Increasing placebo response in antipsychotic trials: a clinical perspective

Markus Dold, Siegfried Kasper

Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria
Correspondence to Dr Markus Dold, markus.dold@meduniwien.ac.at

ABSTRACT

An increase in placebo response is often cited as rationale for the continuously diminishing drug-placebo differences in randomized controlled trials (RCTs) evaluating antipsychotic and antidepressant drugs. As a consequence, the probability for negative study results in placebo-controlled RCTs grows. This alarming trend conveys the impression that the newer marked psychopharmacological medications are less efficacious compared to the older ones although particularly trial methodological reasons contribute to the mitigation of the drug-placebo contrasts over the last decades. With regard to antipsychotic RCTs, the present article aims to elucidate the magnitude of the raising placebo response, factors contributing to this increase, and potential reasons for this phenomenon. Therefore, we summarize and critically discuss the findings of two recent meta-analyses on this topic. Both research projects revealed that the mean improvement of schizophrenic symptoms in the placebo groups of antipsychotic trials increased considerably over time. Factors that were significantly associated with larger placebo response in antipsychotic trials comprise with respect to participants characteristics younger age and shorter duration of illness. The results in terms of symptom severity at baseline were conflictive. In terms of trial methodology factors, shorter study duration, a larger number of study sites and participants, fewer academic/university sites, and a lower percentage of patients randomized to placebo were identified as potential predictors for high placebo response. The implications of these findings for the interpretation of antipsychotic trial results and meta-analyses are presented.

INTRODUCTION

In psychopharmacological randomised controlled trials (RCTs), the increasing placebo response during the study phase represents a meaningful issue for the interpretation of clinical trial results. A number of systematic and narrative reviews revealed continuous enhancement of the magnitude of symptom improvement in the placebo groups of RCTs over the past decades.[1–5] This phenomenon is described for antipsychotic as well as antidepressant trials.[6] As a consequence, it becomes more and more difficult for the active medication groups to separate statistically significant from placebo, which causes diminishing drug-placebo differences and subsequently a higher likelihood of so-called negative trials. The problem of poor signal detection arises, as the 'noise' of the placebo response is so apparent that no 'signal' of the investigated drug can be observed within a clinical trial. With regard to the development of new antipsychotic and antidepressant compounds, the consequences of this trend are alarming: the risk for a newly developed drug (new drug application) to fail the market approval because of negative phase III studies increases. As such late failure in the drug development process is associated with the loss of enormous costs for the pharmaceutical industry, this risk could potentially, in the worst case, lead to a slowdown of research efforts for new compounds. Furthermore, when comparing the effect sizes obtained from recent placebo-controlled antipsychotic and antidepressant trials with those of older studies, clinicians can get the impression that the newer marked psychiatric drugs are less potent than the older ones or even that the older drugs have lost efficacy over the past decades.[6] However, the decreased effect sizes are mainly caused by the high magnitude of placebo response in the recently conducted trials.

In this clinical review, we aim to summarise and discuss the factors contributing to the enhancing placebo response in antipsychotic RCTs. For clinicians, it appears highly relevant to consider the phenomenon of increasing placebo response when evaluating the efficacy of a drug based on RCT results. The knowledge of the mechanisms causing the continuously rising placebo response should enable clinicians to better judge the clinical value of an antipsychotic compound against the background of altering trial methodology. This is especially relevant with regard to the newly introduced psychopharmacological agents. In our review, we focus on research projects investigating antipsychotic trials in schizophrenia and related disorders. However, we see no rationale for assuming that the factors and reasons contributing to the increasing placebo response are substantially different from those in antidepressant trials.[3]

FACTORS CONTRIBUTING TO THE RISING PLACEBO RESPONSE IN ANTIPSYCHOTIC TRIALS

Two recently published comprehensive systematic reviews focused on the elucidation of the constantly increasing placebo response in antipsychotic trials. Agid *et al*[7] sought to identify various potential contributors to the high placebo response in RCTs comparing antipsychotics with placebo in schizophrenia. The authors included a total of 50 RCTs published between 1970 and 2010 and could demonstrate that the mean reduction in the 'Positive and Negative Syndrome Scale (PANSS)[8]' of the placebo groups increased significantly over time. In meta-regression analyses, they were able to uncover a significant relationship between greater placebo response and younger age, shorter illness duration, shorter trial duration and higher symptom severity at baseline (box 1). The latter finding varies from other study results suggesting that high baseline severity leads to an increase in drug-placebo differences.[9] Depending on the study year, a larger number of study

