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Review

Is the ongoing use of placebo in relapse-prevention clinical trials in schizophrenia justified?

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ABSTRACT

Background: Placebo-controlled randomised controlled trials (RCTs) continue to be required or recommended by regulatory authorities for the licensing of new drugs for schizophrenia, despite ongoing concerns regarding the risks to trial participants.
Methods: In this article we consider the scientific and ethical pros and cons associated with use of placebo in RCTs in schizophrenia, systematically review the published relapse-prevention placebo-controlled RCTs with second generation antipsychotics (SGAs) in schizophrenia, and examine the risks associated with these trials.
Results: We identified 12 studies involving 2842 participants of which 968 received placebo. Relapse rates were 56% for placebo and 17.4% for active treatment groups. There is a lack of well-designed longitudinal studies investigating the psychosocial and biological consequences of exposure to placebo, to treatment discontinuation and to relapse in schizophrenia.
Conclusion: In the absence of such studies it is risky to assume that patients are not at risk of significant distress and long-term harm, and therefore it is difficult to justify the ongoing use of placebo in relapse-prevention RCTs in schizophrenia.

1. Introduction

Antipsychotics are the mainstay of treatment for schizophrenia. Their efficacy and safety for acute and maintenance treatment have been established on the basis of extensive clinical development programs, of which an integral component is the placebo-controlled, randomised, controlled trial (RCT). In maintenance treatment RCTs, the superiority of antipsychotic medications compared to placebo has been clearly demonstrated (Leucht et al., 2012) and relapse-prevention by means of continuous treatment is considered a major treatment goal (Kane, 2007). Despite this, in real-world clinical settings discontinuation of antipsychotic treatment is common, with most patients typically experiencing multiple relapses during the course of their illness (Robinson et al., 1999). In clinical settings the decision to discontinue treatment is largely patient driven, and usually against medical advice (Perkins et al., 2008). Another setting where active treatment is discontinued or withheld is the placebo-controlled RCT. The difference in this case is that discontinuation or withholding of active treatment is pre-planned, with the full participation of clinicians. Given the high risk of relapse associated with antipsychotic treatment discontinuation (Gilbert et al., 1995), it is not surprising that concerns have long been voiced regarding the risks to participants in placebo-controlled RCTs in schizophrenia (Weijer, 1999) and the debate over their continued use when proven treatments exist continues to be lively (Kim, 2003). There is a tension between the need for scientifically valid trials of new psychotropic drugs and concern about the risks associated with conducting placebo-controlled RCTs, when this requires that some patients be denied effective therapy (Laughren, 2001). Consequently, many experienced schizophrenia researchers are unwilling to take part in placebo-controlled RCTs, with many citing the attitude of local ethics committees as the reason for their reluctance (Fleischhacker and Burns, 2002). Risk to trial participants is likely to be greatest in maintenance treatment, or relapse-prevention RCTs where patients, once stabilised, are switched to placebo sometimes for considerable periods, and substantial numbers need to experience a relapse event before a treatment effect can be statistically demonstrated. Despite these concerns, current practice permits the use of placebos in such settings, as long as the benefits are considered to outweigh the risks and burdens. In this critical review we 1) briefly summarise the ethical and scientific pros and cons of placebo in relapse-prevention RCTs in schizophrenia, 2) systematically review the published relapse-prevention RCTs with second-generation antipsychotics (SGAs) in schizophrenia and 3) examine the risks of harm associated with such trials.

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2. The pros and cons of use of placebo in RCTs

According to the World Medical Association's Declaration of Helsinki, the use of placebo is acceptable in studies where there is no proven intervention, or where compelling and scientifically sound methodological reasons exist for the use of placebo to determine efficacy or safety of an intervention, and where patients who receive placebo will not be exposed to any risk of serious or irreversible harm. The Declaration emphasises the need for extreme care to be taken to avoid abuse of this option, and that the interest of science and society should never take precedence over considerations related to the well-being of the individual patient (World Medical Association, WMA, 2008). Specific criteria are proposed for judging the ethical acceptability of including placebo controls in a RCT, including the likelihood that the experimental intervention will have clinically significant advantages over existing treatments, the existence of compelling reasons for placebo use, a subject selection procedure that minimizes the risk of serious adverse consequences, and a risk-versus-benefit analysis that favours the advantages from placebo use over the risks to subjects (Carpenter et al., 2003).

2.1. The case for placebo

A comparison between the test drug and placebo provides the most powerful method of establishing efficacy. It is impossible to determine in an active control group with non-inferiority design whether both treatments were effective or ineffective. Some regard the use of placebos in RCTs in schizophrenia as an essential component of a comprehensive drug evaluation for new antipsychotic medications, and to be both ethically and scientifically justified (Addington, 1995). Indeed, placebo-controlled relapse prevention studies continue to be required by regulatory authorities in the United States and Canada, and strongly recommended in the European Union, for the licensing of new drugs (Addington, 1995; Fleischhacker et al., 2003; European Medicines Agency Committee for Medicinal Products for Human Use, 2012; U.S. Food and Drug Administration Center for Drug Evaluation and Research, 2012). These agencies consider that it is not possible to conduct a valid evaluation of a treatment for schizophrenia without placebo-controlled studies (Correll et al., 2011). The ongoing use of placebo has been justified on the basis of there being no clear evidence of increased risk of persistent morbidity or mortality, and because alternative study designs may not be as good at demonstrating efficacy and tolerability (Beasley et al., 2003). It has been argued that the fundamental reason to favour a test to demonstrate superiority of an active intervention over placebo rather than active control is that the response of a specific population to placebo or the active intervention can be highly variable across studies. Therefore, a non-inferiority design cannot be reliably interpreted (Beasley et al., 2003). A trend towards increasing placebo effects and a decrease in the drug effect size has been reported in RCTs comparing both investigational and approved antipsychotics with placebo in RCTs submitted for new drug applications (Kemp et al., 2010). The argument for continued use of placebo in RCTs is therefore that there is a need to establish assay sensitivity, and there is a moral imperative to guard against ineffectual treatments being approved for use in clinical practice. In one study, the choice of placebo as comparator was considered to be safe and ethical based on three premises: 1) Available empirical evidence at that time suggested no increