TECHNICAL COMMENTARY

Valproate

Introduction

Valproate and its derivitive, divalproex, are anticonvulsants used primarily in the treatment of epilepsy and migraine headaches. Anticonvulsant medications influence the actions of neurotransmitters leading to a decrease in brain cell (neuron) excitability. In bipolar disorder, valproate is used mainly for the treatment of mania or mixed symptoms.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2010 that report results separately for people with a diagnosis of bipolar or related disorders. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of review topics were found, the most recent and/or comprehensive review was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews reporting less than 50% of items have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found six reviews that met our inclusion criteria[3-8].

- For symptoms, moderate to low quality evidence suggests a medium-sized effect of greater improvement in acute depression symptoms with valproate than with placebo. Moderate to high quality evidence suggests medium-sized effects of greater improvement in acute mania symptoms with lithium than placebo, topiramate or risperidone, although there was greater improvement in mania symptoms with tamoxefin than with lithium.
- For relapse prevention, moderate to high quality evidence suggests small effects of valproate alone over placebo for preventing relapses to mania, but not to depression. Moderate quality evidence suggests valporate + lithium may also be effective for preventing relapses to mania when compared to placebo, however, placebo was

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significantly better tolerated than valporate + lithium.

- Moderate quality evidence suggests small to medium-sized effects of fewer relapses in general with valproate + lithium or valproate + aripiprazole than with imipramine. There were also fewer relapses with valproate + aripiprazole than with paliperidone. Lamotrigine was significantly better tolerated than valporate + lithium.
- For side effects, moderate quality evidence suggests valproate can result in higher rates of polycycstic ovary syndrome, hyperandrogenism, and mentrual disorders than other medications.
- Moderate quality evidence suggests no significant differences in suicidality between divalproex and placebo.

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Azorin JM, Bowden CL, Garay RP, Perugi G, Vieta E, Young AH

Possible new ways in the pharmacological treatment of bipolar disorder and comorbid alcoholism

Neuropsychiatric Disease and Treatment 2010; 6: 37-46

View review abstract online

Comparison	**Valproate for people with bipolar disorder and alcoholism.**
Summary of evidence	**Low quality evidence (small samples, unable to assess consistency or precision, direct) is unclear as to any benefit of valproate for dual diagnosis.** **However, review authors conclude that anticonvulsant valproate may be effective for reducing excessive alcohol consumption.**
1 x 12-week RCT (N = 27) found less relapse with valproate (0%) than placebo (21%). 1 x 24-week open-label trial (N = 20) found alcohol use and mania symptoms reduced by 50% with valproate. 1 x 52-week RCT (N = 50) found reduced alcohol use in women, but not in men, with valproate compared to olanzapine. 1 x 12-week RCT (N = 30) found no differences in alcohol use with valproate compared to risperidone. 1 RCT (duration not reported, N = 21) found *less* abstinence with valproate alone (43%) than with naltrexone + valproate (71.4%).	
Consistency in results‡	Unable to assess, no measure of consistency is reported.
Precision in results§	Unable to assess, CIs not reported.
Directness of results‖	Direct

Miura T, Noma H, Furukawa TA, Mitsuyasu H, Tanaka S, Stockton S, Salanti G, Motomura K, Shimano-Katsuki S, Leucht S, Cipriani A, Geddes JR, Kanba S

Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: A systematic review and network meta-analysis

The Lancet Psychiatry 2014; 1: 351-9

View review abstract online	
Comparison 1	**Valproate vs. placebo.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, some imprecision and indirectness) suggests small effects of valproate alone for preventing relapses to mania, but not to depression. Moderate quality evidence (imprecise) suggests valporate + lithium may also be effective for preventing relapses to mania. However, placebo was significantly better tolerated than lithium + valproate.**
Any relapse	
Valproate had a significantly lower risk of any relapse than placebo (all small to medium-sized effects); Valproate: N = 368, RR = 0.63, 95%CI 0.47 to 0.83, $p < 0.05$ Valproate + lithium: N = 110, RR = 0.52, 95%CI 0.35 to 0.77, $p < 0.05$ Valproate + aripiprazole: N = not reported, RR = 0.29, 95%CI 0.22 to 0.76, $p < 0.05$	
Mania relapse	
Valproate had a significantly lower risk of mania relapse than placebo (all small to medium-sized effects); Valproate: N = 368, RR = 0.66, 95%CI 0.43 to 1.00, $p < 0.05$ Valproate + lithium: N = 110, RR = 0.42, 95%CI 0.23 to 0.76, $p < 0.05$	
Depression relapse	
No significant differences between groups; Valproate: N = 368, RR = 0.78, 95%CI 0.50 to 1.16, $p > 0.05$ Valproate + lithium: N = 110, RR = 0.70, 95%CI 0.41 to 1.17, $p > 0.05$	
Risks	Placebo was significantly better tolerated than lithium + valproate.
Consistency in results	Authors state that the data were consistent.
Precision in results	Precise for all relapses valproate and lithium + valproate, imprecise for valproate + aripiprazole. Imprecise for mania and depression analyses.
Directness of results	Some indirectness
Comparison 2	**Valproate vs. other pharmaceutical treatments.**

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Summary of evidence	**Moderate quality evidence (consistent, imprecise, some indirectness) suggests small to medium-sized effects of fewer relapses with valproate + lithium or valproate + aripiprazole than with imipramine. There were fewer relapses with valproate + aripiprazole than with paliperidone. However, lamotrigine was significantly better tolerated than lithium + valproate.**
Any relapse	
Valproate had a significantly lower risk of relapse than imipramine or paliperidone (all small to medium-sized effects); Valproate + lithium vs. imipramine: RR = 0.52, 95%CI 0.35 to 0.77, $p < 0.05$ Valproate + aripiprazole vs. imipramine: RR = 0.30, 95%CI 0.11 to 0.84, $p < 0.05$ Valproate + aripiprazole vs. paliperidone: RR = 0.34, 95%CI 0.12 to 0.99, $p < 0.05$	
Risks	Lamotrigine was significantly better tolerated than lithium + valproate.
Consistency in results	Authors state that the data were consistent.
Precision in results	Mostly imprecise
Directness of results	Some indirectness

