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

MEDICINE REVIEW

1. Executive Summary

Date: 01 May 2019
Medicine (INN): Carbamazepine
Medicine (ATC): N05AF01
Indication (ICD10 code): F31.3, F31.4, F31.7 Bipolar disorder: treatment and prevention of 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: Medical Officer
Current standard of Care: Carbamazepine is in the current algorithm for treatment of bipolar depression, together with options of lithium, valproate, lamotrigine, and fluoxetine plus olanzapine
Efficacy estimates: (preferably NNT) n/a
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)[1], no eligible studies
  vs placebo: at 8 weeks (Selle 2014,[2] 1 RCT, n=70), response rate ratio 1.84 [1.01–3.34], NNT 3, but difference in change of depression scale non-significant, SMD 0.209 (-0.291, 0.709) p=0.41
- *Maintenance treatment of depression*: Relapse of depression
  vs placebo: (Miura, 2014)[3]: Non-significant for prevention of any mood episode Risk Ratio 0·68 (95% CI 0·44–1·06) on network meta-analysis, not included in closed loop network for prevention of depression or mania
  vs lithium: (Miura, 2014, 1 RCT, n=53), NNT -5 (favors lithium)

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] As treatment of acute episodes is often continued into maintenance care, it should be informed by evidence for prevention of relapse and side effect burden in long-term treatment. In current standard of care, carbamazepine is an option in the acute treatment of depression but maintenance treatment is unclear.

Benefits of carbamazepine should outweigh potential adverse effects.[4] Drug: drug interactions are significant with inefficacy of concomitant medications, including ART. Rare but severe adverse effects include dermatological (Stevens Johnson syndrome and toxic epidermal necrolysis) and haematological (aplastic anaemia, agranulocytosis, pancytopenia) reactions. Carbamazepine is a teratogen, with a reported 2.9% risk of congenital malformations.

5. Purpose/Objective

To review the evidence of carbamazepine in the management of depression in BD

- P: Patients with bipolar disorder
- **I**: Carbamazepine
- **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 Selle et al (2014),[1] Butler et al (2018)[2], Miura et al. (2014)[3], and Kessing et al (2017).[5]
- To ensure no recent studies on carbamazepine 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) 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] Included 1 RCT, N=70.
  Response rate ratio: 1.84 (95% CI 1.01–3.34), NNT 3
  Difference in change of depression symptoms: non-significant, SMD 0.209 [95% CI -0.291 to 0.709]
  Withdrawal due to adverse events: not reported

<u>Maintenance treatment - prevention of relapse/ recurrence of depression</u>

- 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

Table 1. Carbamazepine – efficacy estimates for maintenance treatment, RCTs and network meta-analysis

Intervention vs control	Mood state	Eligible RCTs	NNT	NNH	Butler et al., 2018[2] Time to recurrence	Miura et al., 2014[3] Network meta-analysis
Carbamazepine vs placebo	Any mood episode	No placebo controlled RCTs	-	-		Risk ratio 0.68 (95% CI 0.44, 1.06)
Carbamazepine vs Lithium	Any mood episode	*Coxhead, 1992*, n=31	10	8	Not included	Not included in closed loop network
		Greil, 1997 n=171, BD-I and BD-NOS (not included in Miura et al.)	Events not reported		BD-I group: favors lithium p=0.034 (n=114) BD-II or BD-NOS: NS	
		Kleindienst et al 2000 n=171, BD-I, BD-II, and BD NOS	128	17	Not included	
		Hartong et al 2003 n=53, BD-I and BD-II	-3	-9	Proportional hazard assumption did not hold	
		Combined events	**-20**	**28**		
	Mania/ hypomania	*Hartong et al 2003*	**-8**	-	Not analysed	
	Depression	*Hartong et al 2003*	**-5**	-	Not analysed	

Table 2. Carbamazepine – evidence from observational studies

Paper	Comments
Kessing et al., 2017 Systematic review of observational studies	Of the 9 included studies of monotherapy, carbamazepine use is only noted specifically in one single-centre prospective observational study with N=135 (carbamazepine or lamotrigine, n=41; SGA, n=45; lithium, n=49). Efficacy estimate of carbamazepine not provided (lithium superior to all other medicines combined, log rank p=0.002). Carbamazepine was not specifically noted in any of the 4 studies of combination treatment.
Joas et al., 2017 Observational study of Swedish registries: within-individual analysis for hospitalisation rates	Of the six medicines evaluated, only carbamazepine (n=1253) was non-significant in prevention of any mood episode, hazard ratio [HR] 0.92 (95% CI 0.77–1.10) and depressive episodes, HR 0.98 (95% CI 0.64–1.48), but was effective in prevention of mania HR 0.50 (95% CI 0.29–0.86). As with lamotrigine, olanzapine, and quetiapine, carbamazepine had no efficacy in prevention of mixed episodes, HR 1.65 (95% CI 0.59–4.62).

7. Alternative agents

For treatment and prevention of bipolar depression: lithium; lamotrigine; quetiapine (see individual motivations).

Acute treatment of severe depression: ECT; quetiapine (proposed); possibly antidepressant augmentation of mood stabiliser/ antipsychotic (see antidepressant motivation).

8. Interpretation of the evidence and comments

Evidence of efficacy for carbamazepine in acute bipolar depression (NNT 3 at 8 weeks from 1 small RCT) is not supported by a significant difference vs placebo in change of depression score in the same study. Vs placebo, there is no evidence on network analysis for prevention of any mood episode. Vs lithium, RCT evidence favours lithium for prevention of depression and any mood episode. There are no observational studies suggesting equivalence to lithium in efficacy. The within-individual analysis by Joas et al (2017) suggests that even when carbamazepine is deemed clinically appropriate for the individual patient profile, it does not prevent depression or any mood episode.

In summary, evidence of efficacy in the management of bipolar depression does not outweigh the possibility of severe adverse effects and alternative treatments are available.

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 [ ]	Systematic reviews of RCTS of low to moderate quality: - Muira et al, 2014 - Selle et al, 2014 - Butler et al, 2018
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [ ] Harms outweigh benefits [X] 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 [ ] No [ ] Uncertain [X]	
RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [ ] Uncertain [X]	Cost of medicines/ month (30 days): **Medicine** | **Price (ZAR)** Carbamazepine | 62.16* *Contract circular RT289-2017 – weighted average price of 200mg tab = R 0.345 **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 the evidence review the Adult Hospital Level Committee recommends that carbamazepine not be recommended for management of bipolar depression.
Rationale: Insufficient evidence of efficacy in the management of bipolar depression with the possibility of severe adverse effects. Lithium also shown to be more efficacious than carbamazepine for reducing time to recurrence of any mood episode in BD-I study participants.
Level of Evidence: II 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

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. 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.
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. Lancet Psychiatry. 2014;1(5):351-9.
4. Murru A, Popovic D, Pacchiarotti I, Hidalgo D, Leon-Caballero J, Vieta E. Management of adverse effects of mood stabilizers. Curr Psychiatry Rep. 2015;17(8):603.
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.
6. Joas E, Karanti A, Song J, Goodwin GM, Lichtenstein P, Landen M. Pharmacological treatment and risk of psychiatric hospital admission in bipolar disorder. The British journal of psychiatry : the journal of mental science. 2017;210(3):197-202.