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

MEDICINE REVIEW

1. Executive Summary

Date: 15 May 2019
Medicine (INN): Antidepressants, in monotherapy or as adjunctive therapy with mood stabilizer or antipsychotic
Medicine (ATC): N06A
Indication (ICD10 code): F31.3, F31.4, F31.5, F31.7 Bipolar Disorder, treatment and prevention of depressive relapse
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 guidance
Current standard of Care: Fluoxetine is current standard of care, in combination with olanzapine, for acute treatment of depression. Its role in prevention of depression is unclear. However, antidepressants are often prescribed in practice.
Efficacy estimates: (preferably NNT)
Monotherapy
Acute depression: inconclusive results
Prevention of relapse: inconclusive results
Adjunctive treatment
Acute depression: NNT 20 (McGirr et al., 2016, 6 RCTs N=1383)[1]
Prevention of relapse: Non-significant vs placebo (imipramine + lithium)
Primary outcome:

- *Acute treatment of depression*: Response rate (>50% reduction in depression scale) *and* significant mean difference in change of depression scale score, both at 12 weeks
  - Monotherapy
    Vs placebo (Butler et al., 2018)[2]: Bupropion and paroxetine, NS (1 RCT, n=366)
    Vs lithium (Butler et al., 2018)[2]: Sertraline, NS (1 RCT, n=142 BD-II); venlafaxine NNT 3 (2 RCTs, n=212, BD-II)
  - Adjunctive treatment
    Vs mood stabilizer/ antipsychotic alone (McGirr, 2016, 6 RCTs N=1383)[1]: Response rate NS, NNT 20, pooled result random effects model OR 1·158 (95% CI 0·840–1·597); Mean difference in change of depression symptom score 0·165 (95% CI 0·051–0·278).
- *Maintenance treatment:* Relapse of depression (time to recurrence or relapse rate)
  - Monotherapy
    Vs placebo (Miura, 2014, network meta-analysis)[3]: Non-significant (imipramine)
    Vs placebo (Butler, 2018)[2]: fluoxetine, log rank p=0.03 (1RCT, n=55, all BD-II);
    Vs lithium (Butler, 2018)[2]: fluoxetine, HR 0.04 (95% CI 0.2 – 0.9) (1 RCT, n=54, all BD-II); venlafaxine NS (1 RCT, n=55, all BD-II)
  - Adjunctive treatment
    Vs placebo (Miura, 2014, network meta-analysis)[3]: Non-significant (imipramine + lithium)
    Vs mood stabilizer/ antipsychotic alone (McGirr, 2016)[1]: efficacy in prevention of relapse not estimated (2 RCTs with 52-week extension periods of acute trials)

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

NS=non-significant

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

Bipolar depression is often refractory to treatment. Antidepressants have been used historically, usually adjunctive to a mood stabiliser, but sometimes in monotherapy in BD-II. The current standard of care for acute depression is fluoxetine with olanzapine. Whether it should be continued in maintenance treatment is unclear from the algorithm. Even though other antidepressants are not in the algorithm, they are often prescribed in BD in clinical practice in South Africa.

5. Purpose/Objective

To review the evidence for antidepressants in the treatment and prevention of depression in BD

- **P:** Patients with bipolar disorder
- **I**: Antidepressants
- **C**: Lithium/ valproate
- **O**: Acute treatment: Response rate (>50% reduction in symptoms) and mean difference in change of depression symptom scores. Maintenance treatment: 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)[2], McGirr et al (2016)[1], Miura et al. (2014)[3], and Selle et al. (2014)[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 meta-analysis identified: Lui et al. 2017, Efficacy and safety of long-term antidepressant treatment for bipolar disorders – A meta-analysis of randomized controlled trials.[5] Included 11 RCTs (n=692). However, the paper was poorly comprehensible. In addition, the lack of heterogeneity found between any of the trials in any of the subgroup analyses (I^2=0.0% throughout) is implausible and casts doubt on the overall statistical analysis.

Evidence synthesis:

A: Acute treatment of depression - monotherapy

The outcomes of 4 RCTs, as reported by Butler et al (2018), are presented in Table 1. While it appears that venlafaxine is more effective than lithium in patients with BD-II, the grade of evidence of all four is insufficient to draw any conclusions regarding efficacy or harm.

