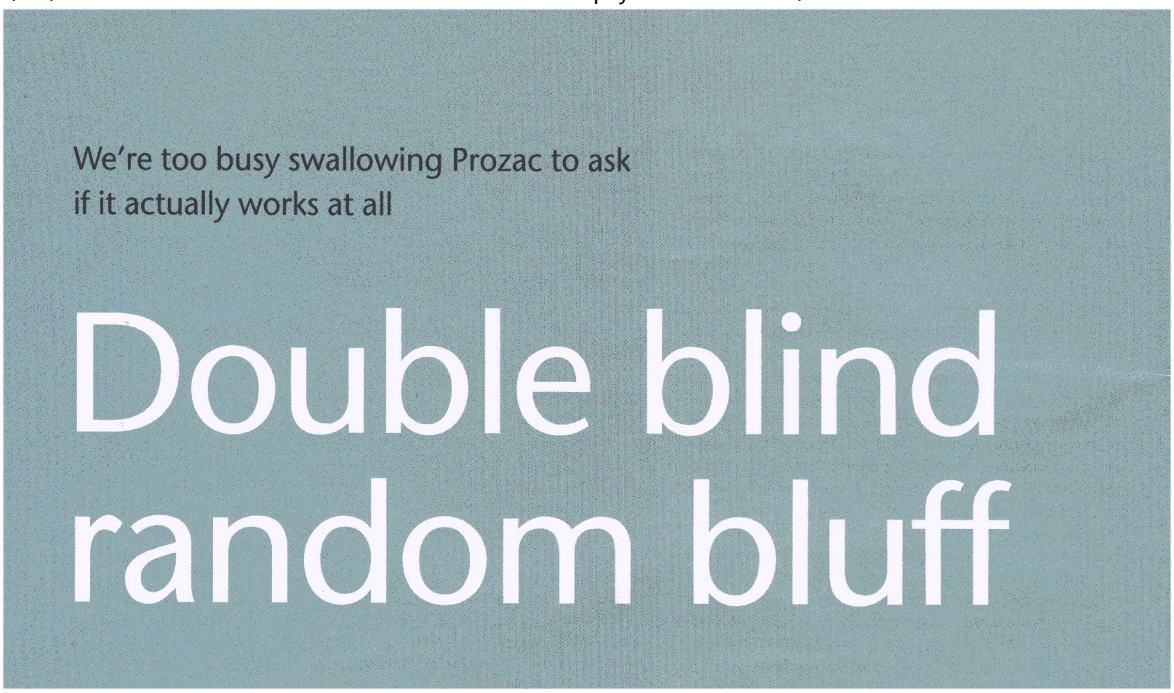

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Antidepressants are generally regarded as an established and important option in the treatment of depression. Results of controlled trials are repeatedly claimed to have proven beyond a shadow of doubt that antidepressants are effective. It's time, proponents say, that the debate moved on to other issues.

However, no matter the vast amount of research that has been undertaken, the effectiveness of antidepressants is still a matter of contention. But to challenge the consensus is no easy matter. Numerous stakeholders have considerable investment in their effectiveness - doctors and the pharmaceutical industry, for two, but also the many, many thousands of people who are taking them. Use of antidepressants has been rising rapidly over the last decade. In the UK prescriptions for them almost tripled in the 11 years up to 2002. By 2000 they had become the world's third-largest therapy class of drugs, with sales amounting to $13.4 billion. In the US they are the top selling category of pharmaceutical.

But the debate is also very topical; the National Institute for Clinical Excellence (NICE) is currently producing a guideline on the management of depression in primary and secondary care. NICE was set up on 1 Apri1 1999 as a special health authority within the NHS in England and Wales. Its role is to provide patients, health professionals and the public with authoritative, robust and reliable guidance on current 'best practice'. The depression guideline is currently in draft form and is due to be finalised in March 2004. Whether or not antidepressants are effective per se, as opposed to by comparison with each other, is surely a fundamental question that NICE needs to address.

The first antidepressants were introduced in the 1950s, on a wave of therapeutic optimism created by the marketing success of chlorpromazine for the treatment of schizophrenia. This optimism was partly a continuation of psychiatry's endeavour to find medical treatments for mental illness, that had previously led to enthusiasms for such interventions as insulin coma therapy, electroconvulsive therapy (ECT) and frontal lobotomy.

