

mentalhealth

today

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Pathways to work

Some of the leading brands of SSRI antidepressants are no more clinically effective than placebo for people with mild or moderate depression. So says a meta-analysis of the SSRIs fluoxetine (Prozac), venlafaxine (Efexor), nefazodone (Serzone) and paroxetine (Seraxat), published in the Public Library of Science (PLoS) journal in February.

But, despite hitting front page news, the study by Irving Kirsch, professor of psychology at the University of Hull, and colleagues at universities in the US and Canada, in fact revealed nothing that was new to the research world.

Kirsch had arrived at the same conclusions, using much the same data, in a study published in *Prevention and Treatment* journal in 2002, a full six years previously. The key difference seems to be that Kirsch was then working in the US, and the study's publication went unnoticed by the media here in the UK.

Kirsch acknowledges antidepressants may have some effect for people with severe depression. 'Antidepressants can be given to people with severe depression, but only if they don't manage to recover from alternative treatment. Antidepressants may still have a role but we must first think of alternative forms of treatment,' he says.

The NICE guideline is now being revised and is to be republished in June next year. In a statement, NICE's clinical and public health director Professor Peter Littlejohns has promised that Kirsch's PLoS paper will be included in the evidence review. But the 2002 paper was scrutinised by NICE when it produced its 2004 guidelines. And a simmering debate over whether NICE's judgement on SSRIs is empirically valid continues.

Kirsch and Joanna Moncrieff, a senior lecturer in social and community psychiatry at University College of London, have in the past publicly criticised the methodology used by NICE for assessing antidepressant

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Are SSRIs clinically worthless? Adam James looks behind the media headlines

Nevertheless, the PLoS study is highly significant. It was based on all the data – published and unpublished – from clinical trials submitted by the drug companies to the US Food and Drug Administration (FDA) during the 80s and 90s to get approval to market their SSRIs. Kirsch used freedom of information laws to retrieve the data. A meta-analysis that includes unpublished trials eliminates 'reporting bias' (caused when the same data is published in several journals and so included in the analysis more than once) and 'selective reporting' (where only the trials that produce positive outcomes of a drug are published, and so only the positive findings are included in the analysis).

Kirsch's view is clear: 'These [SSRI] drugs should never have been licensed – that's the logical response from our study. If one can not draw positive conclusions from the data, there is just no basis to conclude that antidepressants are effective interventions.'

This view is radically different to that of the National Institute of Health and Clinical Excellence (NICE). Its 2004 guideline on effective treatments for depression advises against doctors prescribing SSRIs to people with mild depression, but recommends SSRIs as clinically useful for moderate or severe depression.

Writing in the *British Medical Journal* in 2005, they argued that NICE had reached its conclusions on the effectiveness of SSRIs using categorical analysis – whether the SSRI achieved remission or not – of continuous data (ie. data obtained using scales to measure improvement), thereby distorting the findings. The same continuous data, they say, showed the SSRIs in question were not effective. They cite NICE's own comment, that 'dichotomising scores into remission and non-remission creates an artificial boundary, with patients just over the cut-off score often being clinically indistinguishable from those just under the cut-off score'. In response, the guideline's authors accused Kirsch and Moncrieff of 'an inaccurate and partial reading' of the evidence.

But a new book by Moncrieff is likely to up the anti. In the book, *The Myth of the Chemical Cure*, Moncrieff accuses NICE of massaging the evidence. She writes that, when drawing up its guideline, NICE conducted a second, superfluous statistical analysis on the data to 'present it in such a way that allowed them [the authors] to draw the conclusions they were comfortable with'. A NICE spokeswoman said there was 'no truth' in these accusations.

photo: taysm@morguefile.com

David Healy, professor in psychological medicine at Cardiff University and a long-standing critic of the marketing practices of the pharmaceutical industry, thinks NICE is unlikely to change its mind on SSRI efficacy in the revised guideline. This is largely because, like the FDA in the US, the UK drug regulator, the Medicines and Healthcare products Regulatory Agency (MHRA) has licensed SSRIs for depression. 'It would be highly difficult for NICE to go against what the drug regulators have decided,' Healy says. 'It could have the drug firms on its back trying to sue.'

Nevertheless, the Kirsch paper adds fuel to another major concern in the debate about SSRI efficacy: whether scientific objectivity – to say nothing of public interest and safety – is being compromised by the pharmaceutical industry for its own commercial benefit and that of its shareholders. Just days after the Kirsch study hit the headlines, GlaxoSmithKline (GSK) was rapped by the

clinical trial would not have got involved if they thought that drug company would have put away the results.'

A MHRA spokesman told MHT that independent researchers can apply to see drug firm trial data, unless it breaches commercial or patient information. But will such exceptions be dismantled under the new law? 'We will have to see,' he said.

Meanwhile the debate on how best to treat depression in all its severities goes on. The spiralling number of prescriptions for antidepressants hit a record high of more than 31 million in England in 2006, 16.2 million of which were for SSRIs (selective serotonin reuptake inhibitors). Faced with this mounting bill, the Department of Health is currently investing some £170 million over three years to recruit and train an extra 3600 cognitive behavioural therapists and set up a network of psychological therapy services throughout England to treat a planned 450,000 people with depression and anxiety. Yet, although most mental health charities back the government's move to expand access to psychological therapies, a few lone voices continue to argue that CBT is a bit of a quick fix: 'If a person's living situation is dire, CBT may help them a bit, but it is not going to improve the situation they are actually in,' Andrew McCulloch, chief executive of the Mental Health Foundation, believes.

Joanna Moncrieff is adamant that people should not take SSRIs: 'CBT is better than drugs. Giving drugs to people who are depressed is damaging. Antidepressants are psychoactive drugs – it's no different from putting someone on valium.'

Added into the mix are the thousands of anecdotal accounts from individuals praising SSRIs. Andrew Solomon, author of *The Noonday Demon*, *Mind Book of The Year* in 2002, says: 'I have been on Zoloft [sertraline] for some years. It's my experience that it has been demonstratively life-saving. I also have a less dire view of the pharmaceutical industry. Without this industry and the profit motive the drugs would never have been found. I would not be here if it was not for private enterprise.'

Other users do not agree. Hannah Borno, writing in the *Guardian* in response to the Kirsch study, articulates the difficulties of capturing the positive effect, and whence it derives: 'I loathe the emotional numbness [Prozac] gave me. I also found the physical withdrawal distressing. I did stop weeping when I first started taking it, and consciously taking a pill each morning is a powerful statement of intent which I'm sure could produce a significant placebo effect. But for me antidepressants, placebo or no, are surely only ever short-term solutions for depression.'

Likewise, the website www.seroxatmad.co.uk features numerous comments from people prescribed Seroxat who describe its side effects and those of withdrawal from it, as well as how their suicidal tendencies were exacerbated by the drug. As Diana Rose, co-director of the Service User Research Enterprise at the Institute of Psychiatry in London, found back in 2004 in her analysis of studies into the effects of ECT, what people who receive the treatment say about it can differ very markedly from what the so-called experts report. ■

www.mhra.gov.uk



MHRA for failing to submit studies that indicated its SSRI Seroxat led to suicidal tendencies in young people – and was ineffective in treating major depression, for which it was being widely used. The drug, despite not being licensed for people aged under 18, was being widely prescribed to them by doctors and the MHRA says GSK had the data on the suicide risk and withheld it, despite mounting concerns. The government is now scrambling to close the legal loophole that the MHRA investigation publicly exposed. Public health minister Dawn Primarolo has promised new legislation will be in place this year to make companies disclose 'any information [on their drugs] they have that would have a bearing on the protection of health'.

However, Healy fears independent researchers will still be hampered in their access to the data from the unpublished trials not showing drug efficacy that are submitted to the MHRA. He says it is vital for this trial data to be publicly accessible: 'In some form the drug firm data need to be available to the public generally, not just the regulators, ensuring [independent] experts can look at the data. There are good ethical grounds for doing this. Volunteers who sign up for a drug firm's