NICE National Institute for Health and Care Excellence

Bipolar disorder: assessment and management

Evidence review for changes to valproate recommendations after revised MHRA safety advice

NICE guideline CG185

December 2023

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Introduction

In December 2022 the MHRA announced changes to regulatory status of valproate. NICE convened a streamlined working group to review the most recent evidence about the effectiveness of valproate and agree if any changes needed to be made to recommendations in CG185, to align with the new regulatory position. The update was undertaken so NICE could be ready to respond rapidly to planned MHRA safety updates. There were some delays to the final safety information being published by MHRA so NICE delayed publication of the update until the final alert was published.

Methods

This work was an urgent update and so did not follow the processes described in the Guidelines Manual. Details of the methods used are provided below.

Forming the working group

Because of the urgent nature of this update, open recruitment and the use of a full committee to update recommendations was not possible. Instead, a streamlined working group was convened consisting of an independent chair, 2 psychiatrists, 1 mental health specialist nurse, 1 pharmacist with mental health expertise and 2 lay members. Nominations for the psychiatrists were provided by the Royal College of Psychiatrists. Nominations for lay members were provided by Bipolar UK. Other members of the working group were sought from an open request for assistance to existing NICE networks. All working group members were asked to declare interests and the Declaration of Interests policy was applied.

An MHRA expert on valproate also attended working group meetings to advise on the evidence on valproate safety and the regulatory position.

Evidence review

- An electronic database search (see Appendix 1) identified systematic reviews on the use of valproate for the treatment of bipolar disorder published since the searches were run for the bipolar guideline (from November 2012 to December 2022)

- The full-text papers of 24 systematic reviews were screened for relevance to the existing valproate recommendations in the bipolar disorder guideline, 6 systematic reviews reported relevant evidence that has been summarised below. No quality assessment of the included studies was undertaken as recency was prioritised over quality.
- Three of these relevant systematic reviews included network meta-analyses (NMA; the preferred NICE method for comparing multiple interventions), 2 for the acute management of mania and 1 for the long-term treatment of bipolar to prevent relapse
- The results of these NMAs are presented in detail below, with tables of interventions ranked based on their effectiveness compared to placebo for a number of outcomes, including response to treatment, mania symptoms, discontinuation due to side effects for the acute treatment of mania, and recurrence/relapse (of any mood episode, of depressive episode, and of manic/hypomanic/mixed episodes) for long-term management
- For the systematic reviews that were relevant to the valproate recommendations but did not include a NMA, the overall conclusions of the systematic reviews are summarised below, and these are largely in agreement with the NMA evidence
- An electronic database search of randomised controlled trials (RCTs) published since the search dates of the included systematic reviews were also screened, and 1 relevant RCT was identified, the results of which are summarised below.

Training - introduction to network meta-analysis (NMA)

So that working group members were able to understand and interpret the evidence that was presented, brief training in network meta-analysis was provided.

Objectives of NMA

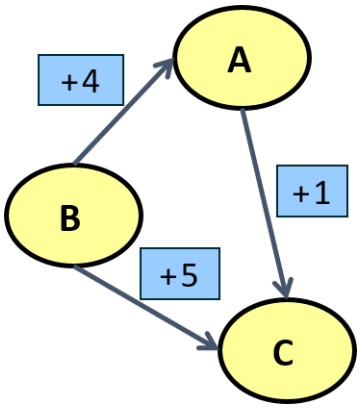
- To assess clinical effectiveness, data is pooled across RCTs (in a way that maintains within-trial randomisation) in order to estimate the effectiveness of an intervention in the target population
- Traditional pairwise meta-analysis pools data across RCTs and estimates the effectiveness of 1 intervention relative to another intervention or a control.

However, there are often more than 2 interventions of interest and performing multiple pairwise meta-analyses (comparing 2 interventions at a time) is not optimal in terms of making coherent and transparent decisions

- NMA allows identification of the best option when there are more than 2 options, by producing an internally coherent set of effect estimates and treatment options can be ranked from best to worst
- NMA also allows for comparisons between interventions that have not been directly compared in a RCT

Principles of NMA

- Network meta-analysis pools direct evidence (interventions have been compared against each other in 1 or more trials) and indirect evidence (interventions have not been compared against each other in a trial but the difference between them is imputed)
- Assumptions of network meta-analysis:
  - consistency in 'true' treatment effects, and loops in a network are important as they allow you to estimate indirect effects
  - The assumption is that the B vs C effect = A versus C effect + A versus B effect
  - This relies on the transitivity assumption: Treatment A has similar (relative) effect in A vs C and A vs B trials



Updating the recommendations

3 working group meetings were held during which the effectiveness data for valproate (published since GC185) on the treatment of acute mania and long-term management was presented. The working group discussed this data and agreed whether or not the recommendations about the use of valproate needed to be changed. The reasons for making any changes were documented.

Consultation

The guideline was updated with some additional information during the safety update to take account of practice points since the original publication in 2014. These changes did not meet the threshold for a full formal consultation.

Evidence

Managing bipolar disorder in primary care

Summary of the recommendation(s):

- Do not start valproate in primary care to treat bipolar disorder

Summary of the recent evidence:

- No update to the evidence required

Managing mania or hypomania in adults in secondary care: Acute management of mania

Summary of the recommendation(s):

- Antipsychotic treatment first-line
- Alternative antipsychotic as second-line
- Next stage(s) is augmentation with lithium **or valproate** (if lithium is ineffective or unsuitable)

Summary of recent evidence from systematic reviews:

Kishi et al. (2022): NMA of pharmacological interventions for adults with acute bipolar mania

Summary of inclusion criteria: RCTs (double-blind or single-blind; published or unpublished) of oral medication monotherapy lasting ≥10 days in adults with acute bipolar mania

Summary of exclusion criteria: use of antipsychotics as a rescue medication during a trial; children and adolescents; open-label studies; selection bias rated as high risk (based on the Cochrane Risk Of Bias tool); dual diagnosis of bipolar disorder with another disorder

Summary study characteristics: mean study duration 3.96 (SD 2.39) weeks; 56/72 studies (across outcomes) were industry sponsored; 21/72 studies rated as overall low Risk Of Bias (ROB); 14/72 studies included, and 26 studies excluded, individuals with rapid-cycling; 38/72 studies included, and 11 studies excluded, individuals with mixed state/episode; 35/72 studies included, and 4 studies excluded, individuals with psychosis

Summary demographics: 49% females; mean age 39.6 years

Search date: March 14, 2021

Outcome: Response to treatment (56 RCTs; 14503 participants)

Outcome measure: usually defined as ≥50% improvement in symptoms and assessed with Young Mania Rating Scale [YMRS] or Mania Rating Scale (Schedule for Affective Disorders and Schizophrenia) [MRS] [ideally assessed at 3-4 weeks]

Interventions compared against placebo and ranked based on effect size (from best to worst). Those that are statistically significant (relative to placebo) are in bold. Interventions with less than 50 participants randomised to them are greyed out

Intervention	K	N *randomised*	RR versus placebo (95% CI)

Tamoxifen	2	43	**7.461 (1.876 to 29.678)**
Carbamazepine	3	250	**1.902 (1.409 to 2.567)**
Risperidone	4	598	**1.689 (1.411 to 2.021)**
Haloperidol	7	991	**1.642 (1.432 to 1.883)**
Olanzapine	11	1448	**1.588 (1.403 to 1.797)**
Cariprazine	3	612	**1.558 (1.262 to 1.924)**
Quetiapine	5	630	**1.552 (1.316 to 1.830)**
Aripiprazole	7	1159	**1.529 (1.327 to 1.762)**
Lithium	12	835	**1.451 (1.275 to 1.652)**
Valproate	9	676	**1.424 (1.188 to 1.707)**
Paliperidone	2	542	**1.393 (1.102 to 1.761)**
Ziprasidone	3	458	**1.351 (1.061 to 1.721)**
Verapamil	1	17	1.324 (0.249 to 7.023)
Asenapine	3	620	**1.281 (1.049 to 1.563)**
Oxcarbazepine	1	30	1.266 (0.865 to 1.853)
Lamotrigine	3	173	1.259 (0.986 to 1.608)
Endoxifen	2	55	1.082 (0.710 to 1.648)
Licarbazepine	1	324	1.019 (0.706 to 1.469)
Eslicarbazepine	2	148	1.013 (0.763 to 1.345)
Topiramate	4	659	0.914 (0.736 to 1.135)

Pairwise comparisons in NMA dataset comparing **valproate** against other interventions showed:

- Valproate significantly more effective than placebo, eslicarbazepine and topiramate
- Tamoxifen significantly more effective than valproate
- For all other drugs there were no statistically significant head-to-head differences relative to valproate

Outcome: Mania rating scale scores (61 RCTs; 15466 participants)

Outcome measure: improvement of mania symptoms, assessed with the Young Mania Rating Scale, Mania Rating Scale developed from the Schedule for Affective Disorders and Schizophrenia, Change Version, or the Manic-State Rating Scale [ideally assessed at 3-4 weeks]

Interventions compared against placebo and ranked based on effect size (from best to worst). Those that are statistically significant (relative to placebo) are in bold. Interventions with less than 50 participants randomised to them are greyed out

