BJPsych | The British Journal of Psychiatry (2018)
213, 454–455. doi: 10.1192/bjp.2018.98

Editorial

# The benefits of antidepressants: news or fake news?

Gordon Parker

**Summary**

Although antidepressant drugs are commonly effective, several meta-analyses of antidepressant drug trials undertaken decades after their introduction suggested that they were effectively acting as placebos. A recent meta-analysis concluded that they were effective. Both conclusions have been widely taken up by the media. This paper seeks to explain the disconnect.

**Declaration of interest**

None.



Few clinical psychiatrists dealing with people with depression doubt that antidepressant drugs can be highly beneficial. They observe many patients with depression improving with an antidepressant, and relapsing if the drug is ceased. To them, the effectiveness of antidepressants appears to be a 'no brainer'.

The first antidepressants emerged in the 1930s: first the psychostimulants, such as dexamphetamine, and then the tricyclics in the 1950s. Over the next six decades, numerous antidepressants have been marketed and licensing of such drugs generally requires that their benefit is demonstrated in several placebo-controlled trials. This requirement alone suggests that if aggregated trial data were examined, antidepressants would show distinctive benefits and superiority to placebo.

Recently, Cipriani *et al*.[1] published a systematic review and network meta-analysis evaluating the efficacy and acceptability of 21 antidepressant drugs and reported that all 'were more efficacious than placebo in adults with major depressive disorder' (p. 1). Their study was widely reported in the international media, with the media's general message being that the study had shown antidepressants to be effective and as if this was new news. Such attention invites the question: Why did such findings (clinically self-evident and seemingly known for over six decades) attract such attention?

The answers lie in the backstory and take us to key issues that continue to be under-recognised. In 2002, Kirsch *et al*.[2] reported an analysis of the six most widely prescribed antidepressants approved by the US Food and Drug Administration (FDA) between 1987 and 1999. Quantifying only a two-point difference between drug and placebo on the Hamilton Rating Scale for Depression, they argued that the effects of 'antidepressant drugs are very small and of questionable clinical significance' (p. 7) and that 'current antidepressants may be little more than active placebos' (p. 8). In the following year, Khan *et al*.[3] reported analysed data from randomised placebo-controlled trials of nine antidepressants approved by the FDA. In the fixed dose trials, only 31% (11/35) showed superiority over placebo. In a later publication, Kirsch *et al*.[4] published a meta-analysis of data on all clinical trials submitted to the US FDA for the licencing of four 'new-generation' antidepressants for the treatment of 'major depression'. They stated that drug–placebo comparisons showed 'virtually no difference' at 'moderate' levels of depression and were 'relatively small' for people with 'very severe depression.'

In a subsequent article Kirsch[5] reported that, on the morning after it was published, his second paper was the front page story in 'all of the leading national newspapers in the United Kingdom' and over the next few years he had been 'transformed …. into a media superhero – or super villain, depending on whom you asked.' (p. 128). Kirsch's conclusion, in effect positioning antidepressants as active placebos along with his suggestion that antidepressants be prescribed as active placebos, continued to receive wide attention from the international media. His widely promulgated views were not only a concern for prescribing clinicians but particularly perturbing to many people who might have gained benefit from an antidepressant or were contemplating whether to start one. Many felt, in essence, duped, while prescribing psychiatrists' credibility was put in doubt.

How has the topic achieved such a state of uncertainty in recent decades? Of the several factors, two will be considered here: antidepressant trial procedures (and their disconnect from 'real world' clinical practice), and the status of major depression as the target condition.

In relation to antidepressant trial procedures, participants with suicidal ideation, more gravid symptoms or comorbid states are excluded. Trials are therefore weighted towards those with milder conditions than observed in clinical practice, and those who are highly likely to have spontaneous remissions or show a placebo response. As quantified by Walsh *et al*.,[6] since the introduction of the DSM-III (1980) diagnosis of major depression, responder rates (both to antidepressant and to placebo) in studies undertaken from 1981 to 2000 increased substantially – quantified at 7% per decade.

The most substantive distortion, however, arises from the standard trial target – of only including participants with a diagnosis of major depression – and reflecting its high cachet value. Major depression can be criticised on a number of grounds. First, as previously overviewed,[7] this diagnostic label eschews aetiology and so limits its specificity. Second, it has no prognostic capacity because length of episode, recurrence and chronicity data are all dependent on nuances of the samples studied. Third, it has no treatment specificity: randomised controlled trials of varying treatments – for instance older antidepressants, newer antidepressants, manualised psychotherapies and St John's Wort – all generate similar overall efficacy levels of some 50–55%.[7] This outcome alone challenges its diagnostic utility. Fourth, major depression's in-built design allows criteria to be judged as positive at the 'lowest order of inference', so risking inclusion of non-clinical mood states.

