TECHNICAL COMMENTARY

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Antidepressants

Introduction

Antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), have been found to be efficacious in the treatment of depression and anxiety. PTSD was originally classed as an anxiety disorder. Antidepressants may work for PTSD by correcting imbalances in neurotransmitters thought to play a role in causing and/or maintaining 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 PTSD. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. When multiple copies of reviews were found, only the most recent version was included. We prioritised reviews with pooled data 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 with less than 50% of items checked have been excluded from the library. 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 our inclusion criteria[3-6].

- Moderate quality evidence found the antidepressants phenelzine (large effect), desipramine (medium-sized effect), paroxetine, venlafaxine, fluoxetine, and sertraline (all small effects) were more effective for PTSD symptoms than placebo.
- Phenelzine was more effective for PTSD symptoms than the antidepressants citalopram, bupropion, sertraline, and imipramine. Phenelzine was also more effective than the anticonvulsants divalproex and tiagabine, the alpha blocker prazosin, and the adrenergic receptor agonist guanfacine.
- Paroxetine and desipramine were more effective for PTSD symptoms than citalopram, divalproex, and prazosin.
- Venlafaxine and fluoxetine were more effective for PTSD symptoms than citalopram and prazosin.
- Citalopram was less effective for PTSD symptoms than the antidepressant

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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mirtazapine and the antipsychotic olanzapine.

- There were fewer dropouts due to adverse events with the antidepressant brofaromine than with the antidepressants sertraline and paroxetine, and the anticonvulsant topiramate.
- Moderate to low quality evidence found no differences between paroxetine or sertraline plus prolonged exposure vs. paroxetine, sertraline or prolonged exposure alone.
- Moderate quality evidence found no differences in PTSD relapse rates after discontinuation of antidepressants or placebo.
- Moderate to high quality evidence found no influence of baseline PTSD symptom severity on efficacy of paroxetine and sertraline after 12 weeks of treatment.

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Batelaan NM, Bosman RC, Muntingh A, Scholten WD, Huijbregts KM, van Balkom A

Risk of relapse after antidepressant discontinuation in anxiety disorders, obsessive-compulsive disorder, and post-traumatic stress disorder: systematic review and meta-analysis of relapse prevention trials

BMJ 2017; 358: j3927

View review abstract online

Comparison	**Relapse rates after discontinuation of antidepressants vs. placebo in people with PTSD.**
Summary of evidence	**Moderate quality evidence (unclear sample size, consistent, imprecise, direct) found no differences in relapse rates after discontinuation of antidepressants or placebo.**
Relapse	
There were no significant differences between groups; 4 RCTs, N not reported, OR = 2.45, 95%CI 0.86 to 6.97, $p > 0.05$, $I^2 = 6.5\%$	
Consistency in results‡	Consistent
Precision in results§	Imprecise
Directness of results‖	Direct

Cipriani A, Williams T, Nikolakopoulou A, Salanti G, Chaimani A, Ipser J, Cowen PJ, Geddes JR, Stein DJ

Comparative efficacy and acceptability of pharmacological treatments for post-traumatic stress disorder in adults: a network meta-analysis

Psychological Medicine 2018; 48: 1975-84

View review abstract online

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Comparison	**Effectiveness of antidepressants vs. placebo and other pharmaceutical agents for PTSD symptoms.** **Mean trial duration was 10.3 weeks.**
Summary of evidence	**Moderate quality evidence (large overall sample, consistent, mostly imprecise, indirect) found the antidepressants phenelzine (large effect), desipramine (medium-sized effect), paroxetine, venlafaxine, fluoxetine, and sertraline (all small effects) were more effective for PTSD symptoms than placebo.** **Phenelzine was more effective than the antidepressants citalopram, bupropion, sertraline, and imipramine. Phenelzine was also more effective than the anticonvulsants divalproex and tiagabine, the alpha blocker prazosin, and the adrenergic receptor agonist guanfacine.** **Paroxetine and desipramine were more effective than citalopram, divalproex, and prazosin.** **Venlafaxine and fluoxetine were more effective than citalopram and prazosin.** **Citalopram was also less effective than the antidepressant mirtazapine and the antipsychotic olanzapine.** **There were fewer dropouts due to adverse events with the antidepressant brofaromine than with the antidepressants sertraline and paroxetine, and the anticonvulsant topiramate.**
PTSD symptoms	
51 RCTs, N = 6,189 *The following antidepressants were more effective than placebo for improving PTSD symptoms;* Phenelzine: SMD = 0.97, 95%CI 0.27 to 1.68, $p < 0.05$ Desipramine: SMD = 0.52, 95%CI 0.02 to 1.02, $p < 0.05$ Paroxetine: SMD = 0.38, 95%CI 0.21 to 0.55, $p < 0.05$ Venlafaxine: SMD = 0.32, 95%CI 0.12 to 0.52, $p < 0.05$ Fluoxetine: SMD = 0.30, 95%CI 0.09 to 0.51, $p < 0.05$ Sertraline: SMD = 0.23, 95%CI 0.09 to 0.38, $p < 0.05$ There were no benefits of mirtazapine, brofaromine, amitriptyline, imipramine, nefazodone, bupropion, or citalopram when compared to placebo.	

