

EDITORIAL

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Why antidepressant clinical trials fail:
the role of expectationsMark Sinyor¹, Ayal Schaffer^{1,2} & Anthony J Levitt^{1,3}

“In many circumstances, a subject may be more likely to respond to placebo if his or her expectation of positive outcome is high than to respond to active medication if his or her expectation of response is low...”

¹Department of Psychiatry, Sunnybrook Health Sciences Center, 2075 Bayview Avenue, Toronto, ON, M4N 3M5, Canada

²Head, Mood & Anxiety Disorders Program, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

³Women's College Hospital, University of Toronto, Toronto, ON, Canada

*Author for correspondence:

Tel.: +1 416 480 4089

Fax: +1 416 480 6878

E-mail: mark.sinyor@utoronto.ca

The final decades of the 20th century may be considered the golden age of antidepressant medications. There was a boom in their development and clinical use as well as a sense that they might represent a major advance towards more targeted treatment for patients suffering from depression. However, recent evidence pointing to the failure of many antidepressant randomized controlled trials (RCTs), particularly for depression of mild-to-moderate severity [1–3], has shaken the field. Multiple factors may explain these less than promising findings. First, we now know that the antidepressant literature has been biased as a result of selective publication of positive trials [4]. There is also an increasing awareness of the heterogeneity of what we understand to be major depressive disorder. Culture and ethnicity, for example, have an important impact on response to psychopharmacology [5], to the extent that trials conducted in different places may yield different results. Indeed, there is even a question of whether our current definition of major depression represents a distinct entity or rather multiple disorders with only some responding to antidepressants [6]. However, the core issue in failed antidepressant trials may not be the lack of response to active treatment, but the narrowing separation between drug and placebo, accounted for in large part by rising placebo response rates [7]. One important, yet underappreciated factor, contributing to placebo response rates is the manner in which patient expectations significantly influence study results.

The reason expectations are so important for psychiatric conditions such as depression and anxiety, as well as a variety of neurological conditions such as pain syndromes, is that people with these conditions are much more likely to improve if they expect to do so. For example, one study that measured the relationship between pretreatment expectations and outcome in a group of patients treated with reboxetine for major depressive disorder, found that 90% of patients who initially expected reboxetine to be ‘very effective’ responded by the end of the trial compared with only 33% of patients who only expected it to be ‘somewhat effective’ [8]. Therefore, expectations are extremely important, and researchers and physicians are modulating them all the time, often without being aware of it. A few years ago, researchers at the California Institute of Technology studied subjects tasting wine and found that both their subjective and objective experience (the latter demonstrated by functional MRI) were more positive when they were told the wine they were drinking was more expensive [9]. Subjects do a similar kind of unconscious calculation in randomized clinical trials. There is a broad literature in medicine demonstrating that research subjects generally expect drugs to be stronger and therefore respond more often to larger pills, colored rather than white pills, capsules rather than tablets and injections rather than pills [10,11].

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Studies examining how these physical characteristics of treatments impact outcome in depression are absent but may represent a worthwhile avenue for future research.

There are, however, other methodological factors that we now know can influence outcome in depression studies. Importantly, we have learned that the design of antidepressant RCTs, particularly those involving placebos, can have a large impact on patient expectations and therefore outcome. Regardless of whether they are randomized to active antidepressant or placebo, subjects enrolled in these trials have been shown to spend time ruminating about the randomization [12]. In particular, those who do not respond worry this is because they are on a placebo, while those who do respond worry that they may be ‘placebo responders’ and therefore that their response is somehow inauthentic. Our own research and that of our colleagues demonstrates that response to either active medication or placebo is correlated with higher odds of receiving the active medication and with lower odds of receiving a placebo [13,14]. We found that subjects randomized to the active antidepressant were 8–13% less likely to respond in trials where there was a chance of being randomized to placebo compared with trials where there were two active comparator arms and no placebo group. We also found that subjects were 10% more likely to respond to placebo when there were two active comparator arms versus placebo rather than only one active comparator arm (i.e., greater perceived odds of receiving an active drug). This is most likely because having higher odds of receiving the active medication fosters more positive expectations whereas higher odds of receiving a placebo increases worry and diminishes expectations.

