Psychiatry should not become hostage to placebo: An alternative interpretation of antidepressant-placebo differences in the treatment response in depression

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Abstract

Background: It is widely believed that in randomized controlled trials of antidepressants the difference between drug and placebo response rates is rather small (around 20%), leading to a common perception that antidepressants have limited efficacy.

Aim: The aim of the present paper was to present an alternative calculation and interpretation of antidepressant-placebo difference in the treatment response to antidepressant in drug trials which may shed a new light on the efficacy of antidepressants.

Issues: We have previously highlighted several controversial points concerning the calculation of antidepressant and placebo response rates in randomised controlled trials, which may influence views concerning the efficacy of drugs, and demonstrated several factors which may lead to overestimation of the placebo effect and underestimation of antidepressant efficacy. The traditional interpretation of antidepressant-placebo difference in randomized controlled trials on major depression has been also challenged previously from at least five points of view but all leading to a conclusion that currently prevailing opinions concerning relative placebo and antidepressant response rates overestimate placebo response, and thereby underestimate efficacy of antidepressant drugs. In our present paper we propose another method for calculating placebo and antidepressant response rates which may shed new light on an overlooked aspect of the efficacy of these drugs.
Conclusions: We contend that opinions on the effectiveness of antidepressants should be reconsidered, and comparisons with placebo should be more carefully applied. Interpretation of the placebo response is of crucial importance for establishing the efficacy of antidepressive medications, and psychiatry should not become the hostage of placebo.

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1. Introduction

Major depressive disorder is one of the most common disorders not only in psychiatry but also in the field of general medicine. With its 12–15% lifetime and 4–6% annual prevalence depression is a major public health problem, affecting a significant portion of the population, causing significant social and economic burdens for patients and their families, and being associated with increased mortality particularly due to suicide (Scott and Dickey, 2003; Paykel et al., 2005; Rihmer, 2007b; Rihmer and Angst, 2009). Furthermore, other conditions, such as other Axis I (anxiety and substance-use) disorders and Axis II (mostly borderline) personality disorders are also frequently associated with depressive episodes and excess suicidality (Pompili et al., 2005; Rimlinger, 2010; Holzel et al., 2011; Leichsenring et al., 2011). However, depression can be effectively treated and successful antidepressant pharmacotherapy of major depressive disorder also reduces suicide morbidity and mortality even in this high-risk population (Nutt and Malizia, 2008; Rihmer et al., 2008). Since many depressed patients do not respond to the currently available antidepressants or do not tolerate them, and also because depression is a highly recurrent condition with approximately half of patients experiencing a recurrence within two years (Scott and Dickey, 2003), it is crucial to develop new medications for both acute and continuation/long-term treatment, and to have an accurate estimate of the efficacy of medications in treating this highly disabling condition. Placebo control is essential in evaluating the potential efficacy of any psychotropic medication during the clinical testing phases of drug development (Baldwin et al., 2003). Although this is accepted practice, it still provokes controversy and debate, particularly because the efficacy and utility of medications is established through investigations of drug and placebo response rates (Laporte and Figueras, 1994; Quitkin, 1999; Walsh et al., 2002; Nutt and Malizia, 2008). Placebo control, however, remains necessary in drug trials especially in combination with active comparators to limit the chances for false positive and false negative study results and to ensure maximum assay sensitivity, and comparison with placebo is also valuable tool to distinguish manifestations of the illness from medication induced adverse reactions (Baldwin et al., 2003; Adam et al., 2005). The aim of the current paper is to present an alternative calculation and interpretation of antidepressant-placebo difference in the treatment response to antidepressants in randomized controlled drug trials on unipolar major depression which may shed a new light on the efficacy of antidepressants and also on the biases due to possible mistakes in interpretation of placebo response rates.

2. The role of placebo control in antidepressive drug studies and controversies in drug-placebo response calculation

It is widely believed that in randomized controlled trials of antidepressants the difference between drug and placebo response rates is rather small (around 20%), leading to a common perception that antidepressants have limited efficacy. Partly due to increasing regulatory obstacles in psychotropic drug development, there has been a notable recent decline in the number of antidepressants entering clinical practice (Eriksson, 2011; Montgomery, 2011; Pedersen, 2011).

We have previously highlighted several controversial points and unanswered questions relating to the calculation of antidepressant and placebo response rates in randomised controlled trials. Taken together, these influence views concerning the efficacy of drugs and demonstrate several factors which may lead to overestimation of the placebo effect and underestimation of antidepressant efficacy (Rihmer, 2007a; Rihmer and Gonda, 2008; Rihmer et al., 2011). Current views regarding the social origins of depression (Brown, 2002; Hankin et al., 2009) and ill-informed judgements about the effectiveness of antidepressants can lead patients to be reluctant to undergo treatment; and may cause health policy makers to limit the social-security based reimbursement of antidepressant prescriptions. In turn this can leave a large proportion of patients untreated, or subject to treatment with cheaper but less effective or less well tolerated antidepressants.

A pooled analysis of randomized placebo-controlled short-term antidepressant trials in patients with unipolar major depressive disorder showed that average rates of antidepressant- and placebo-responders (50% or more drop in the total depression score from baseline) were 50% and 30%, respectively (Walsh et al., 2002). The widely used calculation of antidepressant-placebo difference in these and other drug-trials rests solely on a simple subtraction (i.e. 50-30%=20%, see Fig. 1, part “B”). The apparent message for clinicians, policy makers and the general public is that the drug-placebo difference in antidepressant drug-trials is rather low, suggesting that the clinical usefulness of antidepressants could be questioned.

