTs included by Butler et al and Lindstrom et al. both revealed superiority of the combination in prevention of any mood episode, mania, or depression (Table 1).

- Vs lithium: 1 small observational study (n=95) included by Kessing (2017) found the combination superior to lithium alone for prevention of recurrence, NNT 3, p=0.01.

- Risperidone, oral + lithium or valproate
  - Vs lithium or valproate: post-hoc analysis by Valdes et al (2019) revealed no significant benefit of adjunctive risperidone in prevention of any mood episode or of depression following acute treatment of mania. Results for prevention of mania were inconclusive, with a significantly longer time to mania in the 24 week arm vs the 0 week arm (hazard ratio (HR: 0.14, 95% CI: 0.03, 0.65, P=0.012), but not for the 52 week arm vs 0 weeks (HR: 0.48, 95% CI: 0.15, 1.53) or vs the 24 week arm (HR: 3.33, 95% CI: 0.60, 18.41). However, weight gain increased significantly, and continued to increase with longer duration of treatment. In conclusion, there is no clear benefit from maintenance treatment with oral risperidone in combination with lithium or valproate, but there is evidence of significant weight gain.

7. Alternative agents

- Lithium, valproate, lamotrigine, olanzapine, quetiapine, or clozapine in monotherapy.

8. Interpretation of the evidence and comments

There is a marked paucity of evidence to guide the use of combination treatment. In addition, the available studies utilising events such as relapse rates or hospitalisation and do not reflect more nuanced effects which may impact quality of life or level of function. Nevertheless, one pragmatic study suggests there is no rationale to support combining lithium and valproate, as the combination is not superior to lithium alone. Limited RCT evidence suggests that selected patients may benefit from the combination of olanzapine or quetiapine plus lithium or valproate, supported by limited observational evidence of olanzapine or quetiapine plus lithium. There is no evidence to support maintenance treatment with risperidone in combination with lithium or valproate.

Combination treatment must be weighed up against increased harm, particularly cumulative effects on weight gain when SGAs are combined with valproate. While olanzapine and quetiapine are both associated with weight gain of >15% in the first few weeks of treatment, valproate is associated with > 10% weight gain at 2 – 3 months after commencing treatment and a continued increase in weight gain with duration of treatment.[7] There may be a clinical rationale for using lamotrigine in combination with lithium, valproate, or an SGA in view of efficacy in prevention of depression and its favourable adverse effect profile, however there is an absence of evidence in this regard. There is no evidence at all to support the use of three or more medicines in maintenance treatment.

Thus, for the NDOH treatment algorithm, monotherapy is recommended. However, as not all patients will respond to medication as anticipated, repeated evaluation of treatment is recommended. The use of rating scales and a level of function measure are advised to enable objective evaluation of clinical response. Where medication is added or changed, ineffective medicine must be withdrawn. Combination treatment should therefore be justified with objective measures of response and adverse effects.

Table 1. Combination treatment: prevention of relapse, outcomes as reported by Butler et al. (2018) and Lindstrom et al (2017)

Intervention	Control	Mood state	Eligible RCTs	NNT	NNH	Butler et al., 2018 Time to recurrence Hazard ratio [HR] (95% CI)	Lindstrom et al., 2017 Relapse rate Risk ratio [RR] (95% CI)
Lithium + valproate	vs lithium	Any mood	*Geddes et al. 2010* (Balance trial) n=220 all BD-I with a manic episode	18	20	NS	Not included
			Kemp et al. 2009 N=31, BD-I 75%, BD-II 25%	Events not reported		HR 0.72 (CI 0.32 – 1.65), NS	
		Mania/ hypomania	*Geddes et al. 2010* (Balance trial)	11	-	Not analysed	
			Kemp et al. 2009	Events not reported			
		Depression	*Geddes et al. 2010* (Balance trial)	-28	-		
			Kemp et al. 2009	Events not reported			
	vs valproate	Any mood	*Geddes et al. 2010* (Balance trial) n=220 all BD-I with a manic episode	6	17	HR favours lithium +valproate	
		Mania/ hypomania		6	-	Not analysed	
		Depression		10	-		
Olanzapine + lithium or valproate	vs placebo + lithium or + valproate	Any mood	*Tohen et al. 2004* N=99, all BD I manic or mixed episode	5	Not available*	Log rank NS	RR 0.49 (0.27–0.91)
		Mania/ hypomania		9	-	Not analysed	RR 0.51 (0.21–1.28), NS
		Depression		6	-		RR 0.48 (0.20–0.98)
Quetiapine + lithium or valproate	vs placebo + lithium or + valproate	Any mood	*Suppes et al. 2009* N=623, all BD-I manic, mixed or depressed	3	25	HR 0.32 (0.24–0.42)	Pooled analysis, random effects model RR 0.38 (0.32–0.46)
			Vieta et al. 2008 N=706, all BD-I manic, mixed or depressed	3	-33	HR 0.28 (0.21–0.37)	
		Mania/ hypomania	*Suppes et al. 2009*	8	-	Risk reduction 70%	Pooled analysis, random effects model RR 0.39 (0.30–0.52)
			Vieta et al. 2008	6	-	HR 0.30 (0.20–0.44)	
		Depression	*Suppes et al. 2009*	5	-	Risk reduction 67%	Pooled analysis, random effects model RR 0.38 (0.29–0.49)
			Vieta et al. 2008	7	-	HR 0.26 (0.17–0.41)	