Despite the enthusiasm for the new drug treatments, however, the results of the thousands of early studies of antidepressants were not nearly as conclusive as they are often claimed to be. Around a third of published studies showed no difference between antidepressants and placebo.[1] Two of the largest, independently funded trials of this era, the Medical Research Council trial of 1965 conducted in the UK and the 1970 National Institute of Mental Health study in the US, both found no difference between the antidepressants tested and placebo on their main outcome measures.[2]

Recent research

The most recent reviews of randomised controlled trials find around a ten per cent difference between antidepressant and placebo.[3] What this difference might represent has been illuminated recently in a comprehensive meta-analysis of the results of trials submitted to the US Food and Drug Administration (FDA) for approval of six top selling selective serotonin re-uptake inhibitor (SSRI) antidepressants.[4] They found that the average difference between antidepressants and placebo in these trials was two points on the Hamilton Rating Scale for Depression. The Hamilton Scale is the most commonly used measure of depression, with a total score of 50 or 62, depending on which version is used. A difference of two points seems of doubtful clinical relevance.

Much of the literature on antidepressants presents figures for the number or proportion of people who 'respond' to antidepressants or placebo. These studies show rather more impressive differences between people taking antidepressants and people taking placebo. A 30% difference is sometimes quoted. However these results are usually based on exactly the same data that also show these very small differences in depression scores. The more optimistic results occur because of the way 'response' is defined. An arbitrary definition of response, usually a 50% improvement in symptoms, is applied to the depression scores to allocate participants into the categories of 'responder' and 'non-responder'. But because the 50% is generally close to the mean of what may well be a normal distribution of a set of scores, it will divide into different categories people whose scores are in fact very close. Thus it leads to the illusion of much greater improvement than the drug actually produces.

That the difference between effects of antidepressants and placebos is so small needs to be more widely known. In addition, there are sources of bias that mean that even these apparent minimal differences may be an exaggeration of the true state of affairs.

Methodological biases

Although the research studies of antidepressants are inconsistent, and overall the differences found between

antidepressants and placebo are small, especially in recent studies, there are many studies that suggest that antidepressants are somewhat better than placebo. However there are several factors about the way these studies are conducted and reported that may artificially inflate the apparent benefits of antidepressants.

1. *Publication bias*

We know that positive studies are more likely to be published than negative ones. A recent Swedish study confirmed that some negative studies of antidepressants are not published.[5] If negative studies are not published, meta-analyses that pool the results of published studies will overestimate the effects of antidepressants. This seems to be borne out by the fact that the meta-analysis by Kirsch et al,[4] which included unpublished studies, found smaller differences between antidepressants and placebos than previous meta-analyses.

2 *Amplified placebo effects*

To work out whether antidepressants are really better than placebos, studies need to be done double-blind: neither the participants nor the researchers should know who is taking antidepressants and who is taking placebo tablets. But many studies have shown that often both parties can guess what participants are taking. This should come as no surprise: people involved in clinical trials will of course be curious to know whether they are in the active or placebo group. They may notice that placebo tablets taste different to medication they have previously taken. Active medication, such as antidepressants, may produce side effects that distinguish it from inert placebo tablets. People in the antidepressant group may then experience a so-called amplified placebo effect (the effect whereby people experience changes in mood/condition because they expect to do so), simply because they know or suspect they are taking the active medication as opposed to the dummy tablet. The same expectancy may affect the scoring by the raters in research studies.

Some older studies compared antidepressants with 'active' placebos - that is placebos containing an active substance that is not an antidepressant but has some of the same side effects - to minimise this problem. These studies found small and mostly negligible differences between the antidepressant and the placebo.[6] However, even in these studies participants could often distinguish between antidepressants and the active placebos, possibly because the antidepressants had more profound side effects.

3. *Measurement*

Since depression is a subjective state that probably means different things to different people, measuring it is complex. Most studies of depression and antidepressants now use questionnaires tha): include various combinations of symptoms of depressive states. All these questionnaires contain items that concern symptoms such as sleep, anxiety and agitation that would respond to any drug with sedative effects. Changes on these items may therefore not necessarily indicate a specific effect of the drug on depression or mood.

4. *Analysis and presentation* of *results*

Data can be analysed and presented in a way that exaggerates the effects of a treatment. For example, it is common to use multiple rating scales and measures, and then only to report or highlight the ones that show positive results. If enough measurements are made, some will be positive just by chance. In addition, data from patients who do not complete the study may be discarded, and this has been shown to result in exaggerated treatment effects.

