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): Quetiapine, oral, maximum dose of 300mg
Medicine (ATC): N05AH04
Indication (ICD10 code): F31.3, F31.4, F31.5, F31.7 Bipolar Disorder, treatment and prevention of depression, 3rd line treatment as a safe and effective alternative to lithium and lamotrigine
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: Fluoxetine with olanzapine with or without lithium and/or valproate or lamotrigine or carbamazepine
Efficacy estimates: (preferably NNT)
Acute depression, NNT 6 (Selle, 2014)[1]
Prevention of depression, NNT 8 (RCT events as reported in Miura 2014)[2]
Primary outcome:

- *Acute treatment of depression*: Response rate (>50% reduction in depression rating scale) *and* significant mean difference in change of depression scale score, both at a) 12 weeks or b) 6 or more weeks
  - vs placebo at 12 weeks (Butler, 2018)[3]: no studies
  - vs placebo at 8 weeks (Selle, 2014,[1] 5 RCTs, n=2485): response rate ratio 1.36 (95% CI 1.24–1.49), NNT 6; Standardised Mean Difference (SMD) in change of depression symptoms 0.373 (0.284–0.462) p< 0.0001
- *Maintenance treatment:* Relapse of depression
  - vs placebo (Miura, 2014)[2]: Risk Ratio 0·48 (95%CI: 0·34 - 0·67) on network meta-analysis; NNT 8 on relapse rate
  - vs lithium (Lindstrom, 2017)[4]: Hazard Ratio for time to recurrence 0.54 (95%CI 0.349-0.837)

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

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

Primary reviewer: Dr Lesley Robertson
Other: Ms TD Leong assisted with the estimated budget impact analysis

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.
- Ms TD Leong: National Department of Health, Essential Drugs Programme, Secretariat to the Adult Hospital Level Committee; no conflicts of interest declared.

4. Introduction/Background

As treatment of acute depressive episodes in BD 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 1st line treatment in overall management of BD, including depression due mainly to its effect in reducing suicide and the results of observational

studies. 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.

Lamotrigine, 2nd line treatment for bipolar depression, has no RCT evidence of efficacy for acute treatment. Its evidence of efficacy for prevention of depression is derived mainly from network meta-analysis (albeit non-significant on sensitivity analysis), and observational studies.[5] In Kessing et al., it is noted specifically in 3 of 9 studies, inferior to lithium in two; but non-significant vs lithium in one study of 184 BD patients, NNT 25.[5] Although it has a favourable tolerability profile, the occurrence of severe rash may preclude re-challenge with lamotrigine. A 3rd-line option is needed for non-responders and poor tolerability.

Adverse effects of quetiapine differ from those of lithium and lamotrigine. Sedation (NNH 25)[4] and weight gain (NNH 20)[4] are the predominant adverse effects of quetiapine. An inconsistent association with hypertension and Type 2 DM has been reported.[7] A recent longitudinal cohort study from the UK[8] found quetiapine to be associated with a significantly higher risk of > 15% weight gain than lithium (HR 0.62; 95% CI 0.47–0.80; p < 0.001), but no increased risk of hypertension or Type2 DM.

Quetiapine has been used safely and effectively in pregnancy.[8] A risk of gestational diabetes has been documented but may be related to confounding factors and risks inherent to bipolar disorder.[9] As with other SGAs, quetiapine 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 quetiapine in the treatment and prevention of depression in BD
- **P:** Patients with bipolar disorder
- **I**: Quetiapine
- **C**: Lithium/ valproate
- **O**: Response rate (>50% reduction in symptoms) and mean difference in change of depression 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).[6] 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.

Evidence synthesis:

<u>Acute treatment of depression</u>

- Vs placebo, RCT evidence: Selle et al. (2014)[1]
  Response rate ratio 1.36 (95% CI 1.24–1.49), pooled result (5 RCTs, N=2485), random effects model, NNT 6
  Difference in change of depression symptoms, SMD 0.373 (0.284–0.462) p< 0.0001
  Withdrawal due to adverse events: not reported

Maintenance treatment

- Vs placebo: 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 lamotrigine 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 as 1st line treatment.
- Olanzapine has inconsistent evidence of efficacy in prevention of depression and thus may be protective in selected patients, but not as a general recommendation for those with predominantly depressive course of illness. From RCTs and network analysis, olanzapine has no evidence of efficacy for prevention of depression, in monotherapy[4] or in combination with fluoxetine.[11] From observational studies, it may have efficacy in prevention of depression in BD-I with an index manic episode, and it has evidence of efficacy for prevention of depression on within-individual analysis, hazard ratio 0.80 (95% CI 0.68–0.93).
- ECT is recommended for acute severe depression but it requires admission to a hospital with a psychiatrist, anaesthetist/anaesthesiology Medical Officer, and functioning ECT machine. ECT in pregnancy may increase the risk of fetal distress, preterm labour and neonatal mortality.[12]
- Antidepressants in monotherapy may be used in BD-II patients who respond well (insufficient grade studies in Butler et al) but have no evidence of efficacy on network meta-analysis (imipramine in Miura et al).
- Adjunctive antidepressants in BD-I may improve acute depression symptoms but not response rates.[1, 11] However, they are not shown to have efficacy in maintenance treatment, on meta-analysis (imipramine + lithium in Miura et al), and may cause manic/ hypomanic switch with a NNH 14.[11]

8. Interpretation of the evidence and comments

Quetiapine is a suitable 3rd-line alternative to lithium and lamotrigine in treatment and prevention of depression in BD, with a LoE II. There is no other alternative medicine with consistent evidence from RCTs, network meta-analysis, and observational studies for treatment and prevention of bipolar depression.

Table 1. Quetiapine – efficacy estimates for maintenance therapy (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 Time to recurrence	Lindstrom et al., 2017 Time to recurrence Pooled data - random effects model	Miura et al., 2014 Network meta-analysis Risk ratio (95% CI)
Quetiapine vs placebo	Any mood episode	*Weisler et al 2011* N=1172, all BD-I manic, mixed, or depressed index episode	3	100	Favours Quet HR 0.29 (95% CI 0.23, 0.38), p<0.0001	Pooled data favours Quet HR 0.371 (95% CI 0.305, 0.452)	0.52 (0.40 – 0.68)
		Young et al 2012 N=585, BD-I and BD-II, all depressed	6	1/0	Not included		
		Events combined	**4**	**100**	-		
	Mania / hypomania	*Weisler et al. 2011*	6		Favours Quet HR 0.29 (95% CI 0.21, 0.40), p<0.0001	Pooled data favours Quet HR 0.381 (95% CI 0.290, 0.500)	0.61 (0.42 – 0.92
		Young et al 2012	79		Not included		
		Events combined	**10**		-		
	Depression	*Weisler et al. 2011*	8		Favours Quet HR 0.30 (95% CI 0.20, 0.44), p<0.0001	Pooled data favours Quet HR 0.365 (95% CI 0.279, 0.476)	0.48 (0.34 – 0.67)
		Young et al 2014	7		Not included		
		Events combined	**8**		-		
Quetiapine vs lithium	Any mood episode	*Weisler et al. 2011*	28	-50	Favours Quet HR 0.66 (95% CI 0.49, 0.88), p=0.005	HR 0.660 (95% CI 0.492, 0.884)	Not applicable
	Mania/hypomania	*Weisler et al. 2011*	-102		Not significant	HR 0.780 (95% CI 0.527, 1.14)	
	Depression	*Weisler et al. 2011*	22		Favours Quet HR 0.54 (95% CI 0.35, 0.84), p=0.006	HR 0.540 (95% CI 0.349, 0.837)	

HR= hazard ratio; NNT=number needed to treat; Quet=quetiapine; RCT=randomised controlled trial; RR=risk ratio

Table 2. Quetiapine – evidence from observational studies

Paper	Comments
Kessing et al., 2017 Systematic review of observational studies of maintenance treatment of lithium vs other mood stabilisers	Quetiapine use noted specifically in 3 of the 9 monotherapy studies. Equivalent to lithium, HR 0.91 (95% CI 0.75-1.11), for re-hospitalisation in one nationwide study of BD-I patients (N=2927) discharged from hospital following a manic episode.
Joas et al., 2017 Observational study of Swedish registry-linked data: within-individual analysis for hospitalisation rates	Quetiapine (n=4191) effective in prevention of depressive episodes, hazard ratio [HR (95% CI)] 0.66 (0.54–0.81), and slightly less so for any mood episode HR 0.82 (0.76–0.89), and mania HR 0.73 (0.58–0.93)

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 [ ]	Meta-analyses and systematic reviews of RCTs of low to moderate quality - Butler et al (2018), Miura et al. (2014), Lindstrom et al. (2017), and Kessing et al (2017).
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: n/a Yes [ ] No [ ] 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/ month (30 days):