NNH=number needed to harm (withdrawal due to adverse events in general, calculated from figures provided by Butler et al);

NNT=number needed to treat (response rate, >50% reduction in symptoms, calculated from figures provided by Miura et al or Lindstrom et al);

HR=hazard ratio; NS=not significant; RR=risk ratio

*Only specific adverse effects available (presented under Lindstrom et al in the BD overview), not withdrawal due to any adverse event

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 [ ] Not confident [X] Uncertain [ ]</td><td>Systematic reviews of RCTs of low to moderate quality.
Standard of care.</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: n/a
Yes [ ] No [ ]</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 [ ] No [ ] Uncertain [X]</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 days):
<table><tr><th>Medicine</th><th>Price (ZAR)*</th></tr><tr><td>Lamotrigine 200 mg at night</td><td>53.90</td></tr><tr><td>Olanzapine 5-20 mg at night</td><td>20.34 to 48.06</td></tr><tr><td>Valproate 400-600 mg at night</td><td>15.63 to 19.60</td></tr><tr><td>Quetiapine 100-300 mg at night</td><td>25.39 to 76.38</td></tr></table>Contract circular RT289-2019.
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
	☐	☐	☐	X	☐

Recommendation

Based on this evidence review, the Adult Hospital Level Committee recommends that for patients non-responding to monotherapy, combination therapy of olanzapine/quetiapine plus lithium/valproate or lamotrigine with lithium/antipsychotic be considered for bipolar disorders. This excludes combination therapy, lithium and valproate or risperidone with lithium/valproate; or maintenance treatment with three or more agents. Combination treatment must be weighed up against increased harm with use of rating scales and a level of function measure to enable objective evaluation of clinical response. Where medication is added or changed, ineffective medicine must be withdrawn.

Rationale: Limited RCT evidence suggesting that selected patients may benefit from the combination of olanzapine or quetiapine plus lithium or valproate; whilst lithium with valproate was shown not to be superior to lithium monotherapy. RCT evidence could not be sourced to support maintenance treatment with risperidone in combination with lithium or valproate. There is a paucity of RCT evidence for lamotrigine used with lithium, valproate, or an antipsychotic, but this combination treatment is commonly used in clinical practice for prevention of depression in bipolar disorders. There is also no evidence to support the use of three or more medicines in maintenance treatment.

Level of Evidence: II Systematic reviews of RCTs of low to moderate quality, Standard of care

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
X	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:

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3. Lindström L, Lindström E, Nilsson M, Höistad M. Maintenance therapy with second generation antipsychotics for bipolar disorder – A systematic review and meta-analysis. J Affect Disord [Internet]. 2017;213(February):138–50. Available from: http://dx.doi.org/10.1016/j.jad.2017.02.012
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pharmacological treatments in the maintenance treatment of bipolar disorder: A systematic review and network meta-analysis. The Lancet Psychiatry [Internet]. 2014;1(5):351–9. Available from: http://dx.doi.org/10.1016/S2215-0366(14)70314-1

5. Kessing LV, Bauer M, Nolen WA, Severus E, Goodwin GM, Geddes J. Effectiveness of maintenance therapy of lithium vs other mood stabilizers in monotherapy and in combinations: a systematic review of evidence from observational studies. Bipolar Disord. 2018;20(5):419–31.
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7. Murru A, Popovic D, Pacchiarotti I, Hidalgo D, León-Caballero J, Vieta E. Management of Adverse Effects of Mood Stabilizers. Curr Psychiatry Rep. 2015;17(8).