Intervention	K	N *randomised*	SMD versus placebo (95% CI)
Tamoxifen	2	43	**-1.806 (-2.454 to -1.159)**
Haloperidol	8	1006	**-0.606 (-0.747 to -0.465)**
Risperidone	6	645	**-0.599 (-0.768 to -0.430)**
Carbamazepine	3	250	**-0.581 (-0.844 to -0.318)**
Cariprazine	3	612	**-0.498 (-0.710 to -0.285)**
Olanzapine	14	1565	**-0.492 (-0.614 to -0.370)**
Quetiapine	5	630	**-0.377 (-0.544 to -0.210)**
Paliperidone	2	542	**-0.377 (-0.620 to -0.134)**
Aripiprazole	7	1159	**-0.359 (-0.497 to -0.220)**
Lithium	13	834	**-0.350 (-0.479 to -0.222)**
Oxcarbazepine	1	30	-0.342 (-0.947 to 0.263)
Ziprasidone	3	458	**-0.338 (-0.558 to -0.118)**
Asenapine	3	620	**-0.311 (-0.507 to -0.115)**
Valproate	10	897	**-0.216 (-0.371 to -0.061)**
Eslicarbazepine	2	148	-0.169 (-0.566 to 0.227)
Lamotrigine	2	89	-0.102 (-0.356 to 0.151)
Licarbazepine	1	324	-0.090 (-0.439 to 0.259)
Brexpiprazole	2	321	-0.085 (-0.354 to 0.184)
Verapamil	1	17	0.016 (-0.737 to 0.769)
Topiramate	4	659	0.095 (-0.086 to 0.275)

Pairwise comparisons in NMA dataset comparing **valproate** against other interventions showed:

- Valproate significantly more effective than placebo and topiramate
- Tamxoifen, haloperidol, risperidone, carbamazepine, cariprazine, and olanzapine significantly more effective than valproate

For all other drugs there were no statistically significant head-to-head differences relative to valproate

Outcome: Discontinuation due to side effects (52 RCTs; 14629 participants)

Outcome measure: number of participants that discontinued due to side effects

Interventions compared against placebo and ranked based on effect size (from best to worst). Those that are statistically significant (relative to placebo) are in bold. Ns not reported (unclear which studies included in this analysis)

Intervention	RR versus placebo (95% CI)
Quetiapine	0.539 (0.268 to 1.086)
Brexpiprazole	0.881 (0.334 to 2.321)
Topiramate	1.015 (0.469 to 2.195)
Olanzapine	1.087 (0.714 to 1.656)
Aripiprazole	1.212 (0.850 to 1.728)
Valproate	1.220 (0.697 to 2.137)
Paliperidone	1.248 (0.576 to 2.701)
Ziprasidone	1.270 (0.632 to 2.552)
Risperidone	1.438 (0.800 to 2.585)
Valnoctamide	1.625 (0.303 to 8.734)
Cariprazine	1.658 (0.949 to 2.897)
Lithium	**1.791 (1.093 to 2.936)**
Endoxifen	1.809 (0.153 to 21.317)
Haloperidol	**1.867 (1.255 to 2.776)**
Asenapine	**1.896 (1.117 to 3.218)**
Carbamazepine	1.977 (0.882 to 4.427)
Lamotrigine	1.980 (0.811 to 4.836)

Pairwise comparisons in NMA dataset comparing **valproate** against other interventions showed:

- No statistically significant head-to-head differences in discontinuation due to side effects between valproate and other drugs

Hong et al. (2022): NMA of pharmacological interventions for adults with acute bipolar mania

Summary of inclusion criteria: RCTs (published or unpublished) of active antimanic drugs for the acute treatment of people of all ages with acute mania diagnosed using

primary standard diagnostic criteria (Young Mania Rating Scale (YMRS), the Mania Rating Scale (MRS), Mania Scale (MAS), and Manic State Rating Scale (MSRS))

Summary of exclusion criteria: dietary supplements and botanical drugs; adjuvant or combination therapies with psychotropic medications and lithium carbonate pharmaceuticals; dual diagnosis of bipolar disorder with another disorder; studies that included ≥20% of people with psychotic depression or treatment-resistant depression; studies that included people with a significant concurrent medical condition

Summary study characteristics: median study duration 8 weeks; 57/84 studies were industry sponsored

Summary demographics: 51% females; mean age 34.6 years; mean mania baseline score 29.7

Search date: Dec 18, 2021

Outcome: Mania rating scale scores (84 RCTs; 18716 participants)

Outcome measure: improvement of mania symptoms, assessed with the Young Mania Rating Scale (YMRS), the Mania Rating Scale (MRS), Mania Scale (MAS), and Manic State Rating Scale (MSRS) [ideally assessed at 3-4 weeks]

Interventions compared against placebo and ranked based on effect size (from best to worst). Those that are statistically significant (relative to placebo) are in bold. Ns not reported by arm

Intervention	K	Mean difference versus placebo (95% CI)
Tamoxifen	2	**-22.0 (-26.0 to -18.0)**
Risperidone	5	**-6.6 (-8.4 to -4.9)**
Carbamazepine	4	**-6.1 (-8.4 to -3.7)**
Haloperidol	10	**-5.4 (-6.9 to -3.9)**
Ziprasidone	3	**-5.4 (-7.9 to -2.8)**
Cariprazine	4	**-5.2 (-7.2 to -3.1)**
Olanzapine	13	**-5.0 (-6.3 to -3.6)**

Intervention	K	Mean difference versus placebo (95% CI)
Aripiprazole	11	**-4.3 (-5.6 to -3.0)**
Quetiapine	9	**-4.3 (-5.8 to -2.8)**
Eslicarbazepine	1	-4.1 (-9.1 to 0.80)
Lithium	21	**-4.1 (-5.3 to -2.8)**
Paliperidone	2	**-4.1 (-6.6 to -1.5)**
Asenapine	4	**-3.6 (-5.4 to -1.9)**
Valproate	16	**-2.8 (-4.3 to -1.4)**
Oxcarbazepine	1	-2.7 (-7.3 to 1.7)
Endoxifen	2	-2.6 (-6.2 to 0.96)
Melatonin	1	-1.7 (-7.4 to 3.9)
Valnoctamide	1	-1.5 (-5.0 to 2.0)
Licarbazepine	1	-1.1 (-4.6 to 2.4)
Brexpiprazole	1	-0.92 (-3.6 to 1.7)
Lamotrigine	5	-0.82 (-3.0 to 1.4)
Allopurinol	1	-0.41 (-4.5 to 3.6)
Verapamil	1	0.30 (-8.8 to 9.2)
Topiramate	2	0.98 (-1.1 to 3.0)

Data for pairwise (head-to-head) comparisons relative to valproate are not available.

Summary of reviews with pairwise meta-analyses:

- Jochim et al. (2019; 'Valproate for acute mania'). Overall conclusion of Cochrane review was: valproate was more effective than placebo for response rate for acute mania for adults (but not significantly so for children and adolescents); olanzapine may be more effective than valproate for adults, and risperidone may be more effective than valproate for children and adolescents

RCTs of valproate published post-SRs (from 2020 onwards):

- Talaei et al. (2022) RCT (N=48 included in efficacy analysis) comparing oxcarbazepine (900–2400 mg/day) and sodium valproate (about 20 mg/kg/day) for 6 weeks in adults with a diagnosis of bipolar I disorder in an acute manic episode, where all participants were already receiving risperidone. Mania symptoms improved with both oxcarbazepine and valproate but there was no significant difference between these 2 drugs.

Managing mania or hypomania in adults in secondary care: Long-term treatment of bipolar to prevent relapse

Summary of the recommendation(s):

- Lithium first-line long-term pharmacological treatment
- If lithium unsuitable, consider **valproate** or olanzapine (or quetiapine if previously effective)
- Augmentation with **valproate** if lithium is ineffective

Summary of recent evidence from systematic reviews:

Kishi et al. (2021): NMA of mood stabilisers and/or antipsychotics for bipolar in the maintenance phase

Summary of inclusion criteria: RCTs (blinded or open-label) of antipsychotics or mood stabilisers (duration ≥12 weeks) for adults with any bipolar disorder subtype in the maintenance phase; any mood symptoms at recruitment

Summary of exclusion criteria: children or adolescents; continuation studies which randomly assigned patients with acute symptoms to treatment groups; monotherapy and/or combination therapy studies of antidepressants with mood stabilizers or antipsychotics

Summary study characteristics: mean study duration 70.5 (SD 36.6) weeks; 29/41 studies (across outcomes) were industry sponsored; 3/41 studies open-label; 16/41 studies included individuals with rapid-cycling

Summary demographics: 54% females; mean age 40.7 years

Search date: May 22, 2020

Outcome: Recurrence/relapse rate of any mood episode (29 RCTs; 6890 participants)

Outcome measure: variable (unclear which studies included in analysis)

Interventions compared against placebo and ranked based on effect size (from best to worst). Those that are statistically significant (relative to placebo) are in bold. Ns not reported (unclear which studies included in this analysis)

Intervention	RR versus placebo (95% CI)
Asenapine	**0.262 (0.133 to 0.517)**
Aripirazole + valproate	**0.292 (0.114 to 0.748)**
Lithium + oxcarbazepine	**0.409 (0.212 to 0.792)**
Olanzapine	**0.500 (0.400 to 0.625)**
Aripiprazole once-monthly	**0.519 (0.335 to 0.803)**
Lithium + valproate	**0.525 (0.363 to 0.760)**
Quetiapine	**0.526 (0.411 to 0.674)**
Aripiprazole + lamotrigine	**0.530 (0.324 to 0.868)**
Aripiprazole	**0.619 (0.383 to 0.999)**
Lithium	**0.624 (0.537 to 0.725)**
Valproate	**0.634 (0.485 to 0.829)**
Risperidone long-acting injectable	**0.637 (0.484 to 0.839)**
Carbamazepine	0.684 (0.442 to 1.057)
Lamotrigine	**0.764 (0.628 to 0.930)**
Paliperidone	0.835 (0.575 to 1.212)

Pairwise comparisons in NMA dataset comparing **valproate** against other interventions showed:

- Valproate significantly more effective than placebo
- Asenapine significantly more effective than valproate
- For all other drugs there were no statistically significant head-to-head differences relative to valproate

Pairwise comparisons in NMA dataset comparing **lithium + valproate** against other interventions showed:

- Lithium + valproate significantly more effective than placebo
- For all other drugs there were no statistically significant head-to-head differences relative to lithium + valproate

Outcome: Recurrence/relapse rate of depressive episodes (25 RCTs; 6438 participants)

Outcome measure: variable (unclear which studies included in analysis)

Interventions compared against placebo and ranked based on effect size (from best to worst). Those that are statistically significant (relative to placebo) are in bold. Ns not reported (unclear which studies included in this analysis)

Intervention	RR versus placebo (95% CI)
Aripirazole + valproate	**0.273 (0.076 to 0.986)**
Lithium + oxcarbazepine	0.294 (0.086 to 1.002)
Asenapine	0.385 (0.138 to 1.069)
Lamotrigine + valproate	**0.470 (0.278 to 0.793)**
Quetiapine	**0.480 (0.364 to 0.633)**
Aripiprazole + lamotrigine	0.574 (0.315 to 1.046)
Lamotrigine	**0.713 (0.547 to 0.930)**
Lithium + valproate	0.741 (0.481 to 1.142)
Olanzapine	**0.742 (0.562 to 0.979)**
Lithium	**0.791 (0.660 to 0.948)**
Valproate	0.848 (0.596 to 1.206)
Aripiprazole	0.900 (0.417 to 1.942)
Aripiprazole once-monthly	1.061 (0.573 to 1.962)
Risperidone long-acting injectable	1.287 (0.857 to 1.932)
Paliperidone	1.311 (0.796 to 2.157)
Carbamazepine	2.729 (0.635 to 11.735)

Pairwise comparisons in NMA dataset comparing **valproate** against other interventions showed:

- Quetiapine significantly more effective than valproate
- For all other drugs there were no statistically significant head-to-head differences relative to valproate

Pairwise comparisons in NMA dataset comparing **lithium + valproate** against other interventions showed:

- No statistically significant head-to-head differences relative to lithium + valproate

Outcome: Recurrence/relapse rate of manic/hypomanic/mixed episodes (25 RCTs; 6438 participants)

Outcome measure: variable (unclear which studies included in analysis)

Interventions compared against placebo and ranked based on effect size (from best to worst). Those that are statistically significant (relative to placebo) are in bold. Ns not reported (unclear which studies included in this analysis)

Intervention	RR versus placebo (95% CI)
Asenapine	**0.208 (0.082 to 0.529)**
Lithium + oxcarbazepine	**0.301 (0.101 to 0.899)**
Aripiprazole once-monthly	**0.302 (0.166 to 0.550)**
Olanzapine	**0.347 (0.265 to 0.453)**
Risperidone long-acting injectable	**0.368 (0.268 to 0.507)**
Lithium + valproate	**0.397 (0.263 to 0.599)**
Aripiprazole	**0.416 (0.206 to 0.843)**
Aripiprazole + lamotrigine	**0.513 (0.265 to 0.993)**
Aripirazole + valproate	0.516 (0.119 to 2.228)
Lithium	**0.540 (0.445 to 0.655)**
Lamotrigine + valproate	0.543 (0.189 to 1.560)
Quetiapine	**0.555 (0.435 to 0.707)**
Paliperidone	**0.592 (0.403 to 0.870)**
Valproate	**0.640 (0.477 to 0.857)**
Lamotrigine	0.890 (0.650 to 1.219)
Carbamazepine	**2.069 (0.257 to 16.663)**

Pairwise comparisons in NMA dataset comparing **valproate** against other interventions showed:

- Valproate significantly more effective than placebo
- Asenapine, aripiprazole once-monthly, olanzapine, risperidone long-acting injectable, and lithium + valproate significantly more effective than valproate

- For other drugs there were no statistically significant head-to-head differences relative to valproate

Pairwise comparisons in NMA dataset comparing **lithium + valproate** against other interventions showed:

- Lithium + valproate significantly more effective than placebo, valproate and lamotrigine
- For all other drugs there were no statistically significant head-to-head differences relative to lithium + valproate

Summary of reviews with pairwise meta-analyses:

- Nestsiarovich et al. (2022; 'Preventing new episodes of bipolar disorder in adults'). Overall conclusion of SR was: Significantly lower risk of relapse associated with: aripiprazole, asenapine, lithium, olanzapine, quetiapine, and risperidone long-acting
- Yee et al. (2021; 'Long-term treatment of bipolar with valproate). Overall conclusion of SR was: valproate more effective than placebo for preventing relapse, but no significant differences between valproate and lithium, or second-generation antipsychotics (quetiapine/olanzapine), or other anticonvulsants (carbamazepine/lamotrigine)

Changes made to recommendations

Previous recommendation in CG185	Revised recommendation(s)	Rationale
1.2.8 Do not start valproate in primary care to treat bipolar disorder	1.2.8 Do not start valproate in primary care to treat bipolar disorder	No changes made. This recommendation is in line with the new regulations and therefore doesn't need to be changed
1.5.5 If an alternative antipsychotic is not sufficiently effective at the maximum licensed dose, consider adding lithium. If adding lithium is ineffective, or if lithium is not suitable (for example, because the person does not agree to routine blood monitoring), consider adding valproate instead. Do not offer valproate to women or girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years) for long-term treatment or to treat an acute episode, unless other options are ineffective or not tolerated and the pregnancy prevention programme is in place. Follow the MHRA safety advice on valproate use by women and girls	1.5.5 If an alternative antipsychotic is not sufficiently effective at the maximum licensed dose, consider adding lithium. 1.5.6 If adding lithium is ineffective, or if lithium is not suitable (for example, because the person does not agree to routine blood monitoring), consider adding valproate instead. 1.5.7 Do not start valproate for the first time in people (male or female) younger than 55 years, unless 2 specialists independently agree and document that there is no other effective and tolerated treatment, or there are compelling reasons that the reproductive risks do not apply. Ensure the pregnancy prevention programme is in place if valproate is used in women and girls of childbearing potential. Follow the MHRA safety advice on the use of valproate.	Recommendation broken up to make it easier to understand and what the sequence of interventions is. For adults, the updated evidence, shows valproate has comparable effectiveness to the other interventions that are recommended by the guideline. Therefore it would be consistent to retain it as a treatment option. The recommendation is to use valproate as the last option which would be in line with the new regulations (no other effective and tolerated treatment). Recommendation added to specify the new regulations.
1.5.8 If the person is already taking valproate or another mood stabiliser as prophylactic treatment, consider increasing the dose, up to	1.5.10 If the person is already taking a mood stabiliser as prophylactic treatment, consider increasing the dose, up to the maximum level in	The existing recommendation is about what to do if someone is already taking valproate (not a

Previous recommendation in CG185	Revised recommendation(s)	Rationale
the maximum level in the BNF if necessary, depending on clinical response. If there is no improvement, consider adding haloperidol, olanzapine, quetiapine or risperidone, depending on the person's preference and previous response to treatment. Follow the recommendations on using antipsychotics and valproate in section 1.10. If a woman or girl of childbearing potential is already taking valproate, advise her to gradually stop the drug because of the risk of fetal malformations and adverse neurodevelopmental outcomes after any exposure in pregnancy. See the MHRA safety advice on valproate use by women and girls.	the BNF if necessary, depending on clinical response. If there is no improvement, consider adding haloperidol, olanzapine, quetiapine or risperidone, depending on the person's preference and previous response to treatment. Follow the recommendations on using antipsychotics in section 1.10. 1.5.11 If the person is already taking valproate and develops mania or hypomania review their treatment including adherence and: • consider increasing the dose if tolerated, but be aware of the increased risk of side-effects at higher doses, or • consider changing to an alternative treatment. Follow the recommendations on using valproate in section 1.10. 1.5.12 If a woman or girl of childbearing potential is already taking valproate, advise her to gradually stop the drug under medical supervision because of the risk of fetal malformations and adverse neurodevelopmental outcomes after any exposure in pregnancy. Follow the MHRA safety advice on the use of valproate.	recommendation about a new prescription). The recommendation has been broken up into two: the first covering mood stabilisers in general and the second covering valproate specifically. The recommendation about valproate has been changed to recommend consider changing to an alternative treatment.
1.6.5 If a person develops moderate or severe bipolar depression and is already taking valproate, consider increasing the dose within	1.6.5 If a person develops moderate or severe bipolar depression and is already taking valproate, review their treatment including adherence and	The existing recommendation is about what to do if someone is already taking valproate(not a

Previous recommendation in CG185	Revised recommendation(s)	Rationale
the therapeutic range. If the maximum tolerated dose, or the top of the therapeutic range, has been reached and there is a limited response to valproate, add fluoxetine combined with olanzapine or add quetiapine, depending on the person's preference and previous response to treatment. • If the person prefers, consider adding olanzapine (without fluoxetine) or lamotrigine to valproate. • If there is no response to adding fluoxetine combined with olanzapine, or adding quetiapine, stop the additional treatment and consider adding lamotrigine to valproate. Follow the recommendations in section 1.10 on using valproate, antipsychotics and lamotrigine. If a woman or girl of childbearing potential is already taking valproate, advise her to gradually stop the drug because of the risk of fetal malformations and adverse neurodevelopmental outcomes after any exposure in pregnancy. See the MHRA safety advice on valproate use by women and girls.	consider increasing the dose if tolerated but be aware of the increased risk of side effects at higher doses. Follow the recommendations in section 1.10 on using valproate. 1.6.6 If the maximum tolerated dose, or the top of the therapeutic range for valproate, has been reached and there is a limited response, add either of the following options, depending on the person's preference and previous response to treatment: • fluoxetine combined with olanzapine or • quetiapine. Follow the recommendations in section 1.10 on using valproate and antipsychotics 1.6.7 If the person does not wish to try adding fluoxetine combined with olanzapine or adding quetiapine, consider: • adding olanzapine (without fluoxetine) or • adding lamotrigine or • changing from valproate to an alternative treatment. Follow the recommendations in section 1.10 on using valproate, antipsychotics and lamotrigine.	recommendation about a new prescription). The recommendation was long and complicated so has been broken up into more easy to understand sections. The treatment options from the existing recommendation (adding other medications to valproate) have been retained as the remit of this update was to look at new prescriptions of valproate. However minor amendments have been made to include reviewing treatment, including adherence, and including the option of changing valproate to an alternative medication.

Previous recommendation in CG185	Revised recommendation(s)	Rationale
	1.6.8 If there is no response to adding fluoxetine combined with olanzapine or adding quetiapine, consider stopping the additional medications and consider: • adding lamotrigine to valproate or • changing from valproate to an alternative treatment. Follow the recommendations in section 1.10 on using valproate, antipsychotics and lamotrigine. 1.6.9 If a woman or girl of childbearing potential is already taking valproate, advise her to gradually stop the drug under medical supervision because of the risk of fetal malformations and adverse neurodevelopmental outcomes after any exposure in pregnancy. Follow the MHRA safety advice on the use of valproate.	
1.6.6 Follow the recommendations on using antipsychotics in section 1.10 and be aware of the potential interactions between valproate and fluoxetine, lamotrigine and olanzapine. See the MHRA safety advice on valproate use by women and girls.	1.6.10 Follow the recommendations on using antipsychotics in section 1.10 and be aware of the potential interactions between valproate and fluoxetine, lamotrigine and olanzapine. Follow the MHRA safety advice on the use of valproate.	No changes made. Recommendation is about safety considerations, rather than initiation of valproate.
1.7.6 Offer lithium as a first-line, long-term pharmacological treatment for bipolar disorder and: • if lithium is ineffective, consider adding valproate	1.7.5 When considering long-term treatment, discuss with the person the possible benefits and risks of each drug for them, following the recommendations in section 1.10.	There is evidence from the review conducted for this update, that a number of antipsychotics are more effective than valproate alone so these have been recommended as 2nd line treatment. The interventions

Previous recommendation in CG185	Revised recommendation(s)	Rationale
• if lithium is poorly tolerated, or is not suitable (for example, because the person does not agree to routine blood monitoring), consider valproate or olanzapine instead or, if it has been effective during an episode of mania or bipolar depression, quetiapine. Discuss with the person the possible benefits and risks of each drug for them, following the recommendations in section 1.10. If a woman or girl of childbearing potential is already taking valproate, advise her to gradually stop the drug because of the risk of fetal malformations and adverse neurodevelopmental outcomes after any exposure in pregnancy. See the MHRA safety advice on valproate use by women and girls.	1.7.6 Offer lithium as a first-line, long-term pharmacological treatment for bipolar disorder. 1.7.7 If lithium is ineffective, poorly tolerated or is not suitable (for example, because the person does not agree to routine blood monitoring), consider an antipsychotic (for example asenapine, aripiprazole, olanzapine, quetiapine or risperidone). 1.7.8 If the first antipsychotic is poorly tolerated at any dose (including rapid weight gain) or ineffective at the maximum licensed dose, consider an alternative antipsychotic from the drugs listed in recommendation 1.7.7. 1.7.9 If an alternative antipsychotic is not effective, consider a combination of valproate with either: • an antipsychotic or • lithium. 1.7.10 Do not start valproate for the first time in people (male or female) younger than 55 years, unless 2 specialists independently agree and document that there is no other effective and tolerated treatment, or there are compelling reasons that the reproductive risks do not apply. Ensure the pregnancy prevention programme is in place if valproate is used in women and girls of	given as examples in recommendation 1.7.7. are those shown in the NMAs in the evidence review to have better efficacy than valproate. There is evidence from the NMA ranking that lithium and valproate is more effective than lithium alone or valproate alone. There is also evidence that aripiprazole and valproate is more effective than lithium alone or valproate alone or some antipsychotics alone. Given the risks of using valproate, and the increased side effects of combination therapy, the working group agreed to recommend an alternative antipsychotic as 2nd line treatment. The option to use valproate in combination was only recommended as 3rd line treatment. Recommendation added to specify the new regulations.

Previous recommendation in CG185	Revised recommendation(s)	Rationale
	childbearing potential. Follow the MHRA safety advice on the use of valproate. 1.7.11 If a woman or girl of childbearing potential is already taking valproate, advise her to gradually stop the drug under medical supervision because of the risk of fetal malformations and adverse neurodevelopmental outcomes after any exposure in pregnancy. Follow the MHRA safety advice on the use of valproate.	
1.10.27 Do not offer valproate to women or girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years) for long-term treatment or to treat an acute episode, unless other options are ineffective or not tolerated and the pregnancy prevention programme is in place. See MHRA safety advice on valproate use by women and girls.	1.10.27 Do not start valproate for the first time in people (male or female) younger than 55 years, unless 2 specialists independently agree and document that there is no other effective and tolerated treatment, or there are compelling reasons that the reproductive risks do not apply. Ensure the pregnancy prevention programme is in place if valproate is used in women and girls of childbearing potential. Follow the MHRA safety advice on the use of valproate.	Updated wording to be in line with new regulations
1.10.28 If a woman or girl of childbearing potential is already taking valproate, advise her to gradually stop the drug because of the risk of fetal malformations and adverse neurodevelopmental outcomes after any exposure in pregnancy. See the MHRA safety advice on valproate use by women and girls.	1.10.28 If a woman or girl of childbearing potential is already taking valproate, advise her to gradually stop the drug under medical supervision because of the risk of fetal malformations and adverse neurodevelopmental outcomes after any exposure in pregnancy. Follow the MHRA safety advice on the use of valproate.	No changes made. Text hyperlinking to MHRA advice updated.
Starting valproate 1.10.29 When starting valproate, measure the person's weight or BMI and carry out a full blood	1.10.29 When starting valproate, measure the person's weight or BMI and carry out a full blood count and liver function tests.	Link to MHRA safety advice removed from the recommendations as is

Previous recommendation in CG185	Revised recommendation(s)	Rationale
count and liver function tests. Do not offer valproate to women and girls of childbearing age (including young girls who are likely to need treatment into their childbearing years) unless other options are ineffective or not tolerated and the pregnancy prevention programme is in place. See the MHRA safety advice on valproate use by women and girls.		already included in the preceding two recommendations.
1.10.30 Advise people taking valproate, and their carers, how to recognise the signs and symptoms of blood and liver disorders and to seek immediate medical help if any of these develop. Stop valproate immediately if abnormal liver function or blood dyscrasia is detected. Although the absolute values of hepatic enzymes are a poor indicator of the extent of hepatic damage, it is generally accepted that if these are persistently elevated to over 3 times the upper normal limit, continuing to rise or accompanied by clinical symptoms, the suspected drug should be withdrawn. Raised hepatic enzymes of any magnitude accompanied by reduced albumin or impaired clotting suggest severe liver disease.	1.10.30 Advise people taking valproate, and their carers, how to recognise the signs and symptoms of blood and liver disorders and to seek immediate medical help if any of these develop. Stop valproate immediately if abnormal liver function or blood dyscrasia is detected. Although the absolute values of hepatic enzymes are a poor indicator of the extent of hepatic damage, it is generally accepted that if these are persistently elevated to over 3 times the upper normal limit, continuing to rise or accompanied by clinical symptoms, the suspected drug should be withdrawn. Raised hepatic enzymes of any magnitude accompanied by reduced albumin or impaired clotting suggest severe liver disease.	No changes made. Not affected by change to regulations.
1.10.31 When prescribing valproate, be aware of its interactions with other anticonvulsants (particularly carbamazepine and lamotrigine) and with olanzapine and smoking.	1.10.31 When prescribing valproate, be aware of its interactions with other anticonvulsants (particularly carbamazepine and lamotrigine) and with olanzapine and smoking.	No changes made. Not affected by change to regulations.
Monitoring valproate	Monitoring valproate	No changes made. Not affected by change to regulations.

Previous recommendation in CG185	Revised recommendation(s)	Rationale
1.10.32 Do not routinely measure plasma valproate levels unless there is evidence of ineffectiveness, poor adherence or toxicity.	1.10.32 Do not routinely measure plasma valproate levels unless there is evidence of ineffectiveness, poor adherence or toxicity.	
1.10.33 Measure the person's weight or BMI and carry out liver function tests and a full blood count again after 6 months of treatment with valproate and repeat annually.	1.10.33 Measure the person's weight or BMI and carry out liver function tests and a full blood count again after 6 months of treatment with valproate and repeat annually.	No changes made. Not affected by change to regulations.
1.10.34 Monitor sedation, tremor and gait disturbance carefully in older people.	1.10.34 Monitor sedation, tremor and gait disturbance carefully in older people.	No changes made. Not affected by change to regulations.
Stopping valproate 1.10.32 If stopping valproate, reduce the dose gradually over at least 4 weeks to minimise the risk of relapse.	1.10.32 If stopping valproate, to change to an alternative medication, reduce the dose gradually over at least 4 weeks to minimise the risk of relapse.	No changes made. Not affected by change to regulations.
1.11.10 Do not offer valproate to girls or young women of childbearing potential. See the MHRA safety advice on valproate use by women and girls.	1.11.10 Do not offer valproate to children unless 2 specialists independently agree and document that there is no other effective and tolerated treatment, or there are compelling reasons that the reproductive risks do not apply. Follow the MHRA safety advice on the use of valproate.	Updated wording to be in line with new regulations

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Nestsiarovich, A., Gaudiot, C. E., Baldessarini, R. J., Vieta, E., Zhu, Y., & Tohen, M. (2022). Preventing new episodes of bipolar disorder in adults: systematic review and meta-analysis of randomized controlled trials. European Neuropsychopharmacology, 54, 75-89.

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Yee, C. S., Vázquez, G. H., Hawken, E. R., Biorac, A., Tondo, L., & Baldessarini, R. J. (2021). Long-Term Treatment of Bipolar Disorder with Valproate: Updated Systematic Review and Meta-analyses. Harvard Review of Psychiatry, 29(3), 188-195.

Appendix 1 – Search strategy

RCTs

Database: CENTRAL – Wiley interface

ID	Search
#1	MeSH descriptor: [Bipolar and Related Disorders] explode all trees
#2	MeSH descriptor: [Cyclothymic Disorder] this term only
#3	MeSH descriptor: [Mania] this term only
#4	((bi?polar near/5 (depress* or disorder* or psychos* or psychotic)) or ((rapid or ultradian) near/5 cycl*) or cyclothymi* or hypomani* or mania* or manic* or "mixed episode*" or rcbd):ti,ab
#5	{or #1-#4}
#6	MeSH descriptor: [Valproic Acid] this term only
#7	(convulsofin or delepsine or depacon* or depaken* or depakin* or depakote or depalept or deprakine or "di n propylacetate" or "di n propylacetic acid" or diplexil or "dipropyl acetate" or "dipropyl acetic acid" or dipropylacetate or "dipropylacetatic acid" or "dipropylacetic acid" or diprosin or divalproex or epilam or epilex or epilim or episenta or "epival cr" or ergenyl or "espa valept" or everiden or goilim or hexaquin or labazene or leptilan or leptilanil or micropakine or mylproin or "myproic acid" or orfil or orfiril or orlept or petilin or "propylisopropylacetic acid" or propymal or "sodium 2 propylpentanoate" or "sodium 2 propylvalerate" or "sodium di n propyl acetate" or stavzor or valberg pr or valcote or valepil or valeptol or valerin or valhel pr or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprodura or "valproic acid" or valprosid or valprotek or valsup or vupral):ti,ab
#8	#6 or #7
#9	#5 and #8 with Publication Year from 2014 to 2022, in Trials

Database: CINAHL – Ebsco interface

Search History

#	Query	Limiters/Expanders
S36	S19 AND S35	Limiters - Published Date: 20140101-20221231; English Language Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S35	S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S34	AB (cluster W3 RCT)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase

S33	(MH "Crossover Design") OR (MH "Comparative Studies")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S32	AB (control W5 group)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S31	PT (randomized controlled trial)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S30	(MH "Placebos")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S29	(MH "Sample Size") AND AB (assigned OR allocated OR control)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S28	TI (trial)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S27	AB (random*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S26	TI (randomised OR randomized)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S25	(MH "Cluster Sample")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S24	(MH "Pretest-Posttest Design")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S23	(MH "Random Assignment")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S22	(MH "Single-Blind Studies")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase

S21	(MH "Double-Blind Studies")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S20	(MH "Randomized Controlled Trials")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S19	S10 NOT S18	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S18	S11 OR S14 OR S15 OR S16 OR S17	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S17	TI (rat or rats or mouse or mice)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S16	(MH "Rodents+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S15	(MH "Animals, Laboratory")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S14	S12 NOT S13	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S13	(MH "Human")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S12	(MH "Animals+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S11	PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT “questions and answers” or PT response or PT software or PT teaching materials or PT website	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase

S10	S5 AND S9	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S9	S6 OR S7 OR S8	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S8	AB (convulsofin or delepsine or depacon* or depaken* or depakin* or depakote or depalept or deprakine or "di n propylacetate" or "di n propylacetic acid" or diplexil or "dipropyl acetate" or "dipropyl acetic acid" or dipropylacetate or "dipropylacetatic acid" or "dipropylacetic acid" or diprosin or divalproex or epilam or epilex or epilim or episenta or "epival cr" or ergenyl or "espa valept" or everiden or goilim or hexaquin or labazene or leptilan or leptilanil or micropakine or mylproin or "myproic acid" or orfil or orfiril or orlept or petilin or "propylisopropylacetic acid" or propymal or "sodium 2 propylpentanoate" or "sodium 2 propylvalerate" or "sodium di n propyl acetate" or stavzor or valberg pr or valcote or valepil or valeptol or valerin or valhel pr or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprodura or "valproic acid" or valprosid or valprotek or valsup or vupral)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S7	TI (convulsofin or delepsine or depacon* or depaken* or depakin* or depakote or depalept or deprakine or "di n propylacetate" or "di n propylacetic acid" or diplexil or "dipropyl acetate" or "dipropyl acetic acid" or dipropylacetate or "dipropylacetatic acid" or "dipropylacetic acid" or diprosin or divalproex or epilam or epilex or epilim or episenta or "epival cr" or ergenyl or "espa valept" or everiden or goilim or hexaquin or labazene or leptilan or leptilanil or micropakine or mylproin or "myproic acid" or orfil or orfiril or orlept or petilin or "propylisopropylacetic acid" or propymal or "sodium 2 propylpentanoate" or "sodium 2 propylvalerate" or "sodium di n propyl acetate" or stavzor or valberg pr or valcote or valepil or valeptol or valerin or valhel pr or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprodura or "valproic acid" or valprosid or valprotek or valsup or vupral)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S6	(MH "Valproic Acid")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S5	S1 OR S2 OR S3 OR S4	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S4	AB (bipolar or "bi polar") n5 (depress* or disorder* or psychos* or psychotic)) or ((rapid or ultradian) n5 cycl*) or cyclothymi* or hypomani* or mania* or manic* or "mixed episode*" or rcbd)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S3	TI (((bipolar or "bi polar") n5 (depress* or disorder* or psychos* or psychotic)) or ((rapid or ultradian) n5 cycl*) or cyclothymi* or hypomani* or mania* or manic* or "mixed episode*" or rcbd)	Expanders - Apply equivalent subjects

		Search modes - Boolean/Phrase
S2	(MH "Mania")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S1	(MH "Bipolar Disorder+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase

Database: Embase – Ovid interface

Database(s): **Embase** 1996 to 2022 December 19

Search Strategy:

#	Searches	Results
1	exp mania/	80764
2	((bi?polar adj5 (depress* or disorder* or psychos* or psychotic)) or ((rapid or ultradian) adj5 cycl*) or cyclothymi* or hypomani* or mania* or manic* or mixed episode* or rcbd).ti,ab.	74532
3	1 or 2	98434
4	valproic acid/	61382
5	(convulsofin or delepsine or depacon* or depaken* or depakin* or depakote or depalept or deprakine or di n propylacetate or di n propylacetic acid or diplexil or dipropyl acetate or dipropyl acetic acid or dipropylacetate or dipropylacetatic acid or dipropylacetic acid or diprosin or divalproex or epilam or epilex or epilim or episenta or epival cr or ergenyl or espa valept or everiden or goilim or hexaquin or labazene or leptilan or leptilanil or micropakine or mylproin or myproic acid or orfil or orfiril or orlept or petilin or propylisopropylacetic acid or propymal or sodium 2 propylpentanoate or sodium 2 propylvalerate or sodium di n propyl acetate or stavzor or valberg pr or valcote or valepil or valeptol or valerin or valhel pr or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprodura or valproic acid or valprosid or valprotek or valsup or vupral).ti,ab.	25237
6	4 or 5	63956
7	3 and 6	9678
8	letter.pt. or letter/ or note.pt. or editorial.pt. or case report/ or case study/ or (letter or comment*).ti.	4320261
9	randomized controlled trial/ or random*.ti,ab.	1831880
10	8 not 9	4268239
11	(animal/ not human/) or nonhuman/ or exp animal experiment/ or exp experimental animal/ or animal model/ or exp rodent/ or (rat or rats or mouse or mice).ti.	6956736

12	10 or 11	10908393
13	7 not 12	6080
14	(random* or factorial* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or assign* or allocat* or volunteer* or placebo*).ti,ab.	2399555
15	crossover procedure/ or single blind procedure/ or randomized controlled trial/ or double blind procedure/	756968
16	14 or 15	2495203
17	13 and 16	1545
18	limit 17 to english language	1483
19	limit 18 to dc=20140120-20221220	503
20	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.	5139554
21	19 not 20	362

Database: HMIC – Ovid interface

Database(s): **HMIC Health Management Information Consortium** 1979 to September 2022

Search Strategy:

#	Searches	Results
1	bipolar disorder/	134
2	((bi?polar adj5 (depress* or disorder* or psychos* or psychotic)) or ((rapid or ultradian) adj5 cycl*) or cyclothymi* or hypomani* or mania* or manic* or mixed episode* or rcbd).ti,ab.	341
3	1 or 2	370
4	(convulsofin or delepsine or depacon* or depaken* or depakin* or depakote or depalept or deprakine or di n propylacetate or di n propylacetic acid or diplexil or dipropyl acetate or dipropyl acetic acid or dipropylacetate or dipropylacetatic acid or dipropylacetic acid or diprosin or divalproex or epilam or epilex or epilim or episenta or epival cr or ergenyl or espa valept or everiden or goilim or hexaquin or labazene or leptilan or leptilanil or micropakine or mylproin or myproic acid or orfil or orfiril or orlept or petilin or propylisopropylacetic acid or propymal or sodium 2 propylpentanoate or sodium 2 propylvalerate or sodium di n propyl acetate or stavzor or valberg pr or valcote or valepil or valeptol or valerin or valhel pr or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprodura or valproic acid or valprosid or valprotek or valsup or vupral).ti,ab.	17
5	3 and 4	6
6	limit 5 to english	6
7	limit 6 to yr="2014 -Current"	0

Database: INAHTA

Line	Query
11	#10 AND #6 FROM 2014 TO 2022 AND (English)[Language]
10	#9 OR #8 OR #7
9	((convulsofin or delepsine or depacon* or depaken* or depakin* or depakote or depalept or deprakine or "di n propylacetate" or "di n propylacetic acid" or diplexil or "dipropyl acetate" or "dipropyl acetic acid" or dipropylacetate or "dipropylacetatic acid" or "dipropylacetic acid" or diprosin or divalproex or epilam or epilex or epilim or episenta or "epival cr" or ergenyl or "espa valept" or everiden or goilim or hexaquin or labazene or leptilan or leptilanil or micropakine or mylproin or "myproic acid" or orfil or orfiril or orlept or petilin or "propylisopropylacetic acid" or propymal or "sodium 2 propylpentanoate" or "sodium 2 propylvalerate" or "sodium di n propyl acetate" or stavzor or valberg pr or valcote or valepil or valeptol or valerin or valhel pr or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprodura or "valproic acid" or valprosid or valprotek or valsup or vupral))[abs]
8	((convulsofin or delepsine or depacon* or depaken* or depakin* or depakote or depalept or deprakine or "di n propylacetate" or "di n propylacetic acid" or diplexil or "dipropyl acetate" or "dipropyl acetic acid" or dipropylacetate or "dipropylacetatic acid" or "dipropylacetic acid" or diprosin or divalproex or epilam or epilex or epilim or episenta or "epival cr" or ergenyl or "espa valept" or everiden or goilim or hexaquin or labazene or leptilan or leptilanil or micropakine or mylproin or "myproic acid" or orfil or orfiril or orlept or petilin or "propylisopropylacetic acid" or propymal or "sodium 2 propylpentanoate" or "sodium 2 propylvalerate" or "sodium di n propyl acetate" or stavzor or valberg pr or valcote or valepil or valeptol or valerin or valhel pr or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprodura or "valproic acid" or valprosid or valprotek or valsup or vupral))[title]
7	"Valproic Acid"[mh]
6	#5 OR #4 OR #3 OR #2 OR #1
5	((((bipolar or “bi polar” and (depress* or disorder* or psychos* or psychotic)) or ((rapid or ultradian) and cycl*) or cyclothymi* or hypomani* or mania* or manic* or “mixed episode” or “mixed episodes” or rcbd))[abs]
4	((((bipolar or “bi polar” and (depress* or disorder* or psychos* or psychotic)) or ((rapid or ultradian) and cycl*) or cyclothymi* or hypomani* or mania* or manic* or “mixed episode” or “mixed episodes” or rcbd))[title]
3	"Mania"[mh]
2	"Cyclothymic Disorder"[mh]
1	"Bipolar and Related Disorders"[mhe]

Database: Medline – Ovid interface

Database(s): **Ovid MEDLINE(R) ALL** 1946 to December 19, 2022

Search Strategy:

#	Searches	Results
1	exp "Bipolar and Related Disorders"/ or Cyclothymic Disorder/	44757

2	Mania/	376
3	((bi?polar adj5 (depress* or disorder* or psychos* or psychotic)) or ((rapid or ultradian) adj5 cycl*) or cyclothymi* or hypomani* or mania* or manic* or mixed episode* or rcbd).ti,ab.	58755
4	or/1-3	70775
5	Valproic Acid/	13758
6	(convulsofin or delepsine or depacon* or depaken* or depakin* or depakote or depalept or deprakine or di n propylacetate or di n propylacetic acid or diplexil or dipropyl acetate or dipropyl acetic acid or dipropylacetate or dipropylacetatic acid or dipropylacetic acid or diprosin or divalproex or epilam or epilex or epilim or episenta or epival cr or ergenyl or espa valept or everiden or goilim or hexaquin or labazene or leptilan or leptilanil or micropakine or mylproin or myproic acid or orfil or orfiril or orlept or petilin or propylisopropylacetic acid or propymal or sodium 2 propylpentanoate or sodium 2 propylvalerate or sodium di n propyl acetate or stavzor or valberg pr or valcote or valepil or valeptol or valerin or valhel pr or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprodura or valproic acid or valprosid or valprotek or valsup or vupral).ti,ab.	20050
7	5 or 6	22002
8	4 and 7	2934
9	Letter/ or Editorial/ or News/ or exp Historical Article/ or Anecdotes as Topic/ or Comment/ or Case Report/ or (letter or comment*).ti.	4847192
10	Randomized Controlled Trial/ or random*.ti,ab.	1504034
11	9 not 10	4815858
12	(Animals/ not Humans/) or exp Animals, Laboratory/ or exp Animal Experimentation/ or exp Models, Animal/ or exp Rodentia/ or (rat or rats or mouse or mice).ti.	6088381
13	11 or 12	10739827
14	8 not 13	1972
15	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt.	674357
16	drug therapy.fs.	2556942
17	(groups or placebo or randomi#ed or randomly or trial).ab.	3399535
18	Clinical Trials as Topic/	200659
19	trial.ti.	275852
20	or/15-19	5655754
21	14 and 20	1589
22	limit 21 to english language	1488
23	limit 22 to dt=20140120-20221220	398

24	limit 23 to ed=20140120-20221220	356
25	23 or 24	398

Database: PsycINFO – Ovid interface
Database(s): **APA PsycInfo** 2002 to December Week 2 2022
Search Strategy:

#	Searches	Results
1	exp bipolar disorder/	24901
2	((bi?polar adj5 (depress* or disorder* or psychos* or psychotic)) or ((rapid or ultradian) adj5 cycl*) or cyclothymi* or hypomani* or mania* or manic* or mixed episode* or rcbd).ti,ab.	35342
3	1 or 2	36323
4	Valproic Acid/	1576
5	(convulsofin or delepsine or depacon* or depaken* or depakin* or depakote or depalept or deprakine or di n propylacetate or di n propylacetic acid or diplexil or dipropyl acetate or dipropyl acetic acid or dipropylacetate or dipropylacetatic acid or dipropylacetic acid or diprosin or divalproex or epilam or epilex or epilim or episenta or epival cr or ergenyl or espa valept or everiden or goilim or hexaquin or labazene or leptilan or leptilanil or micropakine or mylproin or myproic acid or orfil or orfiril or orlept or petilin or propylisopropylacetic acid or propymal or sodium 2 propylpentanoate or sodium 2 propylvalerate or sodium di n propyl acetate or stavzor or valberg pr or valcote or valepil or valeptol or valerin or valhel pr or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprodura or valproic acid or valprosid or valprotek or valsup or vupral).ti,ab.	4317
6	4 or 5	4360
7	3 and 6	1693
8	(letter or editorial or comment reply).dt. or case report/	154151
9	(letter or comment*).ti.	28741
10	8 or 9	159668
11	exp randomized controlled trial/	1333
12	random*.ti,ab.	188475
13	11 or 12	188535
14	10 not 13	153872
15	animal.po.	268741
16	(rat or rats or mouse or mice).ti.	73554
17	or/14-16	419035
18	7 not 17	1240

19	clinical trial.md.	31447
20	Clinical trials/ or Randomized controlled trials/ or Randomized clinical trials/	13044
21	(assign* or allocat* or crossover* or cross over*).ti,ab.	110251
22	((doubl* or singl*) adj blind*).ti,ab.	20268
23	(factorial* or placebo* or random* or volunteer* or trial?).ti,ab.	317392
24	or/19-23	380750
25	18 and 24	500
26	limit 25 to english language	469
27	limit 26 to up=20140120-20221220	119

Systematic Reviews

Database: CDSR – Wiley interface

ID	Search
#1	MeSH descriptor: [Bipolar and Related Disorders] explode all trees
#2	MeSH descriptor: [Cyclothymic Disorder] this term only
#3	MeSH descriptor: [Mania] this term only
#4	((bi?polar near/5 (depress* or disorder* or psychos* or psychotic)) or ((rapid or ultradian) near/5 cycl*) or cyclothymi* or hypomani* or mania* or manic* or "mixed episode*" or rcbd):ti,ab
#5	{or #1-#4}
#6	MeSH descriptor: [Valproic Acid] this term only
#7	(convulsofin or delepsine or depacon* or depaken* or depakin* or depakote or depalept or deprakine or "di n propylacetate" or "di n propylacetic acid" or diplexil or "dipropyl acetate" or "dipropyl acetic acid" or dipropylacetate or "dipropylacetatic acid" or "dipropylacetic acid" or diprosin or divalproex or epilam or epilex or epilim or episenta or "epival cr" or ergenyl or "espa valept" or everiden or goilim or hexaquin or labazene or leptilan or leptilanil or micropakine or mylproin or "myproic acid" or orfil or orfiril or orlept or petilin or "propylisopropylacetic acid" or propymal or "sodium 2 propylpentanoate" or "sodium 2 propylvalerate" or "sodium di n propyl acetate" or stavzor or valberg pr or valcote or valepil or valeptol or valerin or valhel pr or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprodura or "valproic acid" or valprosid or valprotek or valsup or vupral):ti,ab
#8	#6 or #7
#9	#5 and #8 with Cochrane Library publication date Between Nov 2012 and Dec 2022, in Cochrane Reviews, Cochrane Protocols

Database: CINAHL – Ebsco interface

Search History

#	Query	Limiters/Expanders
S21	S19 AND S20	Limiters - Published Date: 20121101-20221231; English Language

		Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S20	(TI (systematic* n3 review*)) or (AB (systematic* n3 review*)) or (TI (systematic* n3 bibliographic*)) or (AB (systematic* n3 bibliographic*)) or (TI (systematic* n3 literature)) or (AB (systematic* n3 literature)) or (TI (comprehensive* n3 literature)) or (AB (comprehensive* n3 literature)) or (TI (comprehensive* n3 bibliographic*)) or (AB (comprehensive* n3 bibliographic*)) or (TI (integrative n3 review)) or (AB (integrative n3 review)) or (JN "Cochrane Database of Systematic Reviews") or (TI (information n2 synthesis)) or (TI (data n2 synthesis)) or (AB (information n2 synthesis)) or (AB (data n2 synthesis)) or (TI (data n2 extract*)) or (AB (data n2 extract*)) or (TI (medline or pubmed or psyclit or cinahl or (psycinfo not "psycinfo database") or "web of science" or scopus or embase)) or (AB (medline or pubmed or psyclit or cinahl or (psycinfo not "psycinfo database") or "web of science" or scopus or embase)) or (MH "Systematic Review") or (MH "Meta Analysis") or (TI ("meta analy*" or metaanaly*)) or (AB ("meta analy*" or metaanaly*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S19	S10 NOT S18	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S18	S11 OR S14 OR S15 OR S16 OR S17	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S17	TI (rat or rats or mouse or mice)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S16	(MH "Rodents+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S15	(MH "Animals, Laboratory")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S14	S12 NOT S13	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S13	(MH "Human")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S12	(MH "Animals+")	Expanders - Apply equivalent subjects

		Search modes - Boolean/Phrase
S11	PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT "questions and answers" or PT response or PT software or PT teaching materials or PT website	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S10	S5 AND S9	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S9	S6 OR S7 OR S8	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S8	AB (convulsofin or delepsine or depacon* or depaken* or depakin* or depakote or depalept or deprakine or "di n propylacetate" or "di n propylacetic acid" or diplexil or "dipropyl acetate" or "dipropyl acetic acid" or dipropylacetate or "dipropylacetatic acid" or "dipropylacetic acid" or diprosin or divalproex or epilam or epilex or epilim or episenta or "epival cr" or ergenyl or "espa valept" or everiden or goilim or hexaquin or labazene or leptilan or leptilanil or micropakine or mylproin or "myproic acid" or orfil or orfiril or orlept or petilin or "propylisopropylacetic acid" or propymal or "sodium 2 propylpentanoate" or "sodium 2 propylvalerate" or "sodium di n propyl acetate" or stavzor or valberg pr or valcote or valepil or valeptol or valerin or valhel pr or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprodura or "valproic acid" or valprosid or valprotek or valsup or vupral)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S7	TI (convulsofin or delepsine or depacon* or depaken* or depakin* or depakote or depalept or deprakine or "di n propylacetate" or "di n propylacetic acid" or diplexil or "dipropyl acetate" or "dipropyl acetic acid" or dipropylacetate or "dipropylacetatic acid" or "dipropylacetic acid" or diprosin or divalproex or epilam or epilex or epilim or episenta or "epival cr" or ergenyl or "espa valept" or everiden or goilim or hexaquin or labazene or leptilan or leptilanil or micropakine or mylproin or "myproic acid" or orfil or orfiril or orlept or petilin or "propylisopropylacetic acid" or propymal or "sodium 2 propylpentanoate" or "sodium 2 propylvalerate" or "sodium di n propyl acetate" or stavzor or valberg pr or valcote or valepil or valeptol or valerin or valhel pr or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprodura or "valproic acid" or valprosid or valprotek or valsup or vupral)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S6	(MH "Valproic Acid")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase

S5	S1 OR S2 OR S3 OR S4	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S4	AB (bipolar or "bi polar") n5 (depress* or disorder* or psychos* or psychotic)) or ((rapid or ultradian) n5 cycl*) or cyclothymi* or hypomani* or mania* or manic* or "mixed episode*" or rcbd)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S3	TI (((bipolar or "bi polar") n5 (depress* or disorder* or psychos* or psychotic)) or ((rapid or ultradian) n5 cycl*) or cyclothymi* or hypomani* or mania* or manic* or "mixed episode*" or rcbd)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S2	(MH "Mania")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S1	(MH "Bipolar Disorder+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase

Database: DARE – CRD interface

Line	Search	Hits
1	MeSH DESCRIPTOR Bipolar and Related Disorders EXPLODE ALL TREES IN DARE	126
2	MeSH DESCRIPTOR Cyclothymic Disorder IN DARE	0
3	MeSH DESCRIPTOR Mania IN DARE	0
4	(((bipolar or "bi polar") near5 (depress* or disorder* or psychos* or psychotic))) OR (((rapid or ultradian) near5 cycl*)) OR ((cyclothymi* or hypomani* or mania* or manic* or "mixed episode*" or rcbd)) IN DARE	259
5	#1 OR #2 OR #3 OR #4	259
6	MeSH DESCRIPTOR Valproic Acid EXPLODE ALL TREES	59
7	((convulsofin or delepsine or depacon* or depaken* or depakin* or depakote or depalept or deprakine or "di n propylacetate" or "di n propylacetic acid" or diplexil or "dipropyl acetate" or "dipropyl acetic acid" or dipropylacetate or "dipropylacetatic acid" or "dipropylacetic acid" or diprosin or divalproex or epilam or epilex or epilim or episenta or "epival cr" or ergenyl or "espa valept" or everiden or goilim or hexaquin or labazene or leptilan or leptilanil or micropakine or mylproin or "myproic acid" or orfil or orfiril or orlept or petilin or "propylisopropylacetic acid" or propymal or "sodium 2 propylpentanoate" or "sodium 2 propylvalerate" or "sodium di n propyl acetate" or stavzor or valberg pr or valcote or valepil or valeptol or valerin or valhel pr or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprodura or "valproic acid" or valprosid or valprotek or valsup or vupral))	182
8	#6 OR #7	182

9	#5 AND #8	43
10	* IN DARE WHERE LPD FROM 11/11/2012 TO 20/12/2022	19266
11	#9 AND #10	1

Database: Embase – Ovid interface
Database(s): **Embase** 1996 to 2022 December 19
Search Strategy:

#	Searches	Results
1	exp mania/	80764
2	((bi?polar adj5 (depress* or disorder* or psychos* or psychotic)) or ((rapid or ultradian) adj5 cycl*) or cyclothymi* or hypomani* or mania* or manic* or mixed episode* or rcbd).ti,ab.	74532
3	1 or 2	98434
4	valproic acid/	61382
5	(convulsofin or delepsine or depacon* or depaken* or depakin* or depakote or depalept or deprakine or di n propylacetate or di n propylacetic acid or diplexil or dipropyl acetate or dipropyl acetic acid or dipropylacetate or dipropylacetatic acid or dipropylacetic acid or diprosin or divalproex or epilam or epilex or epilim or episenta or epival cr or ergenyl or espa valept or everiden or goilim or hexaquin or labazene or leptilan or leptilanil or micropakine or mylproin or myproic acid or orfil or orfiril or orlept or petilin or propylisopropylacetic acid or propymal or sodium 2 propylpentanoate or sodium 2 propylvalerate or sodium di n propyl acetate or stavzor or valberg pr or valcote or valepil or valeptol or valerin or valhel pr or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprodura or valproic acid or valprosid or valprotek or valsup or vupral).ti,ab.	25237
6	4 or 5	63956
7	3 and 6	9678
8	letter.pt. or letter/ or note.pt. or editorial.pt. or case report/ or case study/ or (letter or comment*).ti.	4320261
9	randomized controlled trial/ or random*.ti,ab.	1831880
10	8 not 9	4268239
11	(animal/ not human/) or nonhuman/ or exp animal experiment/ or exp experimental animal/ or animal model/ or exp rodent/ or (rat or rats or mouse or mice).ti.	6956736
12	10 or 11	10908393
13	7 not 12	6080
14	systematic review/ or meta-analysis/	499239

15	(meta analy* or metanaly* or metaanaly* or ((evidence or systematic*) adj2 (overview* or review*))).ti,ab.	540432
16	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.	61439
17	(search strategy or search criteria or systematic search or study selection or data extraction or (search* adj4 literature)).ab.	191879
18	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.	410215
19	cochrane.jw.	23912
20	or/14-19	826564
21	13 and 20	890
22	limit 21 to english language	838
23	limit 22 to dc=20121111-20221220	395
24	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.	5139554
25	23 not 24	306

Database: HMIC – Ovid interface

Database(s): **HMIC Health Management Information Consortium** 1979 to September 2022

Search Strategy:

#	Searches	Results
1	bipolar disorder/	134
2	((bi?polar adj5 (depress* or disorder* or psychos* or psychotic)) or ((rapid or ultradian) adj5 cycl*) or cyclothymi* or hypomani* or mania* or manic* or mixed episode* or rcbd).ti,ab.	341
3	1 or 2	370
4	(convulsofin or delepsine or depacon* or depaken* or depakin* or depakote or depalept or deprakine or di n propylacetate or di n propylacetic acid or diplexil or dipropyl acetate or dipropyl acetic acid or dipropylacetate or dipropylacetatic acid or dipropylacetic acid or diprosin or divalproex or epilam or epilex or epilim or episenta or epival cr or ergenyl or espa valept or everiden or goilim or hexaquin or labazene or leptilan or leptilanil or micropakine or mylproin or myproic acid or orfil or orfiril or orlept or petilin or propylisopropylacetic acid or propymal or sodium 2 propylpentanoate or sodium 2 propylvalerate or sodium di n propyl acetate or stavzor or valberg pr or valcote or valepil or valeptol or valerin or valhel pr or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprodura or valproic acid or valprosid or valprotek or valsup or vupral).ti,ab.	17
5	3 and 4	6

6	limit 5 to english	6
7	limit 6 to yr="2012 -Current"	0

Database: INAHTA

Line	Query
11	#10 AND #6 FROM 2012 TO 2022 AND (English)[Language]
10	#9 OR #8 OR #7
9	((convulsofin or delepsine or depacon* or depaken* or depakin* or depakote or depalept or deprakine or "di n propylacetate" or "di n propylacetic acid" or diplexil or "dipropyl acetate" or "dipropyl acetic acid" or dipropylacetate or "dipropylacetatic acid" or "dipropylacetic acid" or diprosin or divalproex or epilam or epilex or epilim or episenta or "epival cr" or ergenyl or "espa valept" or everiden or goilim or hexaquin or labazene or leptilan or leptilanil or micropakine or mylproin or "myproic acid" or orfil or orfiril or orlept or petilin or "propylisopropylacetic acid" or propymal or "sodium 2 propylpentanoate" or "sodium 2 propylvalerate" or "sodium di n propyl acetate" or stavzor or valberg pr or valcote or valepil or valeptol or valerin or valhel pr or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprodura or "valproic acid" or valprosid or valprotek or valsup or vupral))[abs]
8	((convulsofin or delepsine or depacon* or depaken* or depakin* or depakote or depalept or deprakine or "di n propylacetate" or "di n propylacetic acid" or diplexil or "dipropyl acetate" or "dipropyl acetic acid" or dipropylacetate or "dipropylacetatic acid" or "dipropylacetic acid" or diprosin or divalproex or epilam or epilex or epilim or episenta or "epival cr" or ergenyl or "espa valept" or everiden or goilim or hexaquin or labazene or leptilan or leptilanil or micropakine or mylproin or "myproic acid" or orfil or orfiril or orlept or petilin or "propylisopropylacetic acid" or propymal or "sodium 2 propylpentanoate" or "sodium 2 propylvalerate" or "sodium di n propyl acetate" or stavzor or valberg pr or valcote or valepil or valeptol or valerin or valhel pr or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprodura or "valproic acid" or valprosid or valprotek or valsup or vupral))[title]
7	"Valproic Acid"[mh]
6	#5 OR #4 OR #3 OR #2 OR #1
5	((((bipolar or “bi polar” and (depress* or disorder* or psychos* or psychotic)) or ((rapid or ultradian) and cycl*) or cyclothymi* or hypomani* or mania* or manic* or “mixed episode” or “mixed episodes” or rcbd))[abs]
4	((((bipolar or “bi polar” and (depress* or disorder* or psychos* or psychotic)) or ((rapid or ultradian) and cycl*) or cyclothymi* or hypomani* or mania* or manic* or “mixed episode” or “mixed episodes” or rcbd))[title]
3	"Mania"[mh]
2	"Cyclothymic Disorder"[mh]
1	"Bipolar and Related Disorders"[mhe]

Database: Medline – Ovid interface
Database(s): **Ovid MEDLINE(R) ALL** 1946 to December 19, 2022
Search Strategy:

#	Searches	Results
1	exp "Bipolar and Related Disorders"/ or Cyclothymic Disorder/	44757
2	Mania/	376
3	((bi?polar adj5 (depress* or disorder* or psychos* or psychotic)) or ((rapid or ultradian) adj5 cycl*) or cyclothymi* or hypomani* or mania* or manic* or mixed episode* or rcbd).ti,ab.	58755
4	or/1-3	70775
5	Valproic Acid/	13758
6	(convulsofin or delepsine or depacon* or depaken* or depakin* or depakote or depalept or deprakine or di n propylacetate or di n propylacetic acid or diplexil or dipropyl acetate or dipropyl acetic acid or dipropylacetate or dipropylacetatic acid or dipropylacetic acid or diprosin or divalproex or epilam or epilex or epilim or episenta or epival cr or ergenyl or espa valept or everiden or goilim or hexaquin or labazene or leptilan or leptilanil or micropakine or mylproin or myproic acid or orfil or orfiril or orlept or petilin or propylisopropylacetic acid or propymal or sodium 2 propylpentanoate or sodium 2 propylvalerate or sodium di n propyl acetate or stavzor or valberg pr or valcote or valepil or valeptol or valerin or valhel pr or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprodura or valproic acid or valprosid or valprotek or valsup or vupral).ti,ab.	20050
7	5 or 6	22002
8	4 and 7	2934
9	Letter/ or Editorial/ or News/ or exp Historical Article/ or Anecdotes as Topic/ or Comment/ or Case Report/ or (letter or comment*).ti.	4847192
10	Randomized Controlled Trial/ or random*.ti,ab.	1504034
11	9 not 10	4815858
12	(Animals/ not Humans/) or exp Animals, Laboratory/ or exp Animal Experimentation/ or exp Models, Animal/ or exp Rodentia/ or (rat or rats or mouse or mice).ti.	6088381
13	11 or 12	10739827
14	8 not 13	1972
15	Meta-Analysis/ or Meta-Analysis as Topic/ or "Systematic Review"/	314620
16	(meta analy* or metanaly* or metaanaly* or ((evidence or systematic*) adj2 (overview* or review*))).ti,ab.	438710
17	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.	52554
18	(search strategy or search criteria or systematic search or study selection or data extraction or (search* adj4 literature)).ab.	158167

19	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.	338383
20	cochrane.jw.	16171
21	or/15-20	634446
22	14 and 21	255
23	limit 22 to english language	232
24	limit 23 to dt=20121111-20221220	109
25	limit 23 to ed=20121111-20221220	97
26	24 or 25	115

Database: PsycINFO – Ovid interface

Database(s): **APA PsycInfo** 2002 to December Week 2 2022

Search Strategy:

#	Searches	Results
1	exp bipolar disorder/	24901
2	((bi?polar adj5 (depress* or disorder* or psychos* or psychotic)) or ((rapid or ultradian) adj5 cycl*) or cyclothymi* or hypomani* or mania* or manic* or mixed episode* or rcbd).ti,ab.	35342
3	1 or 2	36323
4	Valproic Acid/	1576
5	(convulsofin or delepsine or depacon* or depaken* or depakin* or depakote or depalept or deprakine or di n propylacetate or di n propylacetic acid or diplexil or dipropyl acetate or dipropyl acetic acid or dipropylacetate or dipropylacetatic acid or dipropylacetic acid or diprosin or divalproex or epilam or epilex or epilim or episenta or epival cr or ergenyl or espa valept or everiden or goilim or hexaquin or labazene or leptilan or leptilanil or micropakine or mylproin or myproic acid or orfil or orfiril or orlept or petilin or propylisopropylacetic acid or propymal or sodium 2 propylpentanoate or sodium 2 propylvalerate or sodium di n propyl acetate or stavzor or valberg pr or valcote or valepil or valeptol or valerin or valhel pr or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprodura or valproic acid or valprosid or valprotek or valsup or vupral).ti,ab.	4317
6	4 or 5	4360
7	3 and 6	1693
8	(letter or editorial or comment reply).dt. or case report/	154151
9	(letter or comment*).ti.	28741
10	8 or 9	159668
11	exp randomized controlled trial/	1333

12	random*.ti,ab.	188475
13	11 or 12	188535
14	10 not 13	153872
15	animal.po.	268741
16	(rat or rats or mouse or mice).ti.	73554
17	or/14-16	419035
18	7 not 17	1240
19	(meta analysis or "systematic review").md.	56015
20	META ANALYSIS/	2881
21	SYSTEMATIC REVIEW/	751
22	(meta analy* or metanaly* or metaanaly*).ti,ab.	43458
23	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.	56716
24	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.	9445
25	(search strategy or search criteria or systematic search or study selection or data extraction).ab.	9454
26	(search* adj4 literature).ab.	13134
27	cochrane.jx.	0
28	((pool* or combined) adj2 (data or trials or studies or results)).ab.	7505
29	(medline or pubmed or cochrane or embase or psychlit or psyclit or cinahl or science citation index or bids or cancerlit).ab.	33713
30	or/19-29	116744
31	18 and 30	167
32	limit 31 to english language	144
33	limit 32 to up=20121111-20221220	70