

Institution: University of Plymouth
Unit of Assessment: UoA4
Title of case study: Meta-analysis of clinical trials of antidepressants has led to changes in guidelines, prescribing habits, and increased public awareness.
<p>1. Summary of the impact</p> <p>Professor Irving Kirsch has conducted a meta-analysis of both published and unpublished clinical trials of antidepressants (Kirsch et al., 2008). This analysis demonstrates that the effects of antidepressants are mostly placebo effects except with extremely severe depression. The analysis opened an international debate on antidepressant efficacy, influenced NICE guidelines for the treatment of depression (NICE, 2010), and led the scientific committee of the European Medicines Agency to reconsider its own approval of antidepressants (Broich, 2009). It also informed public opinion through widespread media coverage, and produced intentions to change prescribing habits among 44% of surveyed UK doctors. Public awareness of Kirsch's work is such that a class action has been taken against Pfizer, a large pharmaceutical company, and the Vatican has convened an international study meeting (14-15 June, 2013) to produce new recommendations for the treatment of depression.</p>
<p>2. Underpinning research</p> <p>In a single, 18-year program of work beginning before Kirsch's first tenure at Plymouth and continuing into it, Kirsch and colleagues conducted three meta-analyses of antidepressants and the placebo response. These are published as Kirsch and Sapirstein (1998: work conducted between 1995 and 1998); Kirsch et al. (2002: work conducted between 1999 and 2002); and Kirsch et al. (2008: work conducted between 2005 and 2007, during Kirsch's first period of tenure at Plymouth University). All of this work was led by Kirsch (as evidenced by first authorship of all of these papers).</p> <p>Kirsch's first meta-analysis (Kirsch and Sapirstein, 1998), published in <i>Prevention and Treatment</i> (an American Psychological Society journal), indicated that 25% of the response to antidepressants was due to natural history and 50% was a placebo effect, leaving only 25% as a true drug effect. This study has been widely cited (more than 400 citations), but was also very controversial because of its claims and because of its early use of meta-analysis.</p> <p>To address the controversy, Kirsch and colleagues (2002, 2008) sought to replicate the 1998 analysis on different data sets. They used the U.S. Freedom of Information Act to obtain the clinical trial data submitted by pharmaceutical companies to the American Food and Drug Agency (FDA) in the process of seeking approval for the six most widely prescribed antidepressants, as about 40% of those trials remained unpublished. An important factor here is the general bias towards publishing results only producing significant effects – meaning that unpublished findings tend not to show significant effects, which should also be taken into account in overall assessments of a drug's efficacy. Analyses of these data, now including the unpublished trials, indicated that 82% of the response to antidepressants was also found in the placebo groups, and that the drug-placebo effect size was well below NICE criteria for clinical significance. The importance of this was that the true drug effect was not clinically significant, according to criteria published in the NICE (National Institute for Clinical Excellence) guidelines.</p> <p>The 2008 meta-analysis was undertaken in response to the concern that antidepressants might be more effective in more severely depressed patients. It found that clinical efficacy could be established only for the most severely depressed patients (approximately 10% of patients diagnosed with MDD). This study has been widely cited (more than 1000 citations). Independent researchers successfully replicated these findings with an independent patient-level database, giving even greater weight to Kirsch et al's findings (Fournier, J. C., DeRubeis, R. J., Hollon, S. D., Dimidjian, S., Amsterdam, J. D., Shelton, R. C., et al. (2010). Antidepressant Drug Effects and Depression Severity: A Patient-Level Meta-analysis. <i>Journal of the American Medical Association</i>, 303(1), 47-53).</p> <p>Kirsch was employed at Plymouth University from 1st June 2004 until 31st January 2007, and then again from 1st November 2011 to the present. The third meta-analysis, published in February 2008, the key publication in this impact case study, was conceived, written and submitted during Kirsch's first period of tenure at Plymouth University (the manuscript was received by PLoS on 23rd January 2007). He has continued this line of research into his second period of tenure at Plymouth, starting in November 2011.</p> <p>All co-authors are based in locations other than Plymouth. The co-authors are Blair T.</p>

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Johnson, (University of Connecticut, USA, 2006-2008); Tania B. Huedo-Medina, (University of Connecticut, USA, 2006-2008); Thomas J. Moore, (Institute for Safe Medication Practices, USA, 1998-2008); Alan Scoboria, (University of Windsor, Canada, 1998-2008); and Brett J. Deacon, (University of Wyoming, USA, 2006-2008). Kirsch was the lead for the vast majority of this work. He is first author for all three meta-analyses (including the 2008 meta-analysis). He conceived the studies, supervised the data extraction, contributed to analysing the data, and took the lead in writing the articles. All of the work was carried out independently of any commercial sponsors.

