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

1. Executive Summary – Summary of overall review of treatment for Bipolar Disorder

Date: 14 March 2019
Recommended medicines

- 1st line
  - Any mood episode, acute treatment and prevention of relapse: lithium (LoE I)
- 2nd line
  - Mania, acute treatment and prevention of relapse: valproate, risperidone (both LoE III), olanzapine (LoE II)
  - Depression, acute treatment and prevention of relapse: lamotrigine (LoE III); quetiapine (LoE II)
- 3rd line
  - Any episode, treatment resistant to above options: clozapine (LoE III)
- Antidepressants
  - Depression, acute treatment – may be used in combination with an anti-manic treatment in BD-I and possibly as monotherapy in BD-II. Not recommended for long-term treatment.

Non-medicine interventions:

- ECT, severe acute depression (LoE III)
- Psychoeducation, all users and families/ caregivers

Medicine (ATC): See attached individual medicine motivations
Patient population: Adults
Indication (ICD10 code): Bipolar Disorder (F30.0-2/F30.8-9/F31.0-9)
Level of Care: Adult Hospital – District and Regional
Prescriber Level: Medical Officer / Specialist
NNT: See individual medicine motivations
Current standard of Care:

- Acute mania: benzodiazepines, oral risperidone, lithium or valproate
- Acute depression: lithium, valproate, lamotrigine, carbamazepine, fluoxetine/olanzapine
- Maintenance: lithium and/or valproate (however maintenance after depressive episode unclear)

Motivator/reviewer name(s): Dr Lesley Robertson
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2. Name of author(s)/motivator(s)

- *Primary reviewer:* 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 recused from the final decision-making process regarding recommendations.

4. Introduction

Bipolar and related disorders (BD) are severe, chronic relapsing illnesses with an onset in youth, persistence in later life, a variable course of depressive, hypomanic and manic episodes, and marked behavioural and functional disturbance.[1, 2] Although mania tends to be more disruptive, depression confers greater long-term disability.

Prevalence rates for South Africa are unknown but are possibly similar to global rates,[3] with a 12-month prevalence of around 1% for Bipolar I Disorder (BD-I) and 1% for Bipolar II Disorder (BD-II).

In South Africa, BD is managed within a deinstitutionalised mental healthcare system, with insufficient general hospital psychiatric beds and almost no community psychiatric services.[4-6] Thus, the burden of care is placed on ill-equipped generalist clinicians at district level. The result is a high demand for care of acute relapse in illness, with high numbers of repeat psychiatric admissions and extended length of stay at district hospital level. There is a need for accessible and optimal maintenance treatment to prevent relapse and recurrent episodes.

The current NDOH STGs recommend lithium as first line for maintenance treatment following a manic episode, and/or valproate for partial or non-responders or intolerability to lithium. However, risperidone is first line for acute mania. The algorithm for acute depression is more complex. Fluoxetine with olanzapine appear to be first line treatment, with or without lithium, valproate, carbamazepine, or lamotrigine, and it is not clear what should be continued for prevention of relapse.

A greater emphasis on maintenance treatment of BD, with a collaborative care approach, is proposed to prevent relapse and to optimise individual functioning. Important considerations include polypharmacy, multimorbidity, prevention of cognitive decline, prevention of suicide, and maintenance during pregnancy and childbirth.

Polypharmacy:

- Common in South Africa and globally.[7-9] Internationally, approximately 36% of patients with BD are prescribed ≥4 psychotropic medications.[7] Complex polypharmacy is more common in patients with a depressed or mixed course of illness (with increased prescribing of antidepressants and benzodiazepines) than those with a pure manic polarity. Lithium followed by valproate are the medicines least associated with polypharmacy. Guideline heterogeneity and poor guideline concordance are contributory factors.
- Acute-phase treatment is often continued into maintenance care, including medicines with no proven efficacy for prevention of relapse.[2, 7] Thus understanding the evidence for long-term treatment has recently received greater attention,[1,10,11] and an argument has been made for lithium, as 1st line maintenance treatment, to be used as 1st line treatment of acute episodes to ensure continuity.[10,12]
- BD does not always respond to lithium or valproate. Both medicines may be poorly tolerated, and both are teratogenic. Furthermore, drug-drug interactions, comorbid renal dysfunction, poor adherence and comorbid substance use may preclude lithium use. Poor clarity regarding alternative treatment choices may contribute to polypharmacy.

Multimorbidity:

- Increasingly recognised, with poor treatment outcomes of comorbid illnesses and high mortality among people with BD.
- Other mental illness: Over 90% of people with BD have a comorbid psychiatric disorder,[2] including anxiety disorders, substance use and personality disorders. Globally, the prevalence of BD among substance users is 4-5 times higher than among non-users.[13]
- NCDs: comorbidity includes cardiovascular and respiratory disease, Type2DM, thyroid disease, neurological disorders, migraine, and obesity.[2, 14] Life expectancy is reduced by 10 – 20 years and excess mortality is mainly attributable to medical illness. Possible mediation by immune-inflammatory systems as well as poor lifestyle and poor medication adherence is proposed.[15] There is evidence that long-term lithium use and maintenance of euthymia are associated with normalisation of pro-inflammatory cytokines.[16]
- HIV: high comorbidity with possible negative impact on HIV outcomes has been documented internationally.[17] In Sweden, prevalence of BD among HIV-infected people is 2.5 to 3 times higher than in the general population.[18] In China, BD confers a 3.6 times higher risk of contracting HIV,[19] and in USA, BD was found to increase HIV transmission behaviour.[20]
- Risk factors for non-adherence to physical health medication include the number of bipolar medications and more severe bipolar symptoms.[21, 22]

Cognitive decline:

- Lithium and anti-epileptics have evidence for neuroprotection,[23] with lithium associated with improvement in grey and white matter volume.[24, 25]

Suicide risk:

- Completed suicide is reported to be 15 – 30 times higher than in the general population.[26] BD is thought to be the highest risk psychiatric disorder, with BD-II possibly carrying a higher suicide risk than BD-I. Lithium is the only psychotropic confirmed to have an anti-suicide effect.

Pregnancy and childbirth:

- Four large cohort studies found a prevalence of previously diagnosed BD among pregnant women of 0.06% (Taiwan), 0.3% (Sweden and United States), and 0.4% (Canada).[27,28] Compared with those without a diagnosis of BD, a history of BD was associated with an increased risk of gestational hypertension (adjusted odds ratio [AOR] 2.81; 95% CI 2.53–3.10), antepartum haemorrhage (AOR 1.60; 95% CI 1.11–2.32), and placenta praevia (AOR 2.13; 95% CI 1.15–3.94). Preterm birth <37 weeks gestation was raised in all four cohorts, with AOR from 1.48; 95% CI 1.08–2.03 in Sweden to 2.08; 95% CI 1.53–2.83 in Taiwan. The Canadian analysis found an increased risk for <32 weeks (AOR 1.70; 95% CI 1.16–2.48) but not <28 weeks. Neonatal findings included an increase in SGA babies <3rd centile (OR 1.31; 95% CI 1.08–1.58), low birth weight (OR 1.66; 95% CI 1.16–2.38), and neonatal morbidity (AOR 2.99; 95% CI 2.44–3.66).
- Mood episodes during pregnancy and postpartum confer a serious risk to mother and infant.[29-31] The overall risk of relapse is 35%; 95% CI 29–41. This is significantly higher in those not taking prophylactic treatment during pregnancy (66%; 95% CI 57–75) than those on maintenance treatment (23%; 95% CI 14–37, p<0.001).[31] In general, prevention of relapse during pregnancy and postpartum is recommended depending on individual course of BD, medical and obstetric comorbidities. Lithium and valproate are teratogens. Although the benefits of lithium may outweigh risk,[32] valproate is contraindicated.[33]

Although the burden of disease due to BD in South Africa is unknown, it is probable that it exerts a healthcare burden greater than its global prevalence suggests. Taking the above factors into consideration, the following recommendations are made for the NDOH STGs for BD:

- Acute episodes are managed with the maintenance treatment of choice for that individual, according to the longitudinal course of illness, medical comorbidity, pregnancy risk, and patient preference.
- Treatment is recovery orientated aiming for euthymia, optimal functioning, and prevention of relapse.
- Rating scales are used to measure treatment response and ensure unnecessary medicines are stopped.
- While there is no evidence that BD may be effectively managed by PHC alone,[34] accessible maintenance care is essential to prevent relapse. Management at district level in consultation with a specialist, with availability of all medicines to at least regional hospital level, is needed.
- Comorbid medical illnesses are managed in an integrated manner with the BD.
- Pregnancy and childbirth are treated as high-risk for poor maternal and fetal outcomes as well as risk of relapse.

Serious limitations of the evidence inhibit decision-making for maintenance care. Restrictive inclusion criteria for RCTs, which commonly exclude people with comorbid psychiatric conditions, substance use, and medical conditions, limits generalisability. Recruitment of study participants with only mild to moderate illness possibly reduces effect sizes and limits generalisability. Bias is conferred by enrichment study design and high attrition rates. Finally, there is a paucity of studies with BD-II participants and bipolar depression; most studies are on BD I with a recent manic or mixed episode. Thus, consistency between different meta-analyses, observational studies, and expert opinion is needed to be certain of efficacy and inform management.

5. Purpose/Objective

The aim of this review is to establish what is best practice in the management of BD with a focus on maintenance treatment. Medicine-specific PICO questions are attached in individual motivations.

- P: Adults with Bipolar Disorder
- **I**: lithium, anti-epileptics, second-generation antipsychotics (SGAs), antidepressants
- **C**: placebo / active control
- **O**: Prevention of relapse into depression or mania during maintenance and reduction of manic or depressive symptomatology in the acute phase.

6. Methods

Search strategy:

To obtain the most recent evidence, Pubmed and Cochrane databases were searched on 03/03/2019 for systematic reviews in English published in the preceding 5 years (since 03/03/2014) using search terms (Bipolar Disorder OR Bipolar Depression OR Mania) AND (treatment OR medication OR antipsychotics OR anticonvulsants OR antidepressants OR lithium). The full search strategy and results are attached in Appendix I (Pubmed) and II (Cochrane).

The reference list of Maudsley Prescribing Guidelines 13th Edition yielded two additional papers evaluating treatments of acute bipolar depression.[35, 36] Both are meta-analyses without a critical appraisal or narrative synthesis of included studies. Selle et al (2014)[35] informs the current NDOH STGs and was included in this review. Taylor et al (2014)[36] was excluded as the funding source is not stated and it has a low AMSTAR score of 3/11 (no funding disclosure and no à priori design, duplicate study selection or data extraction, grey literature search, list of excluded studies, quality assessment, use of quality in conclusions, or assessment of publication bias).

Table 1. Studies included for overall decision-making

Category	Author and Title	Comments	Funding source
Comparative effectiveness systematic reviews and meta-analyses of RCTs	Butler et al. (2018)[2] Treatment for Bipolar Disorder in Adults: A Systematic Review	AMSTAR 11/11 Risk of Bias – adapted from Cochrane Strength of evidence – own tool	Agency for Healthcare Research & Quality
	Dundar et al. (2016)[37] Pharmacological treatment of acute agitation associated with psychotic and bipolar disorder: a systematic review and meta-analysis	AMSTAR 6/11 No a priori study design No duplicate data extraction No grey literature No list of excluded studies	None
	Lindstrom et al. (2017)[11] Maintenance therapy with second generation antipsychotics for bipolar disorder - A systematic review and meta-analysis	AMSTAR 8/11 No grey literature No list of excluded studies No test for publication bias Risk of Bias – Cochrane handbook Strength of evidence – GRADE	Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU)
	Miura et al (2014)[10] Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis	AMSTAR 9/11 No grey literature No list of excluded studies Risk of Bias – Cochrane Collaboration Tool Strength of evidence – GRADE	None
	Selle et al (2014)[35] Meta-analysis of placebo-controlled monotherapy trials for acute bipolar depression	AMSTAR 4/ 11 No duplicate data extraction No grey literature No list of excluded studies No quality assessment/ use in conclusions Stats – can't answer Publication bias not assessed	Non-profit donors

Systematic reviews of individual treatments	Bahji et al. (2018)[38] ECT beyond unipolar major depression: systematic review and meta-analysis of electroconvulsive therapy in bipolar depression	AMSTAR 7/11 No a priori study design No grey literature No list of excluded studies No specific conflict of interests/funding statement	None declared under acknowledgements
	Kessing et al (2018)[39] Effectiveness of maintenance therapy of lithium vs other mood stabilizers in monotherapy and in combinations: a systematic review of evidence from observational studies	AMSTAR 3/10 (Statistics – not applicable) No duplicate data extraction No grey literature No list of excluded studies No quality assessment/ use in conclusions Publication bias not assessed	Wellcome Trust
	Li et al (2015)[40] Clozapine for treatment-resistant bipolar disorder: a systematic review	AMSTAR 7/11 No list of excluded studies No quality assessment/ use in conclusions Publication bias not assessed	Beijing Science and Technology Commission
	McGirr (2016)[41] 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	AMSTAR 8/11 No a priori study design Quality assessment only for risk of bias No use of quality in conclusions Risk of Bias – Cochrane Collaboration Tool Strength of evidence – not assessed	None
Reviews of treatment effect on suicide	Chen et al. (2019)[42] Divalproex and its effect on suicide risk in bipolar disorder: A systematic review and meta-analysis of multinational observational studies	AMSTAR 10/11 No a priori study design	Tri-Service General Hospital Research Foundation
	Smith & Cipriani (2017)[43] Lithium and suicide in mood disorders: Updated meta-review of the scientific literature	Meta-review of systematic reviews of RCTs AMSTAR – not applicable Comprehensive literature search, characteristics of included studies, and quality appraisal performed No statistical analysis	NIHR Oxford cognitive health Clinical Research Facility and by the NIHR Oxford Health Biomedical Research Centre.
Expert opinion	Severus et al. (2018)[12] Efficacy and Effectiveness of Lithium in the Long-Term Treatment of Bipolar Disorders: An Update 2018	Narrative Review – included as expert opinion	Not declared

The results of additional searches regarding individual medicines are attached in Appendix III and discussed in the respective medicine motivations.

