TECHNICAL COMMENTARY

Pharmaceutical treatments for suicide and self-harm

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Introduction

Rates of suicide or self-harm are considerably higher in people with mental disorders compared to people without a mental disorder. There has been much research dedicated to determining potential risk factors for suicide, which may have clinically important applications for prevention. Many of the important risk factors for suicide in the general population can apply to people with mental disorders, including having depression and/or a history of previous suicide attempts.

This topic assesses the current evidence for treatments for prevention of suicide in people with bipolar disorder.

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 with pooled data were prioritised for inclusion. 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, only the most recent version was included.

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 with less than 50% of items checked 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 four systematic reviews that met inclusion criteria[3-6].

- Moderate to high quality evidence suggests self-harm, but not suicide, may be reduced with lithium when compared to placebo or carbamazepine, with no differences in rates of self-harm or suicide between people on lithium and people on lamotrigine, olanzapine, divalproex, or quetapine. Moderate quality evidence also suggests no significant differences in suicidal behaviour between people taking divalproex and people taking placebo.
- Moderate quality evidence suggests there may be an association between increased levels of lithium in drinking water and reduced rates of suicide in the community.

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Cipriani A, Hawton K, Stockton S, Geddes JR

Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis

BMJ 2013; 346: f3646

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Comparison 1	**Lithium vs. placebo in people with bipolar disorder.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, consistent, direct, imprecise) suggests no significant differences in rates of suicide or all-cause death between lithium and placebo, although self-harm may be reduced with lithium.**
Deliberate self-harm, suicide and all-cause death	
A trend, medium-sized effect of less self-harm with lithium, and no significant differences between groups for suicide or all-cause death; Deliberate self-harm: 2 RCTs, N = 1,064, OR = 0.35, 95%CI 0.11 to 1.10, $p = 0.07$, $I^2 = 0\%$, $p = 0.62$ Suicide: 1 RCT, N = 205, OR = 0.14, 95%CI 0.00 to 7.02, $p = 0.32$ All-cause death: 2 RCTs, N = 254, OR = 0.73, 95%CI 0.16 to 3.33, $p = 0.69$, $I^2 = 0\%$, $p = 0.70$	
Comparison 2	**Lithium vs. carbamazepine in people with bipolar disorder.**
Summary of evidence	**Moderate to high quality evidence (medium-sized samples, consistent, direct, imprecise) suggests no significant differences in rates of suicide or all-cause death between lithium and carbamazepine, although self-harm may be reduced with lithium.**
Deliberate self-harm, suicide and all-cause death	
A significant, large effect of less self-harm with lithium, and no significant differences between groups for suicide or all-cause death; Deliberate self-harm: 2 RCTs, N = 285, OR = 0.14, 95%CI 0.02 to 0.83, $p = 0.03$, $I^2 = 0\%$, $p = 0.99$ Suicide: 2 RCTs, N = 285, OR = 0.37, 95%CI 0.09 to 1.51, $p = 0.17$, $I^2 = 0\%$, $p = 0.37$ All-cause death: 2 RCTs, N = 285, OR = 0.37, 95%CI 0.09 to 1.51, $p = 0.17$, $I^2 = 0\%$, $p = 0.37$	
Comparison 3	**Lithium vs. lamotrigine in people with bipolar disorder.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, consistent, direct, imprecise) suggests no significant**