Table 1. Acute depression: antidepressants in monotherapy, outcomes as reported by Butler et al., 2018[2]

Antidepressant & RCT	Control	Efficacy	Harms
Bupropion or paroxetine, *Sachs 2007*, N=366, BD-I 68%, BD-II 33%	Placebo	Events not reported Durable recovery NS; Transient remission NS	Events not reported Withdrawal due to clinical worsening: Antidepressant 34.1%, Placebo 33.7%
Sertraline, *Altshuler, 2017*; N=142, all BD-II All outcomes at 16 weeks	Lithium	Events not reported Response rate NS at 16 weeks	Events not reported; Switching NS
Venlafaxine, *Amsterdam, 2008*; N=129, all BD-II All outcomes at 12 weeks		Response rate NNT 3, p=0.0002 Mean Difference in change of depression scale -4.51 (-8.36 to -0.66), p=0.015	Events not reported; Switching NS
Venlafaxine, *Amsterdam 2016;* N=83, all BD-II All outcomes at 12 weeks		Response rate NNT 2, p=0.0005 Difference in change of depression scale p<0.0001	Events not reported; Switching NS

BD-I=bipolar I disorder; BD-II=bipolar II disorder; NNT=number needed to treat; NS=not significant

B: Acute treatment of depression – adjunctive treatment

See Table 2 for results of 6 RCTs, as reported by McGirr et al., 2016,[1] and for those RCTs also reported on by Butler et al., 2018[2] and Selle et al. 2014.[4]

Of the 6 RCTs only fluoxetine as adjunctive treatment to olanzapine was superior to olanzapine alone. While this trial was an outlier on funnel plot analysis, there was no evidence of publication bias. Pooled analysis of the 6 RCTs revealed no significant difference to mood stabiliser/ antipsychotic alone (OR 1·158 (95% CI 0·840–1·597), moderate heterogeneity, I^2 = 40·12) for response rate, although there was a significant improvement in depression symptom scores.

There was significant heterogeneity between trials using antipsychotics vs those using mood stabilisers, and subgroup analysis was conducted. Antidepressant adjunctive to an antipsychotic was superior to the antipsychotic alone, NNT 7. No significant difference found between adjunctive antidepressant to a mood stabiliser (lithium or antiepileptic) vs mood stabiliser alone.

No increased risk of switching to mania/ hypomania was found with acute adjunctive treatment.

C: Maintenance treatment – monotherapy

See Table 3 for results of monotherapy vs placebo and lithium, as reported by Butler et al., 2018 and Miura et al., 2014.
Network meta-analysis found imipramine vs placebo to be non-significant, and to have poor acceptability (all-cause discontinuation) with a Risk ratio 1·64 (1·06–2·54). Fluoxetine vs placebo was not included in network meta-analysis because had no reporting of mood switching.

D: Maintenance treatment – adjunctive treatment

See Table 3 for results as reported by Miura et al., 2014 (imipramine adjunctive to lithium) and McGirr et al., 2016. Efficacy for prevention of relapse was not estimated by McGirr et al. However, the risk switching to mania or hypomania was estimated from the 52 week extension periods of 2 RCTs (one of agomelatine plus lithium or valproate, the other of citalopram plus any mood stabiliser or antipsychotic).

The pooled risk of switching was significant, NNH 19.

7. Alternative agents

Acute treatment of depression

ECT or quetiapine (proposed) may be used where a rapid response is required due to severity.

Maintenance treatment (prevention of depression): lithium, lamotrigine or quetiapine.

8. Interpretation of the evidence and comments

There is insufficient evidence to support any decision regarding the use of antidepressants in BD. While the standard of care is based on the only study of adjunctive antidepressant use with evidence of efficacy vs placebo (fluoxetine to olanzapine), this is only with one RCT and it is not known if it is specific to this combination or if it may be generalised to all patients with bipolar depression. Monotherapy trials are of small study samples and are insufficient to guide decision-making. Moreover, no observational trials were identified to corroborate positive findings of acute or maintenance treatment, whether in monotherapy or as adjunctive therapy.

Nevertheless, fluoxetine and venlafaxine may have efficacy in the treatment and prevention of depression in selected patients with BD-II. In patients with BD-I who are already on olanzapine, the addition of fluoxetine may assist in short-term treatment of a depressive episode. Long-term treatment with adjunctive antidepressants is not recommended due to increased risk of switching and no evidence of efficacy in prevention of relapse.