7. Results

Salient findings from each review are summarised below. Numbers needed to treat or to harm are calculated directly from the RCT events as reported in the respective meta-analysis. Outcomes for maintenance treatment are divided broadly into prevention of relapse into 'any mood episode', 'mania', or 'depression'. 'Any mood episode' means any relapse, including mania, hypomania, mixed, and depressive episodes, and is reported by RCTs separately to manic/hypomanic and depressive episodes. Most RCTs are on people with BD-I and an index, presenting, or recent past manic or mixed episode. This suggests that 'any mood episode' may be less applicable

to people with BD-II and may refer to prevention of relapse into manic or mixed states rather than depression. Nevertheless, this outcome does imply general affective stability.

COMPARATIVE EFFECTIVENESS REVIEWS:

a. Butler et al (2018)[2] Treatment for Bipolar Disorder in Adults: A Systematic Review

Intention to treat data was extracted, analysed, and discussed for all eligible studies. Data below is as reported by Butler et al.; NNT and NNH are calculated where RCT events are reported (taking into account attrition).

i. ACUTE MANIA (MONOTHERAPY)

Outcomes: For this review, two efficacy outcomes were used, response to treatment (defined as a 50% reduction in symptoms, used for NNT) and mean difference (MD) in change in the Young Mania Rating Scale (YMRS). For tolerability and for NNH, withdrawal due to adverse events is used. All outcomes at 3 weeks of treatment.

Lithium: 3 RCTs with a sufficient grade of evidence to draw conclusions.
vs placebo, *Bowden 2005*, n=193 and individual patient data from *Kushner 2006*, n=654: has efficacy vs placebo in response to treatment (NNT 5) and in change in YMRS. See results as in Table 2.
vs valproate, Bowden 2010, n=270: no significant difference in response rate or change in YMRS.

Anti-epileptic medications: grade of evidence insufficient to draw definite conclusions for all anti-epileptics.

- Carbamazepine, 2 eligible RCTs.

vs placebo, *Weisler 2006*, n=443: Favours carbamazepine for response to treatment (NNT 4) and change in YMRS with difference of 6 points (95% CI not provided). NNH 14 for any adverse event; NNH 20 for severe rash.
vs valproate, *Vasudev 2000*, n=30: No significant difference for response to treatment (however, NNT -5 favours valproate); NNH 2 for any adverse event; NNH 6 for tremor.

- Valproate, 2 eligible RCTs.

vs placebo, *Bowden 2006*, n=364: Response to treatment favours valproate, NNT 7, but mean difference in YMRS only 2.5 points vs placebo (95% CI not provided), NNH 14 for any adverse event; *Tohen 2008*, n=521: no significant difference in response to treatment or change in YMRS.

- Lamotrigine, 1 eligible RCT

vs lithium, *Ichim 2000*, n=30: non-significant for response to treatment, change in YMRS, serious adverse events.

SGAs vs placebo: 23 RCTs of monotherapy with sufficient grade of evidence (Table 2).
Cariprizine, olanzapine, and risperidone all have evidence of efficacy vs placebo in response to treatment and change in YMRS. Aripiprazole NNT 6 but pooled odds ratio of response rate is not significant (OR 1.88 (95% CI 0.96, 3.69). Ziprasidone NNT is 6 from combined events of both RCTs, but odds ratio of response rate in 1 RCT, n=197, is not significant (OR 1.84 (95% CI 1.00, 3.39).

Table 2. Efficacy of lithium and SGAs in monotherapy vs placebo in acute mania (Butler et al.)

Medicine	NNT	Mean Difference in YMRS Random Effects Model, MD (95% CI)	NNH
Lithium, 2 RCTs, (n=847; n=643 for MD and for NNH)	5	5.81 (2.21, 9.4)	42
Aripiprazole, 3 RCTs (n=844 for NNT, MD and NNH)	6 (NS)	4.24 (-0.82, 9.29) NS	-120
Asenapine, 3 RCTs (n=936	10 (NS)	4.37 (1.27, 7.47)	10
Cariprizine, 3 RCTs (n=1047; n=732 for NNH)	5*	5.38 (1.84, 8.92)	15
Olanzapine, 5 RCTs (n=1199 for NNT and MD; n=1236 for NNH)	6*	4.9 (2.34, 7.45)	56
Quetiapine, 5 RCTs (n=1007 for NNT and NNH, n=699 for MD)	6*	4.92 (0.31, 9.53)	-100
Risperidone, oral, 2 RCTs (n=584, for NNT, MD, and NNH)	4	5.70 (2.33, 9.07)	100
Ziprasidone, 2 RCTs (n=302, for NNT and NNH)	6 (NS in 1 RCT)	Not reported	33

MD=Mean difference; NS=not significant; YMRS=Young mania rating scale;
*NNT calculated from pooled data by Butler et al as follows: Cariprizine=5.6; Olanzapine=6; Quetiapine=6.2

SGAs vs active control: 3 RCTs of olanzapine vs valproate with a sufficient grade of evidence to conclude no significant difference between olanzapine and valproate for response to treatment (2 RCTs, n=635, result not pooled) or change in YMRS (3 RCTs, n=750, pooled result, random effects model MD 1.68 (95% CI -0.59, 3.95).

Haloperidol: 2 eligible RCTs, grade of evidence of insufficient to draw definite conclusions.
vs placebo, *McIntyre 2005*, n=199: NNT 5, MD 7.4 (95% CI 3.05, 11.75), NNH 25*; Smulevich 2005*, n=284: NNT 7, MD 5.70 (95% CI 2.33, 9.07), NNH -50.

ii. ACUTE DEPRESSION (MONOTHERAPY)

Outcomes: Response to treatment, defined as 50% reduction in symptoms (used for NNT), mean difference in depression symptom scale, withdrawal due to adverse events (used for NNH), all at 12 weeks (shorter follow-up of acute treatment deemed unlikely to be clinically useful as does not reflect a sustained response).

Lithium: Grade of evidence insufficient to draw any definite conclusions.
vs placebo, no eligible studies
vs active control, see antidepressants

Anti-epileptic medications and SGAs: No eligible studies

Antidepressants: Grade of evidence insufficient to draw any definite conclusions.

- vs placebo, 1 eligible RCT, *Sachs 2007*, n=366 BD-I and BD-II, bupropion or paroxetine vs placebo: non-significant for response to treatment, change in rating scale not reported.

- vs lithium, 3 eligible RCTs.

Altshuler 2017, n=142 BD-II, sertraline vs lithium vs sertraline + lithium: non-significant across all groups for response to treatment, change in rating scale not reported;
Amsterdam 2016, n=129 BD-II and *Amsterdam 2008*, n=83 BD-II, both venlafaxine vs lithium: response to treatment favours venlafaxine, NNT 3 (p=0.0002) and NNT 2 (p=0.0005) respectively; change in depression scale favours venlafaxine (p<0.0001 and p=0.015 respectively).

iii. ACUTE DEPRESSION (ADJUNCTIVE TREATMENT)

Lithium: Grade of evidence insufficient to draw any definite conclusions.
Lithium + optimised personal treatment vs optimised personal treatment alone, Nierenberg 2013, N=283: fewer SGAs used in the lithium arm

Others: Grade of evidence insufficient to draw any definite conclusions.
3 eligible RCTs, one each for lamotrigine, memantine, and paroxetine or bupropion as adjunctive treatment to a mood stabiliser (MS): no significance difference between the intervention + MS vs placebo + MS.

iv. *MAINTENANCE (MONOTHERAPY)*

Outcome: Time to recurrence of any mood episode, mania, or depression in studies of at least 6-months duration.

