

# Prozac revelation

‘Antidepressants no more effective than placebo’, ran February’s headlines. But the evidence has been available for a decade, reports **Penny Louch**

The recent media frenzy over reports that ‘Prozac is no better than placebo’ was based on research into the efficacy of antidepressants (SSRIs) which goes back many years.<sup>1</sup> The article prompting the furore was the third published by Kirsch and colleagues which focused on meta-analyses of antidepressant medication – the first was published in 1998 and the second in 2002.<sup>2,3</sup> So why did the recent publication in PLoS create such enormous and worldwide media interest?

Both of the earlier papers are now difficult to access online, with dead links through Google Scholar, and are absent from other academic search engines like ‘Web of Knowledge’ or ‘Dialog Datastar’. The reference link from the current PLoS paper to the previous work of 2002 does not work either.

I finally found the 2002 paper using ‘Ovid’. Both the earlier articles were published in *Prevention and Treatment*, a journal of the American Psychological Association, which ceased publication in 2003. The only way to locate the journal was through the APA website, all other links being dead. But even having found the journal on the APA website it is impossible to access the full articles unless you are an APA member or are willing to pay to view. *Prevention and Treatment* is not a listed journal on PubMed/Medline either.

The latest article is published in a major open access journal – perhaps one reason for the media attention. Of course, the media always likes a ‘scare story’. Frightening the public will boost circulation and ratings, as past coverage of HRT, the contraceptive pill and statins has amply demonstrated.

The three articles that Kirsch has published between 1998 and 2008 are worth reading, and I have attempted to summarise them here.

## Listening to Prozac but Hearing Placebo

In their 1998 paper, Kirsch and Sapirstein describe how they used a ‘controversial’ statistical approach, meta-analysis, to pool data from

different studies, and then applied it to studies that were different in their subject selection criteria, treatments employed, and statistical methods used. They published their study because both they and their peers considered their findings to have considerable merit. The meta-analysis was conducted on 19 studies which fulfilled the following criteria: patients with a primary diagnosis of depression; sufficient data were reported/obtainable to calculate within-condition effect sizes; there was a placebo control group; random assignment of participants to the experimental drug; antidepressants were prescribed for the acute phase of treatment; any maintenance treatment studies were excluded.

The medications under review were amitriptyline, amylobarbitone, fluoxetine, imipramine, paroxetine, isocarboxazid, trazodone, lithium, liothyronine, adinazolam, amoxapine, phenelzine, venlafaxine, maprotiline, tranlycypromine and bupropion.

Kirsch and Sapirstein’s meta-analysis suggested that 75 per cent of the response to the medications was a placebo response and that at most 25 per cent might be true drug effect. They clarified that this does not mean that only one in four people will respond to the pharmacologic properties of the drug, but that for a typical patient it means three-quarters of the benefit obtained from the active drug would also have been obtained from a chemically inactive placebo.

An analysis by type of medication (i.e. tricyclics and tetracyclics; SSRIs; other antidepressants; and other medications), revealed little variability in drug response and even less variability in the ratio of placebo response to drug response. The inactive placebo response was between 74 per cent and 76 per cent of the active drug response in each of the four groups.

The authors noted the possibility that the drugs could improve depression indirectly, for example by improving sleep or reducing anxiety, but they discount this explanation because response to non-antidepressant drugs was at least as great as that to conventional antidepressants. They argued that antidepressants may function as active placebos, in which the side effects amplify the placebo effect by convincing patients that they are receiving a potent drug.

## The Emperor’s New Drugs

This paper was published in 2002 in response to criticisms of the methods used in Kirsch and Sapirstein’s first paper. Here, Kirsch and colleagues also expand on an earlier analysis of the US Food and Drug Administration (FDA) data on seven new antidepressant medications.<sup>4</sup> The earlier analysis had concluded that depressed patients in clinical trials who receive placebo treatment are not at greater risk of suicide or attempted suicide than those given ‘active’ treatment, and that depressed patients given placebo do gain substantial improvements in symptoms.