3. References to the research

- Khan, A., Faucett, J., Lichtenberg, P., Kirsch, I., & Brown, W. A. (2012). A Systematic Review of Comparative Efficacy of Treatments and Controls for Depression. *PLoS One*, 7, e41778. <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0041778>
Citations: 10. Impact factor 2011: 4.1, 5-year IF 4.244 Journal ranked 7/56 in 'Multidisciplinary Sciences' by IF and 4/56 by Eigenfactor (JCR)
- Kirsch, I (2010) *The Emperor's New Drugs: Exploding the Antidepressant Myth* Perseus Books; Philadelphia
Citations: 158
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- Kirsch, I., Deacon, B. J., Huedo-Medina, T. B., Scoboria, A., Moore, T. J., & Johnson, B. T. (2008). Initial severity and antidepressant benefits: A meta-analysis of data submitted to the Food and Drug Administration. *PLoS Medicine*, 5. <http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.0050045>
Citations: 1011
Impact factor 2011: 16.269; 5-year IF 15.379. Journal ranked 5/155 for 'Medicine, General and Internal' by IF; ranked 8/155 by Eigenfactor (JCR)
- Kirsch, I., & Moncrieff, J. (2007). Clinical trials and the response rate illusion. *Contemporary Clinical Trials*, 28, 348-351. <http://www.sciencedirect.com/science/article/pii/S1551714406001480>
Citations: 24
Impact factor 2011: 1.814; 5-year IF 1.892. Journal ranked 68/112 in 'Medicine' Research and Experimental'; ranked 47/112 by Eigenfactor (JCR)
- Moncrieff, J., & Kirsch, I. (2005). Efficacy of antidepressants in adults. *British Medical Journal*, 331, 155-157. <http://www.bmj.com/content/331/7509/155>
Citations: 230
Impact factor 2011: 14.093; 5-year IF 13.511. Journal ranked 5/155 for 'Medicine, General and Internal' by IF and 4/155 by Eigenfactor (JCR)

4. Details of the impact

There are four specific areas in which this work has had impact

1) Updated NICE guidelines for the treatment of depression

This impact has followed on from the pre-2008 impact. The pre-2008 impact can be summarised as follows: Kirsch was contacted by the NICE commission following the publication of the second of his meta-analyses (2002) as they were in the process of drafting guidelines for the treatment of depression in adults. NICE were also in the process of carrying out their own analysis of the clinical trial data but lacked access to the unpublished trials, hence their interest in the Kirsch et al. (2002) data. Both the 1998 and 2002 meta-analyses were subsequently cited in the 2004 NICE guidelines, with Kirsch being involved in drafts of these guidelines.

Kirsch et al.'s 2008 meta-analysis, which took account of the concern that antidepressants might be more effective in more severely depressed patients, was incorporated into the revised version of the NICE guidelines (NICE, 2010) [1] and credits his work with documenting the importance of the following issues. Page numbers within the NICE guidelines are indicated

- that the benefit of antidepressants is linked to depression severity (pp. 304 & 314)
- the finding that this apparent benefit is "due to the decreasing efficacy of placebo with increasing severity of depression, rather than increasing efficacy of the antidepressant drug per se (Kirsch et al., 2008)" (p. 314)

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- the problem of publication bias towards clinically significant results in the assessment of antidepressant efficacy (p. 309)
- that the large proportion of the antidepressant response is actually a placebo response (p. 314)

This acknowledgement that the effects of antidepressants may be largely a placebo effect has increased the health service's focus on alternative ways of dealing with depression. For example, the Facilitator of the Guideline Development Group for authoring these guidelines has acknowledged that the findings have had a positive influence on the NHS's program for Improving Access to Psychological Therapies [2]. A recent meta-analysis involving Kirsch (Khan et al. (2012), see Section 3) compared improvement rates from various treatments for depression including antidepressants, psychotherapy, antidepressants and psychotherapy combined, physical exercise, and acupuncture. Their meta-analysis of 177 clinical trials involving more than 24,000 patients failed to find significant difference in outcome between these treatments. Thus their data suggests that alternative therapies, potentially less damaging to patients, are at least as effective as antidepressants.

2) Impact on other medical agencies

The 2008 meta-analysis also led the scientific committee of the European Medicines Agency to reconsider its own approval of antidepressants (Broich, 2009) [3]. Also, the meta-analyses are informing an effort by the American Psychological Association to draft guidelines for the treatment of depression in the U.S. The Chair of the APA Advisory Steering Committee charged with developing the US equivalent of the NICE guidelines has indicated the important role that Kirsch's work has played in this redrafting [4].

