Why does the world have such a ‘down’ on antidepressants?

DJ Nutt  
Psychopharmacology Unit, University of Bristol, Bristol, UK.

AL Malizia  
Psychopharmacology Unit, University of Bristol, Bristol, UK.

Any newspaper or TV/radio listener in recent months will have heard reported that antidepressants are no better than placebo. This extravagant claim was fuelled by a press release about an article in JPLOS (Kirsch, et al., 2008), which reported a meta-analysis of antidepressant trials for four newer antidepressants. This has again raised criticisms of our current use of antidepressants and many journalists and even some professionals are suggesting that we should be considering using placebos instead! When added to other recent antidepressant scare stories such as their causing suicide, public confidence in what are highly effective and safe drugs is in danger of becoming undermined. This is a major concern to those treating mental illness for depression is one of the largest public health problems in Europe (Jacobi and Wittchen, 2005) and according to new data projecting, it will be the number one cause of disability in Europe by 2030.

So, why do the media and some elements of the medico/scientific community seem to have such a down on antidepressants? In this editorial, we examine issues relating to the general misconceptions around antidepressant efficacy trials especially the issue of placebo comparisons and explore the other aspects of treatment effectiveness that are consistently ignored by those antagonistic to antidepressants.

Short-term placebo efficacy trials registration trials

The first question to address is that of the utility of placebo-controlled trials of acute efficacy. These were the types of trial subjected to meta-analysis in the Kirsch, et al.’s article. Such trials are of short duration often only 4–8 weeks and are designed to provide optimally controlled data sets for regulatory appraisal. Such short trials in a recurring relapsing condition such as depression may not be the most important ones in determining efficacy, a point made by the European licensing authorities that now require long-term relapse prevention data before licensing.

However, regulators consider short-term, randomised, placebo-controlled trials important for novel medicines. Many of these are, however, ‘failed’ trials in the sense that entry criteria are not appropriately applied that there are not enough people who complete the trial and that outcome measures are not fully recorded. Moreover, many show high placebo response rates – hence, the call for the use of placebo instead of drugs! The design of these placebo-controlled trials is worth considering here – patients are assessed at baseline and then at very frequent intervals during the study. These intervals are much in excess of the schedule that would be followed in clinical practice and can end up inflating placebo response to a considerable extent (Posternak and Zimmerman, 2007). In addition, uncertainty about the nature of treatment decreases the antidepressant response in placebo-controlled trials versus comparator trials (Sneed, et al., 2008). Finally, placebo-controlled trials often include the ability to prescribe hypnotic agents in both groups, thus, invalidating the use of sleep ratings (which can contribute up to 6 points overall in HDRS for example).

In practice, regulators usually ignore such failed trials because they only contribute safety data to the efficacy assessments – rubbish in rubbish out – applies here. These regulatory placebo-controlled trials are very complex in terms of inclusion criteria, exclusion criteria, clinical input and balance of expectations, and it could be argued that their mapping to day-to-day clinical situations is poor. If such trials are added into a meta-analysis, as was done by Kirsch, et al., then the real efficacy of drug treatment will be diluted. Regulatory authorities know this and thus ask that all trials should be submitted, but that only certain ones will be considered for licensing. In spite of these points, antidepressants were still statistically superior to placebo after the addition of these ‘failed’ trials. Additionally, the Kirsch meta-analysis included nefazodone, a drug that is no longer used – and which was quite hard to titrate to an effective dose (37.5 mg/day) – and venlafaxine that is also not efficacious at lower doses. It would be interesting to review their findings if those trials including the lower dose ones were removed.
Even in quality trials, placebo responses can be high, both in terms of change in rating scores or in percent patients reaching a criterion of response; in the case of depression this is usually taken as a change score of more than half the entry (baseline) depression score, for example, the HAMD or MADRAS or CGI. Some agencies, for example, NICE have suggested that for an antidepressant to be considered efficacious, it has to achieve a 3 point greater reduction in HAMD change score (delta score) than that produced by placebo, a difference seen as ‘clinically relevant’. When the change for placebo alone may be in the order of 8 points, critics often say that the additional 3 are really not worth having so antidepressants are not much better than placebo and by implication not needed. The choice of a 3 point difference in HDRS is, however, arbitrary and may have been inappropriately chosen and thus applied in the Kirsch, et al. analysis (Turner and Rosenthal, 2008).