Redden L, Pritchett Y, Robieson W, Kovacs X, Garofalo M, Tracy K, Saltarelli M

Suicidality and divalproex sodium: Analysis of controlled studies in multiple indications

Annals of General Psychiatry 2011; 10 (1)

View review abstract online

Comparison	**Divalproex vs. placebo** **Note; some studies included people with epilepsy or migraine disorders.**
Summary of evidence	**Moderate quality evidence (large sample, direct, consistency unclear, imprecise) suggests no significant differences in suicidality between divalproex and placebo.**
Suicidality	
No significant differences in suicidality between divalproex and placebo;	

13 RCTs, N = 2,319, OR = 0.72, 95%CI 0.29 to 1.84, $p > 0.05$	
Consistency in results	Consistency measure is not reported.
Precision in results	Imprecise
Directness of results	Direct

Selle V, Schalkwijk S, Vazquez GH, Baldessarini RJ

Treatments for acute bipolar depression: meta-analyses of placebo-controlled, monotherapy trials of anticonvulsants, lithium and antipsychotics

Pharmacopsychiatry 2014; 47: 43-52

View review abstract online

Comparison	**Valproate vs. placebo**
Summary of evidence	**Moderate to low quality evidence (medium-sized sample, inconsistent, imprecise, direct) suggests a medium-sized effect of greater improvement in acute depression symptoms with valproate.**
Response for acute depression	
A significant, medium-sized effect of better response with valproate than with placebo; Response: 4 RCTs, N = 140, RR = 2.08, 95%CI 1.18 to 3.65, $p < 0.05$, $I^2 = 0\%$, $p = 0.52$	
Consistency in results	Authors report the results are inconsistent, with 2/4 studies reporting significant results.
Precision in results	Imprecise
Directness of results	Direct

Yildiz A, Nikodem M, Vieta E, Correll CU, Baldessarini RJ

A network meta-analysis on comparative efficacy and all-cause discontinuation of antimanic treatments in acute bipolar mania

Psychological Medicine 2015; 45: 299-317

View review abstract online	
Comparison	**Valproate vs. placebo or other medications.**
Summary of evidence	**Moderate to high quality evidence (large sample size, consistent, mostly precise, some indirectness) suggests medium-sized effects of greater improvement in acute mania symptoms with lithium than placebo, topiramate or risperidone, although there was greater improvement with tamoxefin than with lithium.**
Acute mania symptoms	
A significant, medium-sized effect of greater improvement with valproate than with placebo; Network meta-analysis; 57 studies, N = 14,256, SMD = 0.32, 95%CrI 0.15 to 0.50, $p < 0.05$ *A significant, medium-sized effect of greater improvement with lithium than with topiramate;* Network meta-analysis; 57 studies, N = 14,256, SMD = 0.39, 95%CrI 0.12 to 0.66, $p < 0.05$ *A significant, medium-sized effect of greater improvement with lithium than with risperidone;* Network meta-analysis; 57 studies, N = 14,256, SMD = 0.33, 95%CrI 0.06 to 0.58, $p < 0.05$ *A significant, large effect of greater improvement with tamoxefin than with lithium;* Network meta-analysis; 57 studies, N = 14,256, SMD = 2.59, 95%CrI 2.04 to 3.18, $p < 0.05$ Authors report no other significant differences between lithium and other medications.	
Risks	No significant differences in drop-out rates.
Consistency in results	Authors report data are consistent.
Precision in results	Precise, apart from tamoxefin comparison.
Directness of results	Some indirectness.

Zhang L, Li H, Li S, Zou X

Reproductive and metabolic abnormalities in women taking valproate for bipolar disorder: a meta-analysis

European Journal of Obstetrics, Gynecology, & Reproductive Biology 2016; 202: 26-31

View review abstract online

Comparison	**Valproate vs. other medications.**
Summary of evidence	**Moderate quality evidence (large samples, consistent, indirect,**

	imprecise) suggests valproate results in higher rates of polycycstic ovary syndrome, hyperandrogenism and mentrual disorders than other medications.
Reproductive and metabolic factors	
A significant, large effect of higher rates of polycystic ovary syndrome in patients taking valproate; 3 RCTs, N = 315, OR = 6.74, 95%CI 1.66 to 27.32, *p* = 0.008, I^2 = 0%, *p* = 0.59 *A significant, medium-sized effect of higher rates of hyperandrogenism in patients taking valproate;* 6 RCTs, N = 289, OR = 2.02, 95%CI 1.11 to 3.65, *p* = 0.02, I^2 = 49%, *p* = 0.12 *A significant, small effect of higher rates of menstrual disorders in patients taking valproate;* 5 RCTs, N = 387, OR = 1.81, 95%CI 1.02 to 3.23, *p* = 0.04, I^2 = 73%, *p* = 0.005 Authors report no evidence of publication bias.	
Consistency in results	Consistentm apart from menstrual disorders.
Precision in results	Imprecise
Directness of results	Indirect comparison (mixed comparison drugs)

Explanation of acronyms

CI = Confidence Interval, CrI = credible interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RCT = randomised controlled trial, RR = risk ratio, vs. = versus

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[9].

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† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[9].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[10]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

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‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[9];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

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§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[11].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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