Box 1 Factors contributing to the high placebo response in antipsychotic randomised controlled trials

Trial design factors
- Lower percentage of participants randomised to placebo
- Larger sample size
- Larger number of study sites
- Fewer academic/university sites
- Shorter trial duration

Patients' characteristics
- Shorter duration of illness
- Younger age

This box only lists the factors with strong evidence for an association with high placebo response in antipsychotic randomised controlled trials. The findings with regard to symptom severity at baseline are conflictive.

sites, fewer academic/university or Veterans Affairs sites and a lower percentage of patients randomised to placebo (ie, a higher chance for the individual patient to receive the active drug medication instead of the placebo) could predict high placebo response.

Potential reasons that are often discussed to explain the influence of the number of collaborating academic/university sites on the amount of placebo response contain the patients' collective of university hospitals comprising usually more severely ill patients compared to municipal or private hospitals. Further potential reasons are the personal financial compensation investigators in non-academic sites mostly receive for greater enrolment. Moreover, academic sites usually have a more experienced trial staff with respect to clinical studies and offer standardised training procedures for collaborators.

Interestingly, the origin of the study (USA compared to other countries) showed no significant effect on placebo response in this meta-analysis. This result contrasts with other findings suggesting that trials conducted within the USA are characterised by larger placebo response compared to non-US trials.[2 4] The inclusion of so-called professional research participants in US studies is often discussed as a possible cause in this regard. These subjects are mainly recruited by advertisements and the motivation for study participation is often the prospect of free medication or of experiencing personal financial gain. The inclusion of such professional research participants in RCTs is usually associated with high placebo response as they often aim to please the investigators in order to receive the opportunity to be invited again for participation in a clinical study.[2] These differences in terms of drug-placebo separation between US and non-US trials were also observed in antidepressant trials, for instance in RCTs examining the newly introduced antidepressant vortiotoxine.[10]

In addition to the above discussed systematic review of Agid *et al*,[7] another meta-analysis on this topic incorporated both placebo-controlled trials (N=39) as well as active (head-to-head) comparator studies (N=66).[9] Altogether, 296 study groups representing 24 503 patients with schizophrenia were analysed. For the placebo groups, the authors found a significant positive correlation between the mean improvement (from study baseline to end point) on rating scales such as the PANSS or the 'Brief Psychiatric Rating Scale (BPRS)[11]' and publication year. The mean PANSS/BPRS reduction increased by 2.2 points on the PANSS and 1.1 points on the BPRS (both per decade since 1960) for the participants receiving placebo. This caused a significant mitigation in drug-placebo differences from 1960 to the present. Rutherford *et al*[9] could identify a significant relationship between sample size and placebo response similar to that of the number of study sites and placebo response in the meta-analysis of Agid *et al*.[7] Moreover, Rutherford *et al*[9] compared the drug efficacy in placebo-controlled RCTs to that in RCTs with active medication as control group. There was a significantly larger symptom improvement in the antipsychotic groups when active medication was the comparator in the control groups instead of placebo. Maybe, the higher probability or even certainty to receive an effective treatment accounted for this finding (expectation bias, induction of hope). Interestingly, the intensity of the therapeutic contact during the RCTs measured by the number of scheduled study visits did not significantly influence the placebo response. The authors explain the reason for this finding by the inpatient setting employed in most of the included trials.

However, there are some issues with regard to the analysis of Rutherford *et al*[9] that should be critically taken into account. For instance, their systematic literature search yielded a much lower number of relevant placebo-controlled RCTs compared to the study of Agid *et al*[7] accomplished a few years earlier (39 RCTs vs 50 RCTs). Moreover, Rutherford *et al*[9] did not calculate effect sizes and used correlation analyses rather than meta-regressions which account for the differences in sample sizes. A further major point of criticism is that placebo-controlled trials were analysed for evaluating placebo response while also direct drug (head-to-head) comparisons were considered for ascertaining the drug response. Hence, the authors concluded that the mean PANSS/BPRS improvement decreased significantly in patients receiving antipsychotic medication. This finding contrasts with other analyses demonstrating that in psychopharmacological trials, the rising placebo response is not accompanied by a declining amount of symptom improvement in the medication groups.[12]