	differences in rates of suicide, all-cause death or self-harm between lithium and lamotrigine.
Deliberate self-harm, suicide and all-cause death	
No significant differences between groups; Deliberate self-harm: 2 RCTs, N = 260, OR = 0.15, 95%CI 0.01 to 2.46, p = 0.18, I^2 = 0%, p = 0.94 Suicide: 2 RCTs, N = 497, OR = 1.37, 95%CI 0.08 to 23.23, p = 0.83, I^2 = 34%, p = 0.22 All-cause death: 2 RCTs, N = 497, OR = 1.37, 95%CI 0.08 to 23.23, p = 0.83, I^2 = 34%, p = 0.22	
Comparison 4	**Lithium vs. olanzapine in people with bipolar disorder.**
Summary of evidence	**Moderate quality evidence (large samples, 1 RCT, direct, imprecise) suggests no significant differences in rates of suicide, all-cause death or self-harm between lithium and olanzapine.**
Deliberate self-harm, suicide and all-cause death	
No significant differences between groups; Deliberate self-harm: 1 RCT, N = 431, OR = 0.30, 95%CI 0.05 to 1.76, p = 0.18 Suicide: 1 RCT, N = 431, OR = 7.49, 95%CI 0.15 to 377.68, p = 0.31 All-cause death: 1 RCT, N = 431, OR = 7.53, 95%CI 0.47 to 120.76, p = 0.15	
Comparison 5	**Lithium vs. divalproex in people with bipolar disorder.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, consistent, direct, imprecise) suggests no significant differences in rates of self-harm between lithium and divalproex. Moderate quality evidence (1 RCT) also suggests no differences in all-cause death.**
Deliberate self-harm and all-cause death	
No significant differences between groups; Deliberate self-harm: 2 RCTs, N = 318, OR = 0.64, 95%CI 0.30 to 1.36, p = 0.24, I^2 = 0%, p = 0.52 All-cause death: 1 RCT, N = 220, OR = 0.67, 95%CI 0.11 to 3.90, p = 0.65	
Comparison 6	**Lithium vs. quetiapine in people with bipolar disorder.**
Summary of evidence	**Moderate quality evidence (large sample, 1 RCT, direct, imprecise) suggests no significant differences in rates of self-harm between lithium and quetiapine.**
Deliberate self-harm	
No significant differences between groups;	

Deliberate self-harm: 1 RCT, N = 822, OR = 0.97, 95%CI 0.19 to 4.81, *p* = 0.97	
Consistency in results‡	Consistent where applicable (> 1 RCT).
Precision in results§	Imprecise
Directness of results‖	Direct

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)

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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

Vita A, De Peri L, Sacchetti E

Lithium in drinking water and suicide prevention: a review of the evidence

International Clinical Psychopharmacology 2015; 30: 1-5

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Comparison	**Association between lithium levels in drinking water and suicide**

	rates in the general population.
Summary of evidence	**Moderate quality evidence (large population samples, consistent, uable to assess precision, indirect) suggests there may be an association between increased levels of lithium in drinking water and reduced rates of suicide in the community.**
Suicide	
5 population studies (2 Austrian, 1 Japanese, 1 US, 1 Greek) found higher lithium levels in drinking water were associated with reduced rates of suicide. 1 US study found the same association, but only in counties with lithium levels from 70 - 160 µg/l. 1 Austrian study found the same association, but only in lower altitude regions, while in high-altitude regions, higher lithium levels were associated with increased rates of suicide. 2 population studies (1 Japanese, 1 UK) found no association between lithium levels in drinking water and suicide rates.	
Consistency in results	Authors report data are consistent.
Precision in results	Uable to assess; no confidence intervals are reported.
Directness of results	Indirect association between lithium and suicide.

Yerevanian BI, Choi YM

Impact of psychotropic drugs on suicide and suicidal behaviours

Bipolar Disorders 2013; 15: 594-621

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Comparison	**Assessment of medications for bipolar disorder on risk of suicide.**
Summary of evidence	**Low quality evidence is unable to determine the best treatments for reducing suicidal behaviour in people with bipolar disorder. Authors suggest only lithium provides convincing evidence for reducing the risk of suicide over the long term.**
Suicide	
Authors report that the available studies used various methodologies, making interpretation of the findings difficult. However, they suggest lithium provides convincing evidence that it reduces the risk of suicide over the long term. Antidepressants may *increase* suicidal risk, possibly related to induction of mixed states (concurrent mania and depression).	

There is no evidence that antiepileptic drugs increase suicidal risk in patients with bipolar disorder. There is little known regarding the effects of antipsychotics, anti-anxiety or hypnotic drugs, on suicidal behavior.	
Consistency in results	Unable to assess, no measure of consistency is reported.
Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct

Explanation of acronyms

CI = Confidence Interval, 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, 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 [7].

† 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).

Weighted 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) that 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.[7]

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[8]. 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

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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.

‡ 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;[7]

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

§ 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 [9].

‖ 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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