Lithium: vs placebo, 5 RCTs. See separate motivation for details.
Results not pooled: in general, lithium superior for time to recurrence of 'any mood episode'. *Weisler 2011*, n=768 (considered the best quality of the 5 RCTs), HR 0.46 (95% CI 0.36, 0.59), p<0.0001.
Grade of evidence insufficient to confirm efficacy for time to recurrence of mania or depression. *Weisler 2011*: HR 0.37 (95% CI 0.27, 0.53) for mania and HR 0.59 (95% CI 0.42, 0.84) for depression.

Anti-epileptic medication: grade of evidence insufficient to draw definite conclusions.

- Carbamazepine, 2 eligible RCTs. See separate motivation.

vs lithium, *Greil 1997*, n=171: favours lithium for time to recurrence of any mood episode in BD-I participants, non-significant in BD-II; *Hartong 2003*, n=98: proportional hazard assumption did not hold for any mood episodes. No analysis conducted for prevention of mania or depression.

- Lamotrigine, 4 eligible RCTs.

vs placebo, *Bowden 2003*, n=129 and *Calabrese 2003*, n=242: log rank favours lamotrigine for time to any mood episode (p=0.02 and p=0.03 respectively) and for depression (p=0.002 and p=0.047). Non-significant for mania.

vs lithium, *Bowden 2003*, n=118 and *Calabrese 2003*, n=242: log rank non-significant for time to any mood, mania, or depression.
vs placebo or lithium, *Calabrese 2000*, n=182 with rapid cycling: non-significant between groups
vs discontinuation of mood stabiliser in pregnant women, *Newport 2008*, n=26: lamotrigine superior, NNT 1, for time to recurrence of any mood episode.

- Valproate, 3 eligible RCTs.

vs placebo, *Bowden 2000,* n=281: non-significant for time to recurrence of any mood episode, mania, depression
vs lithium, *Bowden 2000*, n=278; *Calabrese 2005*, n=60; *Geddes 2010*, n=220: all non-significant for all mood states

SGAs: grade of evidence of insufficient to draw definite conclusions.

- Aripiprazole, 2 eligible RCTs.

vs placebo, *Calabrese 2017*, n=266: favours aripiprazole long-acting injectable (LAI) for time to recurrence of any mood episode (p<0.0001, NNT=4), and mania (p<0.0001, events not reported). *Keck 2006*, n=161: favours aripiprazole oral for time to recurrence of any mood episode (HR 0.52 (95% CI 0.30, 0.91)) and mania (HR 0.31 (95% CI 0.12, 0.77)). Both RCTs non-significant for depression.

- Olanzapine, 5 eligible RCTS. See separate motivation for hazard ratios.

vs placebo, *Tohen 2006*, n=361; *Vieta 2012*, n=266; *Berwaerts 2012*, n=231: all favour olanzapine in time to recurrence of any mood episode (results not pooled), *Tohen 2006* and *Berwaerts 2012* favour olanzapine for mania, and *Tohen 2006* for depression.
vs lithium, *Tohen 2005*, n=431: non-significant for any relapse (type not specified)
vs valproate, *Tohen 2003*, n=251: non-significant for any relapse (type not specified)

- Paliperidone, oral, 1 eligible RCT.

vs placebo, *Berwaerts 2012*, n=300: favours paliperidone for time to recurrence of any mood episode (HR 1.43 (95% CI 1.03,1.98) p=0.017) and mania (HR 2.06 (95% CI 1.32,3.22) p<0.001)

- Quetiapine, 1 eligible RCT. See separate motivation for details.

vs placebo, *Weisler 2011*, n=808: favours quetiapine for time to recurrence of any mood episode HR 0.29 (95% CI 0.23, 0.38), mania HR 0.29 (95% CI 0.21, 0.40), and depression HR 0.30 (95% CI 0.20, 0.44).
vs lithium, *Weisler 2011*, n=768: favours quetiapine for time to recurrence of any mood episode, HR 0.66 (95% CI 0.49, 0.88), and depression, HR 0.54 (95% CI 0.35, 0.84), but not non-significant for mania.

- Risperidone LAI, 2 eligible RCTs. No RCTs for oral risperidone.

vs placebo*, Quiroz 2010*, n=303 and *Vieta 2012*, n=398: Log-rank test favours risperidone LAI (Quiroz, p=0.001 (HR 0.40 (95% CI 0.27, 0.59)) and (Vieta, p=0.03) for time to recurrence of any mood episode. Data not analysed for mania or depression.

CONCLUSION
No high- or moderate-strength evidence for any intervention for any phase of BD. Low-strength evidence for lithium in acute mania and for longer time to recurrence of any mood episode. Low-strength evidence for SGAs except aripiprazole in acute mania. Author recommendations revolve around future research methodology.

b. Dundar et al. (2016)[37] Pharmacological treatment of acute agitation associated with psychotic and bipolar disorder: a systematic review and meta-analysis

Systematic review and network meta-analysis of 17 RCTs (N=3841). Acute agitation is noted to not be the same as aggressive/ disruptive behaviour requiring rapid tranquillisation and the reader is referred to Cochrane reviews for the latter indication. Medicines studied: aripiprazole (IM), clonazepam (form of administration not specified), haloperidol (oral and IM), lorazepam (IM), loxapine (inhaled), olanzapine (oral, IM, and orally disintegrating tablet), risperidone (oral and orally disintegrating tablet), and ziprasidone (IM).

Network meta-analysis: No treatment more effective than any other.

Adverse effects: Olanzapine noted to have fewer adverse effects than lorazepam. Haloperidol noted to have more adverse effects than clonazepam.

Conclusion: No firm conclusions could be drawn regarding safety or efficacy of any intervention. Insufficient evidence to recommend one treatment over another for acute agitation in bipolar disorder.

c. Lindstrom et al (2017)[11] Maintenance therapy with second generation antipsychotics for bipolar disorder – A systematic review and meta-analysis

Evaluated 15 RCTs, including aripiprazole, olanzapine, quetiapine, risperidone long-acting injection (LAI) and ziprasidone. No eligible RCTs using oral risperidone were identified.

Outcome: relapse rate. NNTs by antipsychotic and mood episode are presented in Tables 3, 4, and 5 and were calculated, taking attrition into account. Risk ratios and hazard ratios are presented in individual medicine motivations.

Table 3. Efficacy in monotherapy vs placebo for prevention of relapse (Lindstrom et al)

Antipsychotic	NNT, Any mood	NNT, Mania	NNT, Depression
Aripiprazole, 1RCT, N=161 (*Keck 2006*, n=161, all BD-I, index episode manic or mixed	5	7	64
Olanzapine, 2 RCTs, N=617 (*Tohen 2006*, n=361; *Vieta 2012*, n=266, all BD-I, index episode manic or mixed	3	4	18
Quetiapine, 2 RCTs N=1393 (*Weisler 2011,* n=808, all BD-I, index episode manic, mixed or depressed; *Young 2014*, n=585, BD-I and BD-II, all depressed) *	4	10	8
Risperidone LAI, 2 RCTs N=542 (*Vieta 2012*, n=267; *Quiroz 2010*, n=275, both studies all BD-I with manic or mixed episode)	5	4	-35
Ziprasidone, no RCTs vs placebo	-	-	-

*Lindstrom et al only report hazard ratios; NNT calculated from events as reported in Miura et al (2014) for the same two studies

Table 4. Efficacy in monotherapy vs mood stabiliser in prevention of relapse (Lindstrom et al.)

Antipsychotic	NNT, Any mood	NNT, Mania	NNT, Depression
Aripiprazole, no RCTs	-	-	-
Olanzapine, 2 RCTs N=682 (*Tohen 2005*#, n=431, vs lithium, all BD-I, manic or mixed episode; *Tohen 2003*, n=251, vs valproate, all BD-I, manic, mixed)	19	18	-121
Quetiapine, 1 RCT N=768 (*Weisler 2011*, n=768, vs lithium, all BD-I with manic, mixed, or depressed episode) *	28	-102	22
Risperidone LAI, no RCTs	-	-	-
Ziprasidone, no RCTs vs mood stabiliser	-	-	-

Re-analysis by Tohen et al (2016)[44] revealed significantly more time spent in subsyndromal depression in olanzapine arm

*Lindstrom et al only report hazard ratios; NNT calculated from events as reported in Miura et al (2014)

Table 5. Efficacy as adjunctive treatment in prevention of relapse vs placebo (Lindstrom et al)

Antipsychotic	NNT, Any mood	NNT, Mania	NNT, Depression
Aripiprazole, 2RCTs N=688 (*Carlson 2012*, n=351, MS=lamotrigine, all BD-I, manic or mixed episode; *Marcus 2011,* n=337, MS=lithium/valproate, all BD-I, manic/mixed episode	9	12	33
Olanzapine, 1 RCT N=99 (*Tohen 2004*, n=99, MS=lithium/valproate, all BD-I manic or mixed episode)	5	9	6
Quetiapine, 2 RCTs N=1329 (*Suppes 2009*, n=623 and *Vieta 2008*, n=706; MS=lithium/valproate, all BD-I with manic, mixed or depressed episodes)	3	7	6
Risperidone LAI, 1 RCT N=124 (*Macfadden 2009*, n=124, MS='any', BD-I and BD-II, any mood episode)	4	8	16
Ziprasidone, 1 RCT N=2240 (*Bowden, 2011*, n=240, MS=lithium/valproate, all BD-I, manic or mixed	8	No result	No result

LAI=long-acting injection; MS=mood stabiliser

Regarding safety, Table 6 presents the NNH vs control using events as reported by Lindstrom et al. Results with statistical significance, favouring the control (NNH positive) or antipsychotic (NNH negative) are in bold.

Table 6. Numbers needed to harm by adverse effect and antipsychotic (Lindstrom et al.)

Weight gain	NNH
Aripiprazole, 3RCTs, N=790, control: placebo	**16**
Olanzapine, 4 RCTs N=1142, control: placebo, lithium (n=214), valproate (n=126)	**8**
Quetiapine, 2 RCTs, N=1326, control: placebo	**20**
Risperidone, 2 RCTs, N=427, control: placebo	**13**
Tremor	NNH
Aripiprazole, 2RCTs, N=501, control: placebo	**28**
Olanzapine, 2 RCTs N=350, control: placebo, valproate (n=126)	46
Quetiapine, 3 RCTs with 4 comparisons, N=2956, control: placebo, lithium (n=418)	-23
Risperidone, 2 RCTs, N=427, control: placebo	**19**
Ziprasidone, 1 RCT, N=239, control: placebo	37
Akathisia	NNH
Aripiprazole, 2RCTs, N=501, control: placebo	**20**
Olanzapine, 2 RCTs N=682, control: lithium (n=214), valproate (n=126)	57
Quetiapine, 1 RCT, N=623, control: placebo	72
Risperidone, 1 RCT, N=124, control: placebo	-46
Somnolence/sedation	NNH
Aripiprazole, 1RCT, N=160, control: placebo	-49
Olanzapine, 4 RCTs N=1142, control: placebo, lithium (n=214), valproate (n=126)	**17**
Quetiapine, 3 RCTs with 4 comparisons, N=2956, control: placebo, lithium (n=418)	**25**
Risperidone, 1 RCT, N=124, control: placebo	16
Insomnia	NNH
Aripiprazole, 2RCTs, N=501, control: placebo	-24
Olanzapine, 4 RCTs N=1142, control: placebo, lithium (n=214), valproate (n=126)	**-7**
Quetiapine, 3 RCTs with 4 comparisons, N=2956, control: placebo, lithium (n=418)	**-11**
Risperidone, 2 RCTs, N=427, control: placebo	74
Ziprasidone, 1 RCT, N=239, control: placebo	-19

d. Miura et al (2014)[10] Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis

Included 33 RCTs (N=6846). Outcomes measured at longest available follow-up.

Primary outcomes: treatment efficacy, recurrence rate of 'any mood episode'; treatment tolerability, drop-out rate due to adverse events.
Secondary outcomes: treatment efficacy according to type of mood episode, recurrence rate of any mood, manic/hypomanic/mixed, or depressed episode; acceptability, discontinuation for any reason,

Fluoxetine (2 RCTs, N=67) excluded from meta-analysis as treatment emergent symptoms were not reported.

Network analysis of all eligible comparisons for primary outcomes: all treatments efficacious in prevention of any mood episode except aripiprazole (risk ratio [RR] 0·62, [95% CI] 0·38–1·03), carbamazepine (RR 0·68, 0·44–1·06), imipramine (RR 0·95, 0·66–1·36), and paliperidone (RR 0·84, 0·56–1·24).

Closed-loop network of monotherapy/ combination therapy with at least two other treatment nodes: see Table 8 for results. Aripiprazole, carbamazepine, paliperidone all excluded as had only one other treatment node.

Sensitivity analysis: Lamotrigine vs placebo non-significant for prevention of depression on sensitivity analysis for

enrichment study design (RR 0·71, 0·49–1·03) or sponsorship bias (RR 0·72, 0·50–1·02), and non-significant for any mood episode (RR 0·75, 0·55–1·01) and depression (RR 0·68, 0·44–1·01) when restricted to trials of > 52 weeks.

Table 8. Results of closed loop network for prevention of relapse, tolerability and acceptability vs placebo Risk ratio (95% CI), Miura et al., 2014[10]

Medicine (quality of evidence)	Any mood episode	Mania/ hypomania	Depression	Tolerability	Acceptability
Lithium (moderate)	**0·62 (0·53–0·72)**	**0·58 (0·45–0·76)**	**0·76 (0·61–0·93)**	**2·58 (1·33–5·39)**	**0·83 (0·70–0·96)**
Lamotrigine (low)	**0·76 (0·62–0·94)**	0·90 (0·60–1·34)	**0·69 (0·50–0·94)**	0·69 (0·21–2·35)	0·84 (0·67–1·03)
Valproate (low)	**0·63 (0·47–0·83)**	0·66 (0·43–1·00)	0·78 (0·50–1·16)	1·35 (0·35–5·32)	0·79 (0·60–1·03)
Olanzapine (moderate)	**0·50 (0·39–0·63)**	**0·35 (0·25–0·50)**	0·80 (0·57–1·12)	2·18 (0·95–6·13)	**0·68 (0·52–0·87)**
Quetiapine (low)	**0·52 (0·40–0·68)**	**0·61 (0·42–0·92)**	**0·48 (0·34–0·67)**	1·23 (0·57–2·73)	**0·66 (0·49–0·88)**
Risperidone LAI (low)	**0·64 (0·48–0·85)**	**0·42 (0·28–0·64)**	1·32 (0·84–2·09)	1·78 (0·54–6·41)	0·79 (0·58–1·06)
Imipramine (very low)	0·95 (0·66–1·36)	1·31 (0·66–2·61)	0·73 (0·37–1·49)	2·82 (0·05–149·76)	**1·64 (1·06–2·54)**
Lithium + valproate (low)	**0·52 (0·35–0·77)**	**0·42 (0·23–0·76)**	0·70 (0·41–1·17)	4·09 (1·01–16·96)	0·72 (0·47–1·09)
Lithium + imipramine (low)	**0·62 (0·40–0·96)**	0·78 (0·39–1·54)	0·54 (0·27–1·07)	8·82 (0·31–253·41)	0·80 (0·54–1·14)

LAI=long acting injection; significant results in bold

Tables 9 and 10 present the NNT (relapse rate) and NNH (withdrawal due to adverse events) for monotherapy and combination therapy respectively. These are calculated from the events of all included RCTs provided in the supplementary material. For NNT, a negative value favours control. For NNH, a negative value implicates the control.

Table 9. NNT and NNH for monotherapy using RCT events as reported by Miura et al., 2014

Medicine vs placebo	NNT, Any mood	NNT, Mania	NNT, Depression	NNH, Adverse event
Lithium, 10 RCTs, N=1662, any BD	4 10 RCTs, n=1662	7 7 RCTs, n=1415	16 8 RCTs, n=1468	28 4 RCTs, n=1331
Carbamazepine, no placebo-controlled studies	-	-	-	-
Lamotrigine, 4 RCTs, N=706, BD-I (BD-II formed some of participants in one RCT)	9	23 3 RCTs, n=524	11 3 RCTs, n=524	-21 3 RCTs, n=603
Valproate, 1 RCT, N=281, all BD-I	7	21	10	Not reported
Aripiprazole, 1RCT N=161, all BD-I	5	6	64	15
Olanzapine, 2 RCTs N=627, all BD-I	3	5	18	18
Paliperidone, 1 RCT, N=300, all BD-I	12	7	-18	No difference vs placebo
Quetiapine, 2 RCTs, N=1393, BD-I and BD-II	4	10	8	100 1 RCT, n=808; (Other RCT, NNH=1/0)
Risperidone LAI, 2 RCTs, N=542, all BD-I	5	4	-35	43 1 RCT, n=267 (Other RCT, NNH=1/0)
Fluoxetine, 2 RCTs, N=75, all BD-II	-	-	4	1/0 1 RCT, n=63 (Other RCT, not reported)
Imipramine, 2 RCTs, N=38, all BD-II	10	-18 1 RCT, n=12	4 1 RCT, n=12	Not reported
Medicine vs lithium	NNT, Any mood	NNT, Mania	NNT, Depression	NNH, Adverse event

Carbamazepine, 3 RCTs, N=255, any BD	-20	-8 1 RCT, n=53	-5 1 RCT, n=53	28
Lamotrigine, 2 RCTs, N=397, all BD-I	-25	-11	19	-6
Valproate, 3 RCTs, N=558 BD-I and BD-II	16	122	48	-24 2 RCTs, n=280
Aripiprazole, no head to head studies vs lithium	-	-	-	-
Olanzapine, 1 RCT, N=431, all BD-1	11	10	1/0	-15
Paliperidone, no head to head studies vs lithium	-	-	-	-
Quetiapine, 1 RCT, N=768, all BD-I	28	-102	22	-49
Risperidone LAI, no head to head studies vs lithium	-	-	-	-
Fluoxetine, 1 RCT, N=54, all BD-II	-	-	4	1/0
Imipramine, 2 RCTs, N=87, any BD	-4	-4	-99	36 1 RCT, n=78 (Other RCT, not reported)

Table 10. NNT and NNH for combination treatments using RCT events as reported by Miura et al., 2014

Combination treatment vs placebo/active control	NNT, Any mood	NNT, Mania	NNT, Depression	NNH, Adverse event
Lithium +imipramine vs plac 1 RCT, N=13, all BD-II	2	7	2	Not reported
Lithium +imipramine vs lith 2 RCTs, N=153, any BD	-87	-16	-39	36
Lithium +valproate vs lith 1 RCT, N=220, all BD-I	18	11	-28	22
Lithium +valproate vs valp 1 RCT, N=220, all BD-I	6	6	10	22
Lamotrigine +valp vs lamotrigine 1 RCT, N=86, BD-I and BD-II	-	13	4	-23
Aripiprazole +valp vs valp 1 RCT, N=83, all BD-I	6	55	6	-11
Aripiprazole +lamot vs lamot 1 RCT, N=251, all BD-I	9	18	18	31
Oxcarbazepine +lithium vs lith 1 RCT, N=55, BD-I and BD-II	5	8	5	22

Author recommendations: Lithium, in having the most un-biased evidence of efficacy for prevention of manic and depressive relapse, should remain first-line maintenance treatment notwithstanding its higher rate of intolerability. Second and third line treatment may consider individual side-effect profile of medication and the dominant polarity of the patient's illness, with olanzapine being more anti-manic than quetiapine.

e. Selle et al (2014)[35] Meta-analysis of placebo-controlled monotherapy trials for acute bipolar depression

Meta-analysis of 24 RCTs with follow-up duration of 6 – 10 weeks.

Efficacy outcomes: Response to treatment, defined as a 50% reduction in depression symptoms (used for NNT), and standardised mean difference vs placebo (SMD) in depression symptom scale. Results presented in Table 11.

Table 11. Efficacy vs placebo for acute treatment of depressive episodes (Selle et al., 2014)

Medicine	NNT*	Standardised Mean Difference in change of depression symptom scores SMD (95% CI)
Lithium 1 RCT (N=265, 62.2% with BD-I, duration: 8 weeks)	15	0 .142 (-0.099, 0.383) p=0.25
Carbamazepine	3	0 .209 (-0.291, 0.709) p=0.41

1 RCT (N=70, 60.0% with BD-I, duration: 8 weeks)		
Lamotrigine 5 RCTs (N=1 071, 71.6% with BD-I, mean duration: 8.2 weeks)	10	0 .131 (-0.018, 0.280) p=0.09
Valproate 4 RCTs (N=140, 66.9% with BD-I, mean duration: 7 weeks	4	0 .452 (0.114, 0.790) p=0.009
Aripiprazole 2 RCTs (N=690, all BD-I, duration 8 weeks)	>100	0 .077 (-0.072, 0.227) p=0.28
Lurasidone 1 RCT (N=485, all BD-I, duration: 6 weeks)	5	0 .318 (0.128, 0.508) p=0.001
Olanzapine 2 RCTs (N=1 220, all BD-I, mean duration: 7 weeks)	11	0 .187 (0.072, 0.302) p=0.001
Quetiapine 5 RCTs (N=2 485, 66.4% with BD-I, mean duration: 8 weeks)	6	0 .373 (0.284, 0.462) p< 0.0001
Ziprasidone 2 RCTs (N=928, all BD-I, duration 6 weeks)	87	0 .103 (-0.036 to 0.241) p=0.14
Fluoxetine + Olanzapine (OFC) combination treatment 1 RCT (N=437, 82=OFC 355=placebo, all BD-I duration: 8 weeks	2	0 .453 (0.211, 0.695) p< 0.0001

*As calculated by authors.

SYSTEMATIC REVIEWS OF INDIVIDUAL TREATMENTS:

a. Bahji et al. (2018)[38] ECT beyond unipolar major depression: systematic review and meta-analysis of electroconvulsive therapy in bipolar depression

Prompted by the need for interventions in bipolar depression (BDD), which is more refractory to treatment than unipolar major depression (MDD), Bhaji et al hypothesized that ECT could be used more frequently in this disorder. The authors cite evidence that ECT is more effective than pharmacotherapy and is associated with reduced suicide rates in both unipolar major depression (MDD) and BDD. In addition, ECT has been shown to have mood stabilising properties in manic and mixed states. However, ECT is utilised less often for BDD than MDD in clinical practice.

19 studies (N=2422): Pooled result indicates equivalent efficacy of ECT in BDD vs MDD in terms of clinical response (NNT 34 for 50% reduction of symptoms). However, ECT was more efficient in BDD, with significantly fewer sessions required to achieve a clinical response, Standardised Mean Difference -0.23 (95% CI: -0.44 to -0.023) p=0.03.

Sensitivity analysis: findings were consistent on categorical analysis and univariate meta-regression.

Authors' conclusion: Notwithstanding study limitations, it is recommended that ECT be used more readily in BDD.

b. Kessing et al (2018)[39] Effectiveness of maintenance therapy of lithium vs other mood stabilizers in monotherapy and in combinations: a systematic review of evidence from observational studies

Nine observational studies (N=14271) investigating lithium vs alternative monotherapy and 4 studies (N=4627) investigating lithium vs combination therapy were included. High heterogeneity, no pooling of results possible.

Monotherapy: Lithium significantly better than valproate, lamotrigine, olanzapine, quetiapine, unspecified anti-epileptics, and unspecified antipsychotics for various outcome measures (hospitalisation/ re-hospitalisation/ treatment failure/ recurrence/other) in 8 of the 9 studies. The remaining study (Swedish database, N=2927) found no difference between lithium vs valproate, olanzapine or quetiapine in preventing rehospitalisation of BD-I patients discharged after a manic episode.

Lithium vs combination treatment, re-hospitalisation of BD-I patients after hospital discharge following a manic episode:

- Lithium + olanzapine (n=729) superior to lithium (n=859); HR 0.83 (95% CI 0.70-0.98); whereas lithium + valproate (n=202), lithium + quetiapine (n=316), lithium + aripiprazole (n=98) were all equivalent to lithium

- Lithium or valproate + unspecified SGA (n=63) superior to lithium or valproate alone (n=70); HR 0.17 (95% CI 0.05-0.61), whereas lithium or valproate + first-generation antipsychotic (n=68) was not.
- No significant difference between lithium or valproate in combination with either an SGA or FGA vs lithium or valproate alone (N=479)

Lithium vs combination treatment, recurrence among BD-I and BD-II euthymic outpatients:

- Lithium + quetiapine (n=25) was superior to lithium (n=39); recurrence rate 20% vs 53.8% p=0.01

Conclusion: naturalistic data indicates superiority of lithium over other treatments in monotherapy among patients with manic, mixed or depressed index episodes or in remission. Definite conclusion regarding combination therapy cannot be drawn, but it may be beneficial in selected patients. BD-I dominates and most studies did not separate types of BD. Distinguishing between prevention of manic or depressive episodes is not possible.

c. Li et al (2015) Clozapine for treatment-resistant bipolar disorder: a systematic review

Included 15 trials of 'all types' (N=1044). Study details are provided in the separate clozapine motivation.

Limited evidence revealed clozapine use to be associated with improved symptoms, reduced psychiatric hospitalisations, and reduced hospital visits for intentional self-harm in treatment-resistant BD. In comparison to published schizophrenia data, people with BD appeared to have greater clinical improvement on clozapine and fewer adverse effects.

d. McGirr (2016)[41] 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

Included 6 placebo-controlled trials (N=1383). Detailed results are provided in the antidepressant motivation.

Overall, adjunctive antidepressants improved clinician rated symptoms (SMD 0.165 (95% CI 0.051–0.278), p=0·004, but not response rates or remission. Acute treatment was not associated with manic/hypomanic switch. Treatment for 52 weeks (2 RCTs, N=463), significantly increased risk of mood switch, OR 1.774 (95% CI 1.018–3.091), p=0.043 (NNH=14).

Reviews of treatment effect on suicide

a. Chen et al. (2019) Divalproex and its effect on suicide risk in bipolar disorder: A systematic review and meta-analysis of multinational observational studies

Six cohorts with suicide outcomes for valproate (n=11 991 plus 8772 person-years in one cohort) vs no medication (n=2870 plus 23428 person-years in one cohort) and vs carbamazepine (n=1381 plus 1762 person-years). Studies comparing valproate with lithium were excluded as they have been addressed in other meta-analyses.

Valproate vs no medication: no significant difference in the incidence rates of suicide attempts RR 0.921 (95% CI 0.383 - 2.215) or completed suicides RR 0.607 (95% CI 0.180 - 2.043).

Valproate vs carbamazepine: no significant difference in the incidence rates of suicide attempts RR 0.815 (95% CI 0.453 - 1.466) or completed suicides RR 1.009 (95% CI 0.410 - 2.484).

Conclusion: valproate neither increased nor reduced suicide attempts or completed suicide

b. Smith & Cipriani (2017)[43] Lithium and suicide in mood disorders: Updated meta-review of the scientific literature

Included 16 systematic reviews of RCTs which reported suicide rates. Although suicide and mortality data in RCTs are sparse, lithium appears to reduce both suicide and all-cause mortality by >60% vs placebo. However, no

difference was found between lithium and other medication, in contrast to a 2003 observational study (N=20 638) which found a suicide risk 2.7 times higher (95% CI 1.1 - 6.3) in BD treated with valproate vs lithium.

The effect of lithium on deliberate self-harm in RCTs is not clear, being non-significant vs placebo but more effective than carbamazepine, OR 0.14 (95% CI .02–0.83) in the one systematic review (Cipriani, 2013).

EXPERT OPINION

a. Severus et al. (2018)[12] Efficacy and Effectiveness of Lithium in the Long-Term Treatment of Bipolar Disorders: An Update 2018

In a selective review of recent evidence, Severus, Bauer, and Geddes argue that lithium remains first-line treatment in BD despite the availability of other medicines. For clinical practice, they suggest lithium is commenced in acute mania, together with an SGA if needed, and then continued as maintenance treatment with weaning of the antipsychotic if possible.

