Appendix Hoofdstuk 7a Wetenschappelijke onderbouwing farmacotherapie bij manie

7.2.2.1 Clinical review protocol (pharmacological and nutritional interventions for mania, hypomania and mixed episodes)

The review protocol summary, including the review question and the eligibility criteria used for this section of the guideline, can be found in Table 1 (a complete list of review questions and protocols can be found in Appendix 8; further information about the search strategy can be found in Appendix 9)

Table 6: Clinical review protocol summary for the review of pharmacological and nutritional interventions for mania, hypomania and mixed episodes

Topic	Interventions
Review question	RQ2.1: For adults with bipolar disorder, what are the relative benefits and harms of pharmacological and nutritional interventions for mania, hypomania and mixed episodes? What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, (iii) adults (18 to 64) and older adults (65+)?
Objectives	To estimate the efficacy of interventions to treat mania, hypomania and mixed episodes.
Criteria for considering studies for the review	
Intervention	All licensed oral medications (and their combinations). Nutritional interventions will be analysed separately.
Comparator	Placebo Other interventions
Types of participants	Adults (18+) with bipolar disorder who are experiencing an acute episode. Special consideration will be given to the groups above.
Outcomes	Response (50% reduction in symptoms) Discontinuation (due to side effect, other)
Time	The main analysis will include outcomes at the end of the acute treatment phase.

Study design	Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design in which providers and participants were blind to treatment. Quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth, and single-blind studies will be excluded.
Dosage	Fixed or flexible doses within the therapeutic range (BNF recommended).
Study setting	Primary, secondary, tertiary, health and social care
Note. BNF = British National Formulary.	

7.2.2.2 Studies considered[4]

The search for systematic reviews identified a recent review that included a network meta-analysis of pharmacological interventions for mania (Cipriani et al., 2011). The review reported the critical outcomes identified by the GDG, and the results were directly relevant to treatment of bipolar mania in the UK. To determine if new studies could change the conclusions of the review, the GDG conducted a search.

The search for new studies identified five RCTs: ASTRAZENECA2011 (Astrazeneca, 2011), BEHZADI2009 (Behzadi et al., 2009), CHIU2005 (Chiu et al., 2005), KANBA2012 (Kanba et al., 2012) and SZEGEDI2012 (Schering-Plough, 2007; Szegedi et al., 2012). Two studies about 'bipolar anxiety' were excluded from all reviews: SHEEHAN2009 (Sheehan et al., 2009), SHEEHAN2013 (Sheehan et al., 2013). Two open-label studies: SCHAFFER2013 (Schaffer et al., 2013), SINGH2013 (Singh et al., 2013); and three trials of medications neither routinely used nor licensed for the treatment of mental health problems: ZHANG2007 (Zhang et al., 2007), KULKARNI2006 (Kulkarni, 2005; Kulkarni et al., 2006), MCELROY2011 (McElroy et al., 2011) were also excluded from this review. Results could not be obtained for five studies: BOSE2012 (Bose, 2012), BRISTOLMYERSSQUIBB2011 (Bristol-Myers Squibb, 2011), FOREST2012 (Forest, 2012), KNESEVICH2009 (Knesivich, 2009), YANG2009 (Yang, 2009); although they have published several papers about the drug, the manufacturer of cariprazine has not reported the results of clinical trials, and they refused requests from the NCCMH for data.

Of the five new RCTs, three (N = 940; ASTRAZENECA2011, KANBA2012, SZEGEDI2012) could have been considered for the network meta-analysis. The new studies were analysed and their results compared with the results of the network meta-analysis for the critical outcomes. Two additional RCTs (N =1 03) which were not included in the network meta-analysis were also identified.

[4]Here and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study).

These were a trial of folic acid added to valproate (BEHZADI2009) and a trial of omega-3 polyunsaturated fatty acids added to valproate (CHIU2005).

Further information about both included and excluded studies can be found in Appendix 12 and Appendix 32.

7.2.2.3 Clinical evidence for pharmacological interventions for the treatment of mania

The GDG considered the findings of the network meta-analysis (Cipriani et al., 2011) alongside new trials (see Table 2). The network meta-analysis found robust evidence that several pharmacological interventions are efficacious. Furthermore, the network meta-analysis found evidence of differential effectiveness among medications, which is a unique strength of this method. Examining the results of several trials reported after the publication of the network meta-analysis, the GDG concluded that the most recent evidence is consistent with the results of the network meta-analysis and that the inclusion of new studies would not change the conclusions of that review. One study of folic acid added to valproate reported effects that the GDG considered clinically implausible and insufficient to lead to a recommendation (BEHZADI2009). In one study of omega-3 polyunsaturated fatty acids, it was not possible to extract outcomes, however the authors reported no effect of the intervention on manic symptoms. For these reasons, the GDG used the results of the network meta-analysis when considering what recommendations to make.

Table 7: Comparison between new studies and network meta-analysis (all results compared with placebo)

	New study result		**Network result (Cipriani 2011)**	
Mean change (YMRS)	SMD (95% CI)	k (N)	SMD (95% CI)	k (N)
Aripiprazole (KANBA2012)	-0.63 (-0.88, -0.37)	1 (122)	-0.37 (-0.51, -0.23)	7 (2436)
Asenapine (SZEGEDI2012)	-0.24 (-0.46, -0.02)	1 (155)	-0.30 (0.53, -0.07)	2 (960)
Lithium with quetiapine (ASTRAZENECA2011)	-0.29 (-0.50, -0.08)	1 (173)	-0.37 (-0.50, -0.25)	2 (370)
Response	OR (95% CI)	k (N)	OR (95% CI)	k (N)

Aripiprazole (KANBA2012)	0.51 (0.31, 0.85)	1 (128)	0.50 (0.38, 0.66)	7 (2571)
Asenapine (SZEGEDI2012)	0.72 (0.44, 1.15)	1 (159)	0.59 (0.31, 1.13)	1 (480)
Lithium with quetiapine (ASTRAZENECA2011)	0.50 (0.31, 0.81)	1 (173)	0.55 (0.38, 0.79)	2 (370)
Discontinuation	OR (95% CI)	k (N)	OR (95% CI)	k (N)
Aripiprazole (KANBA2012)	0.75 [0.46, 1.23)	1(128)	0.76 [0.55, 1.06)	7 (2631)
Asenapine (SZEGEDI2012)	0.79 [0.50, 1.24)	1(159)	0.98 [0.57, 1.71)	2 (977)
Lithium with quetiapine (ASTRAZENECA2011)	0.65 [0.38, 1.13)	1(173)	1.05 [0.78, 1.43)	2 (402)
Note. k = Number of trials. N = Number of participants receiving the treatment listed. Numbers represent all trials of the investigational drug and all participants assigned to that drug (that is, excluding those assigned to placebo or other comparators).				

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