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Phenelzine showed significantly more symptom improvement than the antidepressants;

Citalopram: SMD = 1.30, 95%CI 0.39 to 2.21, $p < 0.05$

Bupropion: SMD = 1.08, 95%CI 0.06 to 2.15, $p < 0.05$

Sertraline: SMD = 0.74, 95%CI 0.02 to 1.46, $p < 0.05$

Imipramine: SMD = 0.71, 95%CI 0.05 to 1.37, $p < 0.05$

Phenelzine showed significantly more symptom improvement than the anticonvulsants;

Divalproex: SMD = 1.11, 95%CI 0.29 to 1.93, $p < 0.05$

Tiagabine: SMD = 0.95, 95%CI 0.16 to 1.75, $p < 0.05$

Phenelzine showed significantly more symptom improvement than the alpha blocker;

Prazosin: SMD = 1.03, 95%CI 0.28 to 1.79, $p < 0.05$

Phenelzine showed significantly more symptom improvement than the adrenergic receptor agonist;

Guanfacine: SMD = 0.85, 95%CI 0.01 to 1.69, $p < 0.05$

Paroxetine showed significantly more symptom improvement than the antidepressant;

Citalopram: SMD = 0.71, 95%CI 0.11 to 1.91, $p < 0.05$

Paroxetine showed significantly more symptom improvement than the anticonvulsant;

Divalproex: SMD = 0.51, 95%CI 0.07 to 0.96, $p < 0.05$

Paroxetine showed significantly more symptom improvement than the alpha blocker;

Prazosin: SMD = 0.44, 95%CI 0.12 to 0.75, $p < 0.05$

Desipramine showed significantly more symptom improvement than the antidepressant;

Citalopram: SMD = 0.85, 95%CI 0.09 to 1.61, $p < 0.05$

Desipramine showed significantly more symptom improvement than the anticonvulsant;

Divalproex: SMD = 0.66, 95%CI 0.01 to 1.31, $p < 0.05$

Desipramine showed significantly more symptom improvement than the alpha blocker;

Prazosin: SMD = 0.58, 95%CI 0.02 to 1.15, $p < 0.05$

Venlafaxine showed significantly more symptom improvement than the antidepressant;

Citalopram: SMD = 0.65, 95%CI 0.05 to 1.25, $p < 0.05$

Venlafaxine showed significantly more symptom improvement than the alpha blocker;

Prazosin: SMD = 0.38, 95%CI 0.04 to 0.71, $p < 0.05$

Fluoxetine showed significantly more symptom improvement than the antidepressant;

Citalopram: SMD = 0.63, 95%CI 0.02 to 1.24, $p < 0.05$

Fluoxetine showed significantly more symptom improvement than the alpha blocker;

Prazosin: SMD = 0.36, 95%CI 0.02 to 0.69, $p < 0.05$

Mirtazapine showed significantly more symptom improvement than the antidepressant;

Citalopram: SMD = 1.12, 95%CI 0.07 to 2.16, $p < 0.05$

Citalopram showed significantly less symptom improvement than the antipsychotic;

Olanzapine: SMD = 0.84, 95%CI 0.05 to 1.63, $p < 0.05$

There were no other significant differences between antidepressants and other pharmaceutical agents.

Risks	There were fewer dropouts due to adverse events with the antidepressant brofaromine than with the antidepressants sertraline and paroxetine, and the anticonvulsant topiramate.
Consistency in results	Consistent
Precision in results	Mostly imprecise
Directness of results	Indirect

de Vries YA, de Jonge P, van den Heuvel E, Turner EH, Roest AM

Influence of baseline severity on antidepressant efficacy for anxiety disorders: meta-analysis and meta-regression

British Journal of Psychiatry 2016; 208: 515-21

View review abstract online

Comparison	**Effects of baseline severity of PTSD symptoms on efficacy of antidepressants paroxetine and sertraline after 12 weeks vs. placebo.**

Summary of evidence	**Moderate to high quality evidence (large sample size, consistent, imprecise, direct) found no influence of baseline symptom severity on efficacy of paroxetine and sertraline after 12 weeks of treatment.**
PTSD symptoms	
There was no influence of baseline symptom severity on drug efficacy; 7 RCTs, N = 1,810, β = 0.16, 95%CI -0.22 to 0.53, *p* = 0.37	
Consistency in results	Authors report data are inconsistent
Precision in results	Precise
Directness of results	Direct

Hetrick SE, Purcell R, Garner B, Parslow R

Combined pharmacotherapy and psychological therapies for post-traumatic stress disorder (PTSD)

Cochrane Database of Systematic Reviews: CD007316

View review abstract online

Comparison	**Efficacy of paroxetine or sertraline plus prolonged exposure vs. paroxetine or sertraline or prolonged exposure alone for PTSD symptoms.**
Summary of evidence	**Moderate to low quality evidence (small samples, imprecise, direct) found no differences between paroxetine or sertraline plus prolonged exposure vs. paroxetine, sertraline, or prolonged exposure alone.**
PTSD symptoms	
There were no significant differences between groups; Pparoxetine + prolonged exposure vs. prolonged exposure: 1 RCT, N = 65, MD = 2.44, 95%CI -2.87 to 7.35, *p* > 0.05	

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Sertraline + prolonged exposure vs. sertraline: 1 RCT, N = 25, MD = -4.70, 95%CI -10.84 to 1.44, *p* > 0.05	
Consistency in results	NA; 1 RCT per outcome
Precision in results	Imprecise
Directness of results	Direct

Explanation of acronyms

β = beta coefficient, CI = confidence interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MD = mean difference, N = number of participants, OR = odds ratio, *p* = statistical probability of obtaining that result, SMD = standardised mean difference, vs. = versus

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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].

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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).

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 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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