3) Impact on prescribing intentions

Antidepressants are known to have a raft of undesirable side effects (e.g. miscarriage, increased likelihood of suicide, especially in adolescents, and other significant side effects directly affecting health) and so their prescribing must always take into account potential costs, as well as benefits. Kirsch's work demonstrates that the benefits of taking antidepressants are smaller than previously thought and has thus influenced prescribing habits. Forty-four per cent of 490 surveyed UK doctors are reported to have reconsidered prescribing SSRIs (Selective Serotonin Reuptake Inhibitors, a particular class of antidepressants) to patients with depression ("Doctors change prescribing habits on back of SSRI study", OnMedica News, May 23rd, 2008 [5]). Changes in prescribing habits have implications in a number of areas of measurable impact, though it is not possible to put specific figures to those areas because of their complexity, lack of availability of reliable and systematic data, interactions with other areas, and demographic changes and patterns in people's psychological health. However, changes in the prescribing of antidepressants have implications for cost savings for health services, for improved quality of life for sufferers (including the provision of alternative interventions and therapies), reductions in sick leave, and improved health through avoidance of adverse side effects of the drugs.

This change in prescribing habits has occurred at both a national and an international level. For example, a Past President of the International College of Neuropsychopharmacology has gone on record in 2013 [6] to say that Kirsch's work has had a major impact in reducing unnecessary prescribing of antidepressants to patients with mild depression or environmentally induced stress responses, and has improved those patients' quality of life as well as benefitting the integrity of the profession of psychiatry.

4) Impact on public debate and public understanding

Kirsch's meta-analysis has also had a huge impact on public discourse and debate on the efficacy of antidepressants. The 2008 meta-analysis was critiqued in a press release by the American Psychiatric Association, and defended in the *New York Review of Books* in 2011 by the former editor-in-chief of the *New England Journal of Medicine*. The research was covered in a 5-page cover story in *Newsweek* in 2010, a full segment of the popular American news program *60 Minutes* (February 2012), and front page stories in the *Independent*, *Times*, *Guardian*, and *Telegraph*, all in 2008. There are hundreds of other media discussions of the questions raised by the 2008 meta-analysis [7].

In February 2013 a Californian resident filed a consumer class action lawsuit against Pfizer [8],

claiming that they deceptively marketed Zoloft (an antidepressant) as a highly effective treatment for depression whilst in the knowledge that the effects are barely distinguishable from a sugar pill. Kirsch is involved in this action as a key expert.

5. Sources to corroborate the impact

- [1] NICE Guidelines on the treatment of depression, 2010
 NICE. (2010). Depression in Adults (update) Retrieved 18 March, 2010, from <http://guidance.nice.org.uk/CG90/Guidance/pdf/English>
- [2] Director, National Collaborating Centre for Mental Health (centre established by NICE to develop guidance on treatment), who has led the development of most of NICE's guidelines in mental health (corroborating email available)
- [3] An official report by the Committee for Medicinal Products for Human Use (CHMP), the scientific committee of the European Medicines Agency (EMA), requested by the EMA because of two assessments of the efficacy of antidepressants, one of which was Kirsch et al. (2008). It is effectively an apology. This paper can be found as: Broich, K. (2009). Committee for Medicinal Products for Human Use (CHMP) assessment on efficacy of antidepressants. *European Neuropsychopharmacology*, 19, 305-308.
- [4] Chair, Advisory Steering Committee established by the American Psychological Association to oversee the process of developing clinical practice guidelines comparable to those of NICE (corroborating email available)
- [5] Article evidencing doctors' changes in prescribing habits: 'Doctors change prescribing habits on back of SSRI study' *Onmedica News*, May 23, 2008. Retrieved from <http://www.onmedica.com/newsArticle.aspx?id=ae98220c-10e5-4350-8a9b-c85d534c79ea>
- [6] Past President of the International College of Neuropsychopharmacology (corroborating email available)
- [7] Newspaper articles evidencing the stimulation of public debate:
 Laurance, J. (2008, February 26). Antidepressant drugs don't work – official study *Independent*
 Boseley, S. (2008, February 26). Prozac, used by 40m people, does not work say scientists, *Guardian*.
 Smith, R. (2008, February 26). Anti-depressants 'no better than dummy pills', *Telegraph*.
 Angell, M. (2011, June 23). The epidemic of mental illness: Why? *New York Review of Books*.
 Begley, S. (2010, February 8). The Depressing News About Antidepressants. *Newsweek*.
- [8] A press release indicating the class action can be found at <http://www.prweb.com/releases/2013/1/prweb10382265.htm>