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Invited editorial

The place of placebo? The ethics of placebo-controlled trials in bipolar disorder

The use of placebo controls in psychiatric research remains a vexed issue (1–3). There are many aspects to this debate. It is essential that adequate protection of trial participants is woven into trial design, and that only those placebo-controlled trials that are of clear clinical value use such a design. This is concordant with the International Conference on Harmonization guidelines.

Risks of placebo-controlled trials and the ethical dilemmas associated with them are extensively debated in the literature. The principal risks are classified as increased mortality, permanent serious harm and reversible but serious harm or discomfort (4). Many of these have begun to be quantified. For antidepressants, there is a consistent finding in databases comparing placebo and active comparator that there is no increased rate of suicide in placebo-treated subjects. In schizophrenia trials, although the database sizes are less extensive, again no increased suicide risk in placebo-treated individuals has emerged from pooled comparisons of placebo and active comparator. No bipolar data are currently available that document an increased risk of suicide in placebo-controlled trials, although it is true that absence of evidence does not equate to evidence of absence. With regard to the long-term effects of extended drug-free periods in schizophrenia, Carpenter et al. (5) stated that 'the hypothesis that drug free periods have long-term toxic effects is not substantiated'. On the third issue, it is difficult to quantify the morbidity burden of untreated illness, although attempts to do so have clearly shown that the health burden of untreated major psychiatric illness is among the worst global health states described (6,7). The argument essentially resolves around the burdens invoked by placebo treatment against the broader gains that new treatments bring (4) and includes data pertaining to the differential expected in symptom burden in placebo- and active-comparator-treated individuals.

The only alternate to a placebo-controlled design is an active comparator. The power of such a design is far less than a placebo-controlled trial, and to do a meaningful noninferiority study that will be able to detect a small difference in endpoint between the groups will lead to an order of magnitude greater recruitment, which will result in far greater numbers of people being exposed to early-stage trials with potentially ineffective agents.

In bipolar maintenance, there are very few trials that pass muster methodologically. For example, most of the trials of lithium on which its current use is based are limited methodologically by modern standards. It is only data from a couple of new registration trials that have used lithium as a comparator that have given a methodologically adequate signal. This is not true for valproate, where a single failed study is all the data that are available in bipolar maintenance (8). In that trial, there was no difference between valproate, lithium or placebo in maintenance on primary outcomes. This is an ethical issue, as clinical need has allowed valproate to become an established therapy, without corresponding placebo-controlled data. Similarly, there is a paucity of quality data for carbamazepine, and it too has become widely used. The ethical issue resulting from the absence of adequate placebo data is of societal concern. Atypical antipsychotics are already in widespread off-label use globally for bipolar disorder. There is only a single published and one unpublished placebo-controlled trial in maintenance. Given that there are positive and negative trials of many established agents in many indications, on the basis of the available evidence, one cannot say with Cochrane level 1 of evidence that much available therapy is effective.

Placebo treatment is not equivalent to non-treatment. In most trials, a significant percentage of placebo-treated subjects respond with some reduction in the symptoms of their illness. A meta-analysis of available antipsychotics showed that approximately 25% of studies failed to distinguish active medication from placebo (9). There is an important nonspecific clinical benefit from the engagement and attention that flows from

a clinical trial. An obvious extension of this, and much psychopharmacological research, is that the gap between placebo and active comparators is often small, with high placebo response rates and low active placebo differences. There are many reasons for the small gap between active and placebo-controlled designs, and this is increasingly an area of major concern to researchers. Over the past two decades, the proportion of patients responding to placebo has grown by approximately 7% per decade, with a similar rise in active medication response rates (10). The proportion of diagnosed individuals in the community has increased markedly, altering the casemix towards the softer end of the spectrum. While older trials tended to use clinical populations, there is a trend towards advertising for participants, which has the potential to further alter the casemix. While diagnostic criteria have not changed, a number of trial parameters over time have changed, including increasing trial length. Longer trials tend to have higher placebo response rates (10). A high proportion of treatment-refractory individuals enrol in trials, as those who are well and stable do not enter treatment settings. Bipolar disorder has a labile baseline, and this implies that episodes tend to be time limited. A rapidly fluctuating course not surprisingly is a predictor of placebo response (11).

A further caveat in bipolar disorder is the absence of a class effect. Again, there are few trials in bipolar disorder, but for example, quetiapine seems to be a better antidepressant than olanzapine. Not all anticonvulsants work similarly; lamotrigine alone works for depression, and valproate has efficacy in mania, but not for depression. In light of the above, further placebo-controlled trials are essential to establish maintenance efficacy of widely used agents.

Audits of individuals in the community show that although maintenance therapy is generally recommended, the majority of individuals with bipolar disorder do not receive appropriate therapy. Adding to this problem are data that most people in the community do not adhere to such treatment. Johnson et al. (12) have reported that the average duration of maintenance therapy in the community was 76 days. The gap in practice between what evidence there is and the application of such evidence to practice remains of concern. In a recent survey of prescription patterns in bipolar subjects (13), the class of drugs most commonly prescribed first was antidepressants (50% of individuals), followed by mood stabilizers (25%) of which anticonvulsants made up 17% and lithium 8%, a pattern that is at odds from most guidelines. Clearly, much needs to be done both to increase the evidence base and to translate the evidence into practice.

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