It stands to reason that positive expectations by themselves are less likely to produce response in severe depression. Therefore, the fact that antidepressants clearly outperform placebos in severe depression but not necessarily in mild-to-moderate depression is good news. It is a signal that our medications do work. However, we find ourselves in the challenging circumstance whereby expectations and other related-nonspecific factors that impact on antidepressant treatment, such as treatment alliance, take on disproportionate importance in RCTs for mild-to-moderate depression. In many circumstances, a subject may be more likely to respond to placebo if his or her expectation of positive outcome is high than to respond to active medication if his or her expectation of response is low [15]. As a result, antidepressant RCTs for mild-to-moderate depression may fail, not because the medication has necessarily failed but because we have failed to control the trials properly. All future antidepressant trials probably need to measure expectations both pretreatment and during the trial so that this variable can be accounted for in statistical

analyses. Tools to do this such as the Credibility and Expectancy Scale are available and straightforward to administer [16].

Similarly, it is also important to consider the effect of ‘guessing’ on treatment outcomes. There is evidence that many subjects in antidepressant RCTs can correctly guess whether they have been randomized to active medication or placebo [17]. Expectations that result from guessing can have a powerful influence on outcome as well. Higher expectations in the active antidepressant group and lower expectations in the placebo group where patients have correctly guessed what they are taking could lead to the erroneous finding that a medication is more effective than placebo when this is merely an expectation effect. Therefore, in addition to assessing for pretreatment expectations, we must also call for studies to assess for the adequacy of blinding.

The process of assessing and controlling for expectations and blinding should be a requirement for all antidepressant clinical trials. In addition, we need to do more. We need to understand more clearly the role of expectations and their magnitude on RCTs. One method to examine this involves studies in which subjects are randomized to different expectations, for example telling some that they have a 25% chance of receiving an active medication and others that they have a 75% chance. Furthermore, understanding how expectations influence the research clinicians who assess, treat, and rate subject outcomes is also important since they can influence results as well.

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Perhaps the most important areas of exploration for future research are trials that attempt to distinguish between placebo responders and placebo nonresponders. By definition, placebo responders are apt to respond to a variety of nonspecific treatments. What we should be most interested in, therefore, is what treatment is effective for placebo nonresponders, those patients who generally have low expectations or whose illness is unresponsive to the placebo effect despite high expectations. RCT methods that attempt to isolate placebo nonresponders have been proposed, such as the ‘sequential parallel comparison design’ in which those patients who fail an initial trial of placebo are re-randomized to either active medication or placebo in a second step [18]. There are many challenges to this kind of approach including time, cost and the need to expose a larger number of patients to placebo than is

customary (this last issue may raise ethical concerns). Nevertheless, if we could better distinguish between placebo responders and nonresponders then we could focus our understanding of antidepressant treatments on those who need them most, although questions will still remain about the long-term treatment needs for the sizable group of people whose symptoms acutely improve with placebos alone.

The issue of placebo response and expectations should be a key component of the ongoing discussion and debate regarding antidepressant clinical trials. We must do a better job of designing antidepressant clinical trials and controlling for as many nonspecific effects as possible while conducting them. Two large pharmaceutical companies, AstraZeneca and GlaxoSmithKline, have already chosen to abandon research on psychiatric medication at least in part because of the gaps in knowledge and RCT design flaws we have described [19]. Our field is entering a new frontier. This may very well be the century of neuroscience. Imagine if during the explosion of medical treatments of the past century, pharmaceutical companies had stopped researching antibiotics

or antihypertensive agents because of design issues in RCTs. This is a future we may be facing in psychiatry if we do not fix our trials.

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