5. *Discontinuation effects*

People who have had repeated episodes of depression are currently recommended to take antidepressants for several years. However studies of continuation use of antidepressants are potentially even more flawed than short-term treatment studies. This is because they use a discontinuation design, in which patients who have responded to treatment with antidepressants are randomised to continue on the antidepressants or be withdrawn to an inert placebo. This design is potentially flawed, for a number of reasons. It is now agreed that withdrawal from antidepressants of all classes results in a discontinuation syndrome consisting of various symptoms. This withdrawal syndrome itself may be mistaken for relapse or deterioration in the withdrawn patients, thus leading to inflated estimates of relapse in the placebo group. In addition, the withdrawal syndrome may reveal to patients whether they have been withdrawn to the placebo or not. In this case fears about stopping treatment may have a negative impact on the outcome of the placebo group. This may be particularly significant in these trials since the initial sample consists of people who are believed to have responded to antidepressants and hence are likely to have good expectations of treatment.

Pharmaceutical sponsorship

The pharmaceutical industry now funds almost all trials of antidepressants. The trials are increasingly conducted by the flourishing private sector of commercial research organisations, hundreds of which may compete for contracts. Medical writing agencies employed by companies often prepare the reports of trials according to company specifications. It has been shown empirically that trials that are sponsored find larger effects of the sponsor company's drug than other studies. It has also been shown that there is selective reporting and publication of positive results in company sponsored trials.' Over the last decade the industry has funded and conducted various publicity campaigns aimed at increasing levels of diagnosis and treatment of depression. The fact that so much has been invested in, and reaped from, the antidepressant market should make us wary of accepting at face value research that is funded and produced by drug companies. However, for the same reasons, we should be cautious about the products of academic psychiatry, since most psychiatrists that are involved in antidepressant research now have extensive financial links to drug companies.[7]

Specific effects

If the above biases are operating it would seem likely that a vast array of pharmaceuticals might be shown to have antidepressant effects. This is, in fact, the case: many substances not conventionally classified as antidepressants have demonstrated superior efficacy to inert placebos or equivalent efficacy to conventional antidepressants in trials in people with depression. The list includes many antipsychotics, some barbiturates, various benzodiazepines, buspirone, some stimulants and more recently St Johns wort.[2] In addition, antidepressants themselves have a wide range of modes of action. This implies that what helps people recover is not a particular pharmacological effect but the simple fact of taking some type of active medication.

Severe depression

A few studies, mostly with outpatients, have shown that the difference in response to antidepressants and placebo is greatest in people who have the most severe depression. However studies of people in hospital find smaller differences between antidepressants and placebo than do the outpatient studies.[8] Indeed one study of inpatients showed that response to antidepressants was greatest in the least severely ill.[9] The prognosis for hospital treated depression is also very poor, with studies finding that more than half of adults and an even higher proportion of older people have not recovered several years later.

It is arguable that the positive outcomes of antidepressant trials come about because there's a group of patients in the mid-range of severity who show the greatest amplified placebo response. This is because

patients with very mild depression often do not want to take medication, and patients with severe depression are less likely to make any sort of placebo response.

Does it matter?

Despite claims that the effects of antidepressants are well established, many of the studies of antidepressants show negligible differences between antidepressants and placebo, and it is likely that many more negative studies are never published. In addition there are methodological problems with antidepressant trials: the fact.that they are not truly double blind, measurement is imprecise and analysis and presentation of results can be skewed. These problems could easily account for the results of the studies that do find antidepressants to be slightly better than placebos. In addition, many widely differing substances have been shown to have 'antidepressant' effects, suggesting the effects of antidepressants may simply be the result of taking some active medication rather than none.

If antidepressants are not specifically effective in treating depression, does it really matter, so long as they are able to induce a placebo response that might help some people to improve? First, it's a gross waste of public resources. Second, people are suffering unnecessarily all the adverse effects associated with antidepressants, including the fact that some people get dependent on them. Whether this is physical or psychological dependence is debatable, but it is certainly true that many people find it very difficult to stop them. Third, prescribing a drug for depression conveys a very strong message that the problem and its resolution are essentially chemical, and therefore out of our control; that we are the passive victims of our biology. For someone experiencing difficulties in their life, this may hugely undermine their confidence and efforts to find a lasting solution of their own. Even if some people recover more quickly in the short term, through the placebo effects of antidepressants, they may be more susceptible to a recurrence of their depression because they are not able to attribute their recovery to their own efforts.

At another level, the ubiquity of antidepressant use helps to divert attention away from the social and political processes that cause many people to experience their lives as difficult and disappointing. As a society, we are too busy swallowing Prozac to attempt to understand and change these processes. In this sense, medicine as social control has never been more successful. .

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