Table 2. Acute depression: adjunctive antidepressant vs adjunctive placebo, outcomes as reported by Butler et al. (2018)[2], McGirr et al. (2016),[1] and Selle et al. (2014)[4]					
Eligible RCTs	**Antidepressant**	**Mood stabiliser/ antipsychotic**	**Butler et al., 2018 Response to treatment and adverse effects as reported by authors**	**McGirr et al., 2016**	**Selle et al. 2014**
				Response rate (>50% reduction in symptoms), OR (95% CI) Difference in change of depression symptom scale, SMD (95% CI) Treatment emergent mood switching, OR (95% CI)	
Nemeroff et al. 2001 N=78 (35 AD vs 43 placebo) All bipolar disorder (DSM III R) Outcomes at 10 weeks	Paroxetine	Lithium	Not included	Response rate: NS, NNT 15, OR 1·312 (0·534 to 3·220) SMD: NS, 0·294 (-0·154 to 0·743) Switching NS: NNH -22, OR 0·234 (0·011 to 5·033)	Not included
Tohen et al. 2003 N=456 (86 AD vs 370 placebo) All BD-I Outcomes at 8 weeks	Fluoxetine	Olanzapine	Not included	Vs olanzapine: Response rate: NNT 6, OR 1·956 (1·218–3·140) SMD 0·265 (0·030 to 0·500) Switching: NS, NNH 147, OR 1·140 (0·414–3·145)	Vs placebo: Response rate: NNT 2, calculated by authors; Response rate ratio 1.84 (1.44–2.36) SMD 0.453 (0.211–0.695) Switching: not reported by Selle et al.
Shelton et al. 2004 N=20 (10 AD vs 10 placebo) BD-I 60%, BD-II 40% Outcomes at 12 weeks	Paroxetine	Risperidone in addition to lithium, valproate, or carbamazepine	Not included	Response rate: NS, NNT 1/0, OR 1·000 (0·148–6·772) SMD: NS, 0·143 (-0·734 to 1·021) Switching: NS, NNH 1/0	Not included
Sachs et al. 2007 (STEP-BD trial) N=363 (176 AD vs 187 placebo) BD-I 68%, BD-II 33% Outcomes at 26 weeks	Bupropion or paroxetine	Lithium, valproate, carbamazepine, or other FDA-approved antimanic medications	NNT: Events not reported Durable recovery NS; Transient remission NS NNH: Events not reported Withdrawal due to clinical worsening: Antidepressant 34.1%, Placebo 33.7%	Response: NS, NNT -18, OR 0·783 (0·509 to 1·204) SMD: NS, 0·150 (-0·055 to 0·356), NS Switching: NS, NNH -156, OR 0·934 (95% CI 0·476 to 1·829)	Not included
Yatham et al. 2016 N=344 (172 AD vs 172 placebo) All BD-I Outcomes at 8 weeks	Agomelatine	Lithium or valproate	Not included	Response: NS, NNT 86, OR 1·050 (0·681–1·620) SMD: NS, 0·024 (-0·188 to 0·235), NS Switching: NS, NNH 57, OR 1·782 (0·512–6·201)	Not included
Ghaemi SN, 2015 (CAPE-BD trial) N=119 (60 AD vs 59 placebo) BD-I 63%, BD-II 37% Outcomes at 6 weeks	Citalopram	Lithium, valproate, carbamazepine, antipsychotic, lamotrigine or any combination of these	Not included	Response: NS, NNT 39, OR 0·303 (-0·059 to 0·664) SMD: NS, 0·294 (-0·154 to 0·743), NS Switching: NS, NNH -8, OR 0·333 (0·079–1·407)	Not included

AD=Antidepressant; NNH=number needed to harm; NNT=number needed to treat; NS=not significant;

Table 3. Prevention of depression: monotherapy and adjunctive antidepressants, efficacy outcomes as reported by Butler et al. (2018),[2] McGirr et al. (2016),[1] and Miura et al. (2014)[3]