Medicine	Price (ZAR)*
Quetiapine 300 mg daily	76.375

*Contract circular RT289-2019

Estimated budget impact (1 year):

- *Assumptions:*

- BD II prevalence estimated to be 0.5% (Clemente et al, 2017)
- Equates to estimated South African population, age ≥18 years of 40.68 mil (StatSA 2018 mid-year population statistics).
- First line treatment option is lithium; but not all will respond/tolerate lithium – estimated non-responders requiring 2nd line lamotrigine therapy is 31%, extrapolated from Aus/NZ study (Sporthchie et al, 2017) ~63K
- Non-responsive to lamotrigine requiring quetiapine estimated to be ~35% or 22K (Expert opinion).

- *Estimated budget impact for 1 year:*

- Thus, estimated budget required for 12/12's treatment of quetiapine ~ **R20.23 mil.**

- Sensitivity analyses:

- Simulation using lower limit of 15% non-responsiveness to lamotrigine ~ R8.67 mil.
- Upper limit of 55% equates to ~ R31.79 mil.

References:

i. Clemente AS, et al. Bipolar disorder prevalence: a systematic review and meta-analysis of the literature. Braz J Psychiatry. 2015 Apr-Jun;37(2):155-61.

ii. StatsSA, Mid year population statistics, 2018

iii. Sportiche S et al. Clinical factors associated with lithium response in bipolar disorders. Aust N Z J Psychiatry. 2017 May;51(5):524-530.

Additional resources: n/a

EQUITY

Would there be an impact on health inequity?

Yes	No	Uncertain
		X

FEASIBILITY

Is the implementation of this recommendation feasible?

Yes	No	Uncertain
X		

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 illness of a predominantly depressive polarity, non-responsive or poor tolerance to lithium and lamotrigine, quetiapine may be considered as a third line option.

Rationale: Quetiapine has RCT (Lindstrom 2017) and network meta-analysis evidence of efficacy for prevention of bipolar depression, noting that quetiapine may cause more weight gain and somnolence than lamotrigine.

Level of Evidence: II Meta-analyses and systematic reviews 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

Use for other indications, e.g.: schizophrenia

Research priorities

References:

1. Selle V, Schalkwijk S, Vazquez GH, Baldessarini RJ. Treatments for acute bipolar depression: meta-analyses of placebo-controlled, monotherapy trials of anticonvulsants, lithium and antipsychotics. Pharmacopsychiatry. 2014;47(2):43-52.
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.
3. 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.
4. Lindstrom L, Lindstrom E, Nilsson M, Hoistad M. Maintenance therapy with second generation antipsychotics for bipolar disorder - A systematic review and meta-analysis. Journal of affective disorders. 2017;213:138-50.
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 disorders. 2018.
6. Hirsch L, Patten SB, Bresee L, Jette N, Pringsheim T. Second-generation antipsychotics and metabolic side-effects: Canadian population-based study. BJPsych Open. 2018;4(4):256-61.
7. Hayes JF, Miles J, Walters K, King M, Osborn DPJ. A systematic review and meta-analysis of premature mortality in bipolar affective disorder. Acta psychiatrica Scandinavica. 2015;131(6):417-25.
8. Pinheiro EA, Wisner KL, Clark CT. Quetiapine Dose Adjustments in Pregnant and Postpartum Women With Bipolar Disorder. Journal of clinical psychopharmacology. 2018;38(1):89-91.
9. Uguz F. Prophylactic use of olanzapine and quetiapine from pregnancy to the postpartum period in women with bipolar disorder: a case series. J Matern Fetal Neonatal Med. 2017;30(21):2569-71.
10. Haskey C, Galbally M. Mood stabilizers in pregnancy and child developmental outcomes: A systematic review. The Australian and New Zealand journal of psychiatry. 2017;51(11):1087-97.
11. McGirr A, Vohringer PA, Ghaemi SN, Lam RW, Yatham LN. Safety and efficacy of adjunctive second-generation antidepressant therapy with a mood stabiliser or an atypical antipsychotic in acute bipolar depression: a systematic review and meta-analysis of randomised placebo-controlled trials. Lancet Psychiatry. 2016;3(12):1138-46.
12. Leiknes KA, Cooke MJ, Jarosch-von Schweder L, Harboe I, Høie B. Electroconvulsive therapy during pregnancy: a systematic review of case studies. Arch Womens Ment Health (2015) 18:1–39.