In spite of this perception, no treatment guideline recommends, and no clinician routinely uses, placebo as a first choice when treating patients with major depression. Deviation from official treatment guidelines is common in everyday clinical practice, but these deviations never include placebo, probably because experienced clinicians recognise this would not be a NICE idea. The main reason for this is that participants included within phases II and III randomized controlled trials in unipolar major depression
are not representative of those seen in everyday clinical practice, as severely ill, suicidal, physically unwell and non-compliant patients are not included (Zetin and Hoepner, 2007; Wisniewski et al., 2009). Unfortunately treatment guidelines, recommendations, and healthcare policies concerning those in greatest need for an intervention are based on studies from which such typical patients are excluded.

3. Alternative approaches to antidepressant-placebo response rate calculation

We propose a differential method for interpreting placebo and antidepressant response rates which may shed new light on a hitherto overlooked aspect of the efficacy of these drugs. The traditional interpretation of antidepressant-placebo response in RCTs seems to be logically wrong. Should there be 30% and 10% response rates with antidepressant and placebo, respectively (Fig. 1, part “C”), the difference would also be 20%, though three times more patients are seen to respond to antidepressant than to placebo, and the additional benefit of antidepressant over placebo in this case is 200% (because 30 is 200% more than 10). By contrast, if the response rates were 100% and 80% respectively (Fig. 1, part “A”) the difference would also be 20%, though the additional benefit of antidepressant treatment is only 25% (because 100 is just 25% more than 80). In essence, interpretation of the absolute and clinically relevant difference between antidepressant and placebo response rates depends largely on the response rates, and so the result of a simple deduction can be misleading. Because 30% is 200% more than 10%, and 100% is just 25% more than 80%, the logically and clinically correct interpretation of the antidepressant-placebo difference in the pooled analysis reported by Walsh et al. (2002) is in fact 67%, rather than 20% (Fig. 1, part “B”). In other words, if we use placebo in 100 major depressives 30 will respond. If we use an antidepressant the same figure will be 50; and 50 is 67% more than 30. In this case the relative risk of responding to antidepressant is 50/30 = 1.67.

4. Results and discussion

This new interpretation does not change facts, but mirrors the clinical situation more appropriately. The traditional interpretation of antidepressant-placebo difference in randomized controlled trials on major depression has been also challenged from at least five other points of view (1) Rihmer (2007a), Rihmer and Gonda (2008) and Rihmer et al. (2011), (2) Fountoulakis and Moller (in press), (3) Hegerl and Mergl (2010), (4) Gueorguieva et al. (2011) and (5) Isacsson and Adler (in press). These approaches differ in their theoretical basis and assumptions, and use different forms of analysis, but all lead to a conclusion that currently prevailing opinions concerning relative placebo and antidepressant response rates overestimate the response rates to placebo, and thereby underestimate the efficacy of antidepressant drugs. In their short Editorial, “Why does the word have such a “down” of antidepressants”, Nutt and Malizia (2008) pointed out the mechanisms of misinterpretations of antidepressant response in depression summarizing in nutshell why the current environment is so malicious regarding use of these drugs outside of the walls of inpatient psychiatric departments.

Although the number need to treat (NNT) value (i.e. how many patients should be treated with antidepressant to have one more responder than those who are on placebo) is the same (NNT = 5) in all three possibilities shown in Fig. 1, this misleadingly covers the real clinical difference between antidepressant and placebo. It is easy to accept that the difference is much bigger in the case when 200% more patients respond to antidepressant (Fig. 1, right part) than in the case when the additional benefit of antidepressant over placebo is just 25% (Fig. 2, left part). It is inappropriate to include in the calculation of difference those 50% of patients (Fig. 2, striped parts) who do not respond neither to
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Contributors

ZR contributed the main idea of the study, collected and reviewed the relevant literature and wrote the paper.
PD worked on developing the idea, collecting and analysing relevant literature and writing the paper.
DB contributed to analysing the relevant data and writing the paper.
XG contributed to delineating the main concept of the study, collected, reviewed and synthesised the literature and participated in writing the paper.

Conflict of interest

Z. Rihmer has received speaker honoraria from AstraZeneca, GlaxoSmithKline, Eli Lilly and Co., Krka, Lundbeck GmbH, Montrose Kft, Pfizer, Richter Gedeon Ltd., Sanofi-Aventis, Schering-Plough, Servier-EGIS, Solvay-Pharma, Wörwag Pharma and Wyeth Pharmaceuticals; he also received honoraria as a member of scientific advisory boards of AstraZeneca, Eli Lilly and Co., Organon, Pfizer, Richer Gedeon Ltd., Sanofi-Aventis, Schering-Plough and Servier-EGIS.

D.S. Baldwin received honoraria for educational presentations from H. Lundbeck A/S, and has acted as a paid consultant to Eli Lilly, Lundbeck, and Pfizer, and currently holds a research grant (on behalf of his employer) from Lundbeck. He has accepted paid speaking engagements in industry-supported satellite symposia or other meetings hosted by Eli Lilly, Lundbeck, Pfizer and Servier.
P. Dome reports no conflict of interest.
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