Intervention	Monotherapy or adjunctive treatment	Eligible RCTs	NNT response rate	NNH adverse events	Butler et al., 2018 Time to recurrence of depression	McGirr et al., 2016 Treatment emergent affective switch OR (95% CI)	Miura et al., 2014 Network meta-analysis Risk ratio (95% CI)
Monotherapy	vs placebo	*Kane et al 1982:* Imipramine n=12, all BD-II	6	-6	Not included	Not included	(Imipramine only) Efficacy NS RR 0·73 (0·37–1·49) Tolerability NS RR 2·82 (0·05–149·76) Acceptability **1·64 (1·06–2·54)**
		Amsterdam et al 2010: Fluoxetine N=55, all BD-II	5	1/0	Favuors Fluoxetine p=0.03	Not included	
		Events combined	**5**	**-18**	**-**	-	
	vs lithium	*Kane et al 1982:* Imipramine n=9, all BD-II	-7	-6	Not included	Not included	Not applicable
		Prien et al 1984: Imipramine N=78, any BD	126	36	Not included	Not included	
		Amsterdam et al 2010: Fluoxetine N=54, all BD-II	4	1/0	Favours Fluoxetine HR=0.04 (95%CI 0.2,0.9)	Not included	
		Amsterdam et al 2015: Venlafaxine N=55, all BD-II	Not reported	Not reported	Log rank NS	Not included	
		Events combined	**18**	**-115**	-	-	
Adjunctive treatment	vs placebo	*Kane et al 1981* Imipramine +lithium vs lithium, n=75, all BD I	41	36	Not included	Not included	(imipramine + lithium only) Efficacy NS RR 0·54 (0·27–1·07) Tolerability NS RR 8·82 (0·31–253·41) Acceptability NS RR 0·80 (0·54–1·14)
		Kane et al 1982 Imipramine +lithium vs lithium, n=10, all BD-II	12	1/0	Not included	Not included	
		Events combined	**38**	**60**	-	-	
		Yatham et al. 2016: 52-week extension of acute trial (details in Table 2)	Not reported	Not reported	Not included	Combined events: NNH 19 Pooled data, random effects model OR 1·774 (1·018–3·091)	
		Ghaemi SN. 2015: 52-week extension of acute trial (details in Table 2)			Not included		

HR=hazard ratio; NN=number needed to harm; NNT=number needed to treat; NS=not significant; 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>Systematic reviews and meta-analyses of RCTs of low to moderate quality.
(McGirr et al, 2016; Muira et al, 2014; Butler et al, 2018; Selle et al, 2014)</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 [X] No [ ]
Members of the group: SSRIs -
Fluoxetine 20 mg
Citalopram 20 mg
Sertraline 50 mg
Escitalopram 10 mg</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 days):
<table><tr><th>Medicine</th><th>Price (ZAR)</th></tr><tr><td>Fluoxetine 20 mg daily</td><td>6.10*</td></tr><tr><td>Citalopram 20mg daily</td><td>9.53*</td></tr><tr><td>Sertraline 50mg daily</td><td>229.59**</td></tr><tr><td>Escitalopram 10mg daily</td><td>151.79**</td></tr></table>* Contract circular RT289-2019 – weighted average price
** SEP database, accessed 20 June 2019 – average price of generic products
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 the evidence review, the Adult Hospital Level Committee recommends that SSRI antidepressants not be recommended as monotherapy in BD-II or adjunctive therapy or as adjunctive treatment in BD-I, in the Adult Hospital Level EML.

Rationale: Evidence is insufficient for routine use of SSRIs in BD. However, may be efficacious in select patients with olanzapine for short-term treatment of a depressive episode – specialist psychiatrist management at tertiary/quaternary level of care may be required. Long-term treatment with adjunctive antidepressants is not recommended due to increased risk of switching and no evidence of efficacy in prevention of relapse.

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

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:

1. McGirr A, Vöhringer 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. The Lancet Psychiatry. 2016;3(12):1138–46.
2. Butler M, Urosevic S, Desai P, Sponheim SR, Popp J, Nelson VA, et al. Treatment for Bipolar Disorder in Adults: A Systematic Review [Internet]. 2018. Available from: https://effectivehealthcare.ahrq.gov/topics/bipolar-disorder-treatment/final-report-2018
3. 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. The Lancet Psychiatry [Internet]. 2014;1(5):351–9. Available from: http://dx.doi.org/10.1016/S2215-0366(14)70314-1
4. 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 [Internet]. 2014;47(2):43–52. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L53018586%5Cnhttp://dx.doi.org/10.1055/s-0033-1363258
5. Liu B, Zhang Y, Fang H, Liu J, Liu T, Li L. Efficacy and safety of long-term antidepressant treatment for bipolar disorders – A meta-analysis of randomized controlled trials. J Affect Disord [Internet]. 2017;223(June 2017):41–8. Available from: http://dx.doi.org/10.1016/j.jad.2017.07.023