While more consistent use of lithium is endorsed, no recommendations are made for second-line treatment for those who do not respond to lithium or are unable to tolerate its adverse effects. Neither is lithium's efficacy in bipolar depression discussed. Rather, the authors comment on the difficulty in predicting a positive response and tolerability, and in providing the "best possible individualised care."

8. Interpretation of the evidence and comments

Table 12 summarises the evidence of efficacy vs placebo for current standard of care, olanzapine and quetiapine.

Evidence is clear for lithium as first-line treatment, from RCTs (efficacy in prevention of any mood episode and in treatment of acute mania, Butler 2018), network meta-analysis (efficacy in prevention of any mood episode, mania, and depression in Miura 2014), and naturalistic data (superiority vs other monotherapy in prevention of rehospitalisation and recurrence of BD with manic, mixed or depressive index episodes in Kessing 2018).

The choice of 2nd and 3rd line treatments is less clear. For illness of a predominant manic polarity, valproate may be suitable. Although direct RCT evidence is very weak (conflicting findings for acute mania and no significance vs placebo in time to recurrence of mania in Butler, 2018), there is indirect evidence suggested by equivalent efficacy vs lithium and vs olanzapine. Network meta-analysis found valproate to be effective only in prevention of any mood episode. However, valproate may have better results in observational studies. Olanzapine and risperidone are alternatives, with stronger evidence for olanzapine. With no trials of oral risperidone, evidence is only available for Risperidone LAI. However, RCT data for risperidone LAI is not analysed for prevention of mania or depression by Butler et al., and usage of risperidone (LAI or oral) in BD is not evident in any of the observational studies included by Kessing et al (2017), except possibly as one of the 'unspecified antipsychotics.'

For illness of a predominant depressive polarity, lamotrigine and quetiapine are possibilities. Regarding lamotrigine, a disconnect between trial results and clinical experience has been noted,[45] and it may be more effective in BD-II than BD-I. Quetiapine has RCT (Lindstrom 2017) and network meta-analysis evidence of efficacy for prevention of depression but may cause more weight gain and somnolence than lamotrigine. There is insufficient evidence to support use of antidepressants in monotherapy in BD-II or as adjunctive treatment in BD-I other than in selected patients.

Carbamazepine has no evidence of efficacy in treatment or prevention of any episode, mania or depression. There is insufficient evidence to support other SGAs over olanzapine, quetiapine, and risperidone. However, clozapine appears to be an option in treatment resistant BD.

Table 12. Summary of evidence of efficacy vs placebo (new medicines shaded)

Medicine	Prevention of relapse (maintenance treatment)			Acute treatment	
	Any mood episode	Mania	Depression	Mania	Depression
Lithium Proposed as 1st line use	✓ Butler et al; Miura et al; Kessing et al	✓ Miura et al. Kessing et al.	✓ Miura et al Kessing et al Reduced suicide – Smith & Cipriani	✓ Butler et al	✖ in monotherapy ✓ with optimised personal treatment, Butler et al
Olanzapine Proposed as 2nd line for treatment and prevention of mania	✓ Miura et al; Lindstrom et al – equivalent to lithium/valproate	✓ Miura et al; Lindstrom et al – superior to lithium, equivalent to valproate	✖ (monotherapy) Miura et al, Lindstrom et al ✓ (adjunctive) Lindstrom et al	✓ Butler et al	✖ Selle et al., positive effect but NNT 11 [95% CI 7.0–30]
Quetiapine Proposed as 2nd line for treatment and prevention of depression	✓ Miura et al; Lindstrom et al (monotherapy and as adjunctive Rx)	✓ (mean dose 600mg) Miura et al; Lindstrom et al	✓ (mean dose 300mg) Miura et al; Lindstrom et al (monotherapy and as adjunctive Rx)	± Butler et al, NNT 6 but change in rating scale not significant (not clear if mean dose adequate in RCTs)	✓ (mean dose 300mg) Selle et al. NNT 5.9 [95%CI 4.7–7.8]
Risperidone Retain oral preparation for acute mania; insufficient evidence for prevention as none from observational studies	✓ (LAI only, no trials of oral) Miura et al; Lindstrom et al	✓ (LAI only, no trials of oral) Miura et al., Lindstrom et al	✖ (LAI, no trials of oral) Miura et al. Lindstrom et al	✓ (oral risperidone) Butler et al	✖ Selle et al – no eligible trials
Valproate Retain as standard of care Evidence as internal comparator and in observational studies	✓ Miura et al.	± Miura et al: NS Lindstrom et al: comparator in one study (olanzapine vs valproate)	± Miura et al: NS Lindstrom et al: comparator in one study (olanzapine vs valproate)	± Butler et al – 2RCTs, with conflicting results. Indirect evidence – NS vs lithium and vs olanzapine	± Selle et al – positive effect, 4 very small RCTs (total N=140), pooled result, but heterogeneity not analysed
Lamotrigine Retain as standard of care in bipolar depression	✓ Miura et al., at 26 weeks, not 52	✖ Miura et al	✓ Miura et al., at 26 weeks but not in sensitivity analysis. May be better in BD-II and in practice vs RCTs.[45]	✖ Butler et al	✖ Selle et al – NNT=10, small but significant difference in response rate but SMD not significant
Carbamazepine Remove from algorithm for treatment of bipolar depression	✖ Miura et al Butler et al	✖ Miura et al Butler et al	✖ Miura et al Butler et al	± Butler et al – insufficient grade studies suggest efficacy	✖ Selle et al – Only 1 small RCT; NNT=3 but SMD not significant
Clozapine 4th line – for treatment resistant BD	✓ Li et al – evidence for prevention of re-hospitalisation	Not reported	Not reported	✓ Li et al – improvement in YMRS	± Li et al – inconsistent reports for depression
Antidepressants Not for routine use. Retain for individual patients according to response and tolerability	Not applicable	Not applicable	✖ McGirr et al – increased risk of mania or hypomania	Not applicable	✓ McGirr et al – small effect in symptom change, no effect in response/ remission Selle et al (1 RCT, fluoxetine + olanzapine)

✓=evidence of efficacy; ✖=no evidence of efficacy; ±=evidence equivocal; LAI=long-acting injection; NS=not significant; SMD=standardised mean difference; YMRS=Young Mania Rating Scale

The following medication changes to the STGs are proposed:

- Lithium is inserted within the algorithm as treatment of choice in overall management of BD (LoE II)
- Valproate and lamotrigine are retained in the guideline as standard of care, with valproate used preferentially as an anti-manic and lamotrigine as an anti-depressant agent (LoE III for both).
- Carbamazepine is removed from the algorithm.
- Olanzapine is moved from treatment of depression to treatment and prevention of mania (LoE II).
- Quetiapine is added to the algorithm for treatment and prevention of depression (LoE II).
- Risperidone is retained for treatment of acute mania, but not recommended for prevention of mania algorithm (LoE II).
- Fluoxetine is removed from the algorithm for depression and ECT is added for acute severe depression
- Antidepressants are retained for use in *selected* patients with good response and tolerance (preferably managed at tertiary level of care).

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