Many research papers dealing with major depression commence with a statement that 'it' is a severe, recurrent and impairing disease; thereby reifying its status as disease entity. As Kendler[8] observed, this constitutes a 'conceptual error – a categorical mistake' by '*taking an index of a thing for the thing itself*' and which has 'contributed to the impoverishment of psychopathology and has affected our research, clinical work, and teaching in some undesirable ways' (p. 771). Such a judgement was echoed by the Chair of the DSM-5 (2013) Mood Disorders' Work Group in a



https://doi.org/10.1192/bjp.2018.98 Published online by Cambridge University Press

*cri de coeur*: '…. Right now, with major depression as our target, we are shooting in the dark'.[9] In reality, a diagnosis of major depression is simply a domain diagnosis that encapsulates and effectively homogenises a variety of heterogeneous depressive conditions and states that have various psychological, social and biological causes; differing intrinsic trajectories; and differing responses to varying treatment modalities and the passage of time.

As argued previously,[7] an analogy to 'major breathlessness' allows several points to be made. A patient receiving such a non-specific diagnosis would not feel well served. They would prefer to know whether they had a specific disorder (e.g. asthma, pneumonia or a pulmonary embolus) and thus receive a specific treatment (i.e. a bronchodilator, antibiotic or anticoagulant, respectively). In essence, a domain diagnosis is inappropriate as it fails to constrain the intrinsic heterogeneity of the constituent disorders. An additional drawback is that it disallows differing treatment modalities to be validly evaluated. For instance, if the sample studied is weighted to those with a biological melancholic depression, then superiority of an antidepressant drug to placebo might be expected. If the sample principally comprises those with personality styles that cause them to see themselves, the world and their future negatively; the superiority of cognitive–behavioural therapy might be anticipated, and an antidepressant might be quantified as ineffective. If the sample largely includes those with stress-induced 'reactive depressive' disorders, then empathic counselling plus strategies that neutralise or minimise the stressor and/or assist the individual to come to terms with it are appropriate, and an antidepressant might be of questionable benefit. Yet major depression welcomes all these subtypes to its family.

Returning to the major-breathlessness analogy, imagine if a highly effective anti-asthma medication was to be evaluated in a placebo-controlled study. If the sample comprised only subjects with asthma, its efficacy would be demonstrated. If, by contrast, the sample comprised those with a diagnosis of major breathlessness, with only a small percentage having asthma, then the drug would be unlikely to differentiate from placebo and would thus be judged as ineffective.

Although most branches of medicine have refined their diagnostic subgroups over time (for instance 'unpacking' hepatitis or diabetes and not treating either as a uniform entity), the reifying of major depression as a diagnostic entity used for randomised controlled trials has moved psychiatry in the other direction. Such an outmoded approach advances a Procrustean model whereby the treatment received by those with major depression is determined principally by the background training or discipline of the practitioner. Thus, those with the diagnosis of major depression are likely to receive an antidepressant from a medical practitioner, cognitive–behavioural therapy from a psychologist and counselling from a counsellor – with the patient being 'fitted' to the nonspecific diagnosis rather than the treatment being fitted to a more precisely defined depressive subtype (i.e. psychotic or melancholic depression or a set of non-melancholic conditions reflecting acute and/or chronic stressors and predisposing personality styles). Such a model ignores the aetiological determinant and fails to advance a personalised or precision model.

Cipriani *et al*.[1] have certainly undertaken a majestic analysis. Their conclusion that the antidepressants they evaluated are effective provides a much-needed benchmark and goes some way to uproot the seeds of doubt sown by Kirsch (intriguingly not referenced by Cipriani) which had shadowed psychiatry's credibility. However, their claims that results should 'serve evidence-based practice and inform patients, physicians, guideline developers, and policy makers on the relative merits of the different antidepressants' (p. 1) merit a challenge. There are intrinsic limitations to the data (reflecting the diagnostic criterion) and the rank ordering of the differing antidepressants is likely to be very different across differing depressive subtypes. We should be wary of accepting such suggested precision at face value. This would be pseudo-precision psychiatry.

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First received 18 Mar 2018, accepted 26 Mar 2018

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https://doi.org/10.1192/bjp.2018.98 Published online by Cambridge University Press