POTENTIAL REASONS FOR THE CONTINUOUS INCREASE IN PLACEBO RESPONSE

Although this could not be verified in the statistical analysis of Rutherford *et al*,[9] the increased clinical attention participants receive in the placebo group of RCTs is often cited as a reason for the rising placebo response because the contact with the clinical staff (for instance, during the study visits) can already cause positive effects in terms of symptom improvement. The placebo administration in itself is a non-specific treatment.[13] This is particularly the case for participants who are not severely ill and who are nowadays included more and more in RCTs because the enrolment of truly ill patients is often not allowed due to ethical concerns. Another reason for the rising inclusion of only marginally ill patients is the so-called 'baseline inflation'. This phenomenon describes the tendency of investigators, mainly driven by a financial incentive to recruit participants, to rate patients with low baseline symptom severity with a higher baseline score than the objective symptom severity would reflect in order to ensure that these patients fulfil the minimal requirements for study participation.

It should be considered that the two factors 'expectation' and 'clinical attention' are meaningful issues within clinical trials. They are often called 'unspecific effects' of the placebo administration[14] and they do not occur in clinical routine care. RCT participants in placebo groups hope to receive active treatment (hope induction). This hope, however, is not present in patients refusing medication in daily clinical practice. Furthermore, medication-free patients in the psychiatric clinical routine care usually do not have such amount of clinical attention and monitoring of their psychiatric symptoms when compared to RCT participants. Thus, it can be assumed that the effectiveness of a psychiatric drug in the routine care is higher than the effect sizes derived from RCTs indicate. The study situation within an RCT cannot be transferred without reservation to the psychiatric clinical routine and trial aspects such as expectation bias, clinical attention, and the potential inclusion of inappropriate participants need to be critically taken into account. In most cases, the participants of clinical trials do not represent the clinical practice in which a number of schizophrenic patients suffer from severe comorbidities or suicidal ideation. Potentially, exactly those participants who are excluded from RCTs might benefit to a high extent from the psychopharmacological medication. With regard to antipsychotic drugs, for example, it is crucial to consider this phenomenon, especially when evaluating the effectiveness of long-acting injectable (LAI) formulations in schizophrenia.[15] The less severely ill patients incorporated usually in blinded RCTs mitigate the chances for revealing a superiority of LAIs over oral antipsychotic medication in terms of adherence. In contrast, this superiority of LAIs could be verified in a number of naturalistic studies in which more severely ill patients are enrolled who are usually characterised by fewer adherence to treatment.[16]

Measures to reduce the placebo response within antipsychotic trials

There are a number of measures that should be considered in preparation of an RCT in order to alleviate an enormously high placebo response in antipsychotic trials. Any attempt to minimise the placebo response causes greater drug-placebo separation and a higher likelihood for a positive study outcome in placebo-controlled RCTs. Hence, it is

important to avoid trial design aspects identified as potential predictors for a large placebo response (box 1). For instance, the number of collaborating study sites should be kept to the minimum required, and mainly academic/university sites should enrol the participants in multicentre trials. Moreover, a high probability for participants of receiving placebo can counteract a high magnitude of placebo response.

The problem of increasing placebo response in meta-analyses

Besides the RCTs, the continuously rising placebo response should be also considered in the interpretation of meta-analytic findings. In meta-analyses, data from individual trials carried out in different periods of time are often grouped together and the meta-analytic statistics do not consider the large increase of placebo improvement over time which needs to be valued according to predefined standards.[17] Therefore, it appears meaningful to examine the impact of publication years on effect sizes by elaborating meta-regressions or, particularly in the context of multiple-treatments meta-analyses, by removing placebo-controlled studies in sensitivity analyses. For example, this was carried out in the famous multiple-treatments meta-analysis investigating the efficacy and tolerability of 15 antipsychotic compounds in schizophrenia by Leucht *et al*[18] where no meaningful influence of publication years on the hierarchy of drugs could be observed.

CONCLUSIONS

In summary, the reasons contributing to the rising placebo improvement over time and the subsequently decreasing drug-placebo separation should be considered in the interpretation of psychopharmacological clinical trial results. Even though the impression arises that newer drugs are less efficacious compared to older agents, owing to the mitigation of effect sizes, it appears crucial to recognise the trial methodological reasons contributing to this trend. At present, it is much more difficult for a psychopharmacological agent to demonstrate superiority over placebo in RCTs compared to the past. This should be taken into account when judging the clinical benefit of new drugs.

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