This 2002 paper reports on an analysis of data submitted to the FDA between 1987-1999 for the approval of the six most widely prescribed antidepressants, namely fluoxetine, paroxetine, sertraline, venlafaxine, nefazodone and citalopram.<sup>3</sup>

Kirsch and colleagues undertook their new meta-analysis using the FDA data which was used to gain regulatory approval of these drugs. They used the Freedom of Information Act to obtain medical and statistical reviews of every placebo controlled clinical trial for depression reported to the FDA for initial approval of the six most widely used antidepressant drugs approved within the study period.

They analysed forty-seven randomised, placebo-controlled, short-term efficacy trials conducted for the six drugs in support of an approved indication of treatment for depression; data from relapse prevention trials were not analysed.

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The findings of this meta-analysis identified that 80 per cent of the response to the antidepressants was duplicated in the placebo control groups; only 18 per cent of the drug response was due to the pharmacological effects of the medication. Although a small but significant difference between antidepressant drug and inert placebo was apparent, Kirsch and colleagues concluded that the pharmacological benefits of these antidepressants were questionable and could be clinically unimportant.

The placebo effect shown in this analysis was greater than those shown previously.<sup>2,4</sup> Kirsch and colleagues suggested this might be due to two factors: publication bias and missing data in earlier studies. They acknowledged that their assumption that drug effects and placebo effects are additive may not be correct, and that the true drug effect may be greater than drug/placebo difference, and recommended further research to assess how the drug and placebo effects combined.

### Initial Severity and Antidepressant Benefits

The current 2008 study by Kirsch and colleagues notes that the meta-analyses of antidepressant effects published by NICE relied only on published studies (so it left out some of the data held by the FDA).<sup>5</sup> It reported benefits which, although statistically significant, were of marginal clinical importance. The purpose of this new study was to test the hypothesis that antidepressants may still be effective for severely depressed patients, even if not for moderately depressed patients.

What is not clear is whether the authors of this paper re-analysed the published and unpublished data for the six antidepressants which formed the basis of the 2002 paper, or used the same analysis from six years previously.

The drugs under investigation were fluoxetine, paroxetine, venlafaxine, nefazodone, sertraline and citalopram.

Two drugs were subsequently excluded (citalopram and sertraline)

because of incomplete data from their clinical trials, both on the pharmaceutical web sites and within the published literature. The researchers report that they consider they had access to complete data sets (unpublished and published data) for the other four drugs.

Again, this study concluded that the overall effect of new generation antidepressant medications is below recommended criteria for clinical significance. The authors acknowledge that for the most severely depressed patients there is a clinically important effect, but that this is due to a decrease in response to placebo rather than an increase in response to medication.

Their final conclusion is that there is little evidence to support prescribing antidepressants to anyone but the most severely depressed patients, unless alternative treatments have already been tried and have failed to provide benefit.

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### References

- 1 Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnsson BT. Initial Severity and Antidepressant Benefits: A Meta-Analysis of Data Submitted to the Food and Drug Administration. *PLoS Medicine* 2008;**5**:260-8.
- 2 Kirsch I, Sapirstein G. Listening to Prozac but Hearing Placebo: A Meta-Analysis of Antidepressant Medication. *Prevention and Treatment* 1998; **1**(Article 0002a).
- 3 Kirsch I, Moore T, Scoboria A, Nicholls S. The Emperor's New Drugs: An Analysis of Antidepressant Medication Data Submitted to the US Food and Drug Administration. *Prevention and Treatment* 2002; **5**:Article 23.
- 4 Khan A, Warner HA, Brown WA. Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials – An analysis of the food and drug administration database. *Arch Gen Psychiatry* 2000;**57**:311-7.
- 5 NICE, National Collaborating Centre for Mental Health. *Depression: Management of depression in primary and secondary care*. National Clinical Practice Guideline Number 23. London: NICE, 2004.