Such criticisms of prescribed medicines in a clinical scenario are specious in that the true efficacy of a treatment is not that from placebo but from what it would have been if there had been no treatment; that is, the total improvement score from baseline (see Guess, et al., 2002), provided that an active medicine has some advantage over placebo. Psychotherapy trials have for years understood this and usually use a waiting list (no treatment) group as controls, and often finding very large effect sizes as a result. If antidepressants were compared with no treatment, they would seem even more efficacious, but regulators have not approved this methodology, which is one reason why the efficacy of psychotherapy cannot be compared with that of drugs (see Nutt and Sharpe, 2008). Moreover, patients who respond to placebo in short-term drug trials generally do not show and enduring response that, given the current recommendations for 6–12 month adequate treatment of the index episode (BAP guidelines – Anderson, et al., 2008), leaves them vulnerable to relapse.

Finally, a very recent review has suggested that there is a fundamental flaw in the interpretation of placebo-controlled trials (Rhimer and Gonda, 2008). They point out that it is usually assumed that all placebo responders would have responded to antidepressant drug, but if this was not true, then the drug-placebo difference would be much greater – maybe 5+ HDRS points.

**Alternative ways to determine drug efficacy and effectiveness**

Short-term, placebo-controlled efficacy trials are only one way of determining drug effects. Other designs can give a better view of both efficacy and more importantly clinical effectiveness in the real world. Undoubtedly, the most powerful design is that of relapse prevention over at least 6 months and preferably 1 year in which a group of patients are treated in an open fashion and then randomised to either continuing on the drug or being switched to placebo, and relapse is monitored over the subsequent 6- to 12-month period. Although relapse prevention is the main measure from these trials, they do show long-term efficacy also. In depression, the effect of continued antidepressant treatment compared with placebo substitution is massive; Geddes, et al. (2003) studied data from 57 trials with nearly 6000 people. They found that the prophylactic action of antidepressants to prevent relapse in depression was one of the strongest treatment effects in the whole of medicine with a P value of <0.00001 and with a number needed to treat (NNT) value as low as 3 for those most likely to relapse. This is a tremendously powerful therapeutic effect and one, which is hugely more impressive than for instance that of statins to reduce future heart attacks where the NNT is about 30 (see SIGN, 2003).

Clinical effectiveness – defined as the utility of any treatment when rolled out into the real world – is harder to evaluate systematically. For depression, one indirect measure is that of suicide rates, as suicide is the major cause of death in depression (Bostwick and Pankratz, 2000) and up to 2/3 of people who commit suicide are depressed at the time of death. Population register studies in Sweden have shown that the use of antidepressants (especially SSRIs) in that country has increased, suicide rates have fallen (Isacsson, 2000). Similar data have also emerged from data in several states in the United States.

**Can we use placebo instead of drugs?**

We have been repeatedly asked this since the Kirsch, et al. article, and even before. For many reasons – both ethical and scientific the answer is clearly NO!

Placebo responses are seen in all treatment trials in psychiatry, so are not just a facet of depression treatment. They are also found in trials in other areas of medicine, including conditions such as dementia. Over the past 20 years, there has been a trend for the placebo response to increase in psychiatry trials so complicating investigation of new drugs. The reasons for high placebo responses in many antidepressant trials are not fully understood but include factors such as scale score inflation at entry (to accelerate recruitment), multiple long assessments by specialist clinic staff and a desire/belief in the receipt of active compound (see Arana and Nutt, 2007). In addition, recent imaging work has found that placebo responses can produce some changes in the brain similar to those produced by antidepressant drugs (Mayberg, et al., 2002).

The media and some professional critics of antidepressant trials seem to equate placebo with no treatment, which is clearly wrong. The effect of placebo is not that of no drug because in double-blind, placebo-controlled trials both the patient and the doctor are aware (and probably hope) that any patient may be on active treatment. This feeling of course applies to those actually given placebo. This contrasts markedly with the normal clinical situation where if a doctor were to knowingly prescribe a placebo, it would be unethical and their hope for therapeutic value would be much less. The doctor’s expectations would, therefore, be quite different and therapeutic benefit would likely be much less than in the clini-
cal trial. Such an approach would also be highly unethical, reeking of the old days of quackery and snake oils, and would undermine the patient–doctor relationship. Interestingly, it could be argued that counselling and indeed CBT for depression are forms of placebo because they have never been shown to have an efficacy that would allow licensing as equivalent to a drug treatment (Nutt and Sharpe, 2008).

Some other issues with the Kirsch, et al. analysis...

We have some discomfort in the fact that this report is from a group with psychology backgrounds, who may never have conducted drug treatment trials. Several of the authors appear to have a particularly negative writing history on drug treatments or interests in alternative forms of therapy.

Their conclusion that antidepressant drugs should only be used for the most severely ill people is not borne out of the many previously published studies and reintroduces a stigma about depression that we have fought hard to decrease. There is an underlying dilemma here: many people who experience the illness of depression as defined by World Health Organisation or APA will only experience it once or twice in the course of their lifetime, and the median duration will be of about 3–4 months. These people will be able to improve without chemical aids as Kirsch, et al. suggest. Should we thus withhold treatment from these people (as argued above, giving placebo is not ethical or acceptable)? Until we are able to predict completely accurately who has this pattern of depression, the answer has to be NO because the personal and socioeconomic consequences of longer and recurrent episodes in those who will not spontaneously recover far outweigh the cost of prescription and the very slight risks of drug treatment.

Their conclusion that antidepressant drugs should only be used for the most severely ill people unless other treatments have failed is scientifically flawed given the fact that drug–placebo difference is but one measure of efficacy and that ‘true’ drug effect is that of placebo plus drug. Moreover, the central claim of their article that antidepressants should be reserved for those patients who have failed to respond to other forms of treatment shows a disturbing lack of clinical and scientific honesty. This suggestion that other treatments would perform better than antidepressants in the mild/moderately severe group is not evidence based which is presumably why no references to support this contention are provided. Any inclusion of alternatives treatments (other than placebo) would have to depend on evidence that other treatments would perform better than antidepressants in the mild/moderately severe group. As we have discussed previously in Journal of Psychopharmacology (Nutt and Sharpe, 2008), there are NO placebo-controlled efficacy trials of CBT or other treatments (e.g., counselling) in depression that would allow them to be licensed according to the same regulations as apply to drug treatments, let alone any meta-analysis of the type conducted by these authors on the antidepressant drugs. If argued for, this unbalanced assessment of evidence would rather question scientific impartiality unless one suggested that the efficacy of psychotherapy in depression is the placebo effect. If so, then in practice, a great deal of placebo treatment is already being implemented!

Are there any useful messages in this new meta-analysis? One point with which we would agree is that the efficacy of antidepressants is better in those patients with more severe depression. Indeed, the efficacy of antidepressants in milder (or perhaps shorter lasting) depression has long been questioned (Kahn, et al., 2005). It was a pity that this potentially clinically useful message was lost in the subsequent media skirmish. To this extent, any UK psychiatrist reading this article need not worry about his/her own practice. Psychiatrist in the UK only sees people with treatment resistant, complicated or very serious depressive disorders. Most of the patients described in the reported trials are treated in primary care.

...and finally, contemporary divinity: the media

The press coverage produced by the Kirsch, et al. article was quite remarkable both in scale and lack of balance. We find it disappointing that the media seem to take a perverse pleasure in negative reporting of modern antidepressant drugs (especially the SSRIs) that seem to have taken over from the benzodiazepines as the whipping boys of drug treatments. Would a comparable meta-analysis showing that psychotherapy was ineffective have made it to the front page of three leading UK broadsheets?

We suspect that underneath the value of scaremongering to sell news copy; there lays a significant problem of devaluing the utility of these agents, of stigmatising mental illness and of assuming that psychiatric disorders must be amenable to control by strong character. This is likely because there is still a failure of the media to accept the seriousness of depression and related psychiatric illnesses (see Nutt, 2003). This is despite the well-known huge effects they have in relation to personal life, economic prosperity and life expectancy and the fact that their origins are clearly explained by altered brain functions. It is disappointing that such stigma, originally found in medieval religious writings, is still deep rooted.

Declarations of interests

DJN and ALM are practising consultant psychiatrists/clinical psychopharmacologists who run affective disorders clinics and use antidepressant drugs a great deal. Both have received many grants, honoraria and consulting fees from drug companies with an interest in psychotropics including antidepressants. They have conducted and are conducting treatment trials in depression and other psychiatric conditions. DJN was member of the Advisory Committee on NHS Drugs from 1995–2000 and the Committee on Safety of Medicines from 2000–2005. He is currently national advisor to the BNF on psychiatric...
drugs and editor of the Journal of Psychopharmacology. Also he is the past president of the BAP and president of the European College of Neuropsychopharmacology, two institutions that promote research in antidepressant and other psychotropic drugs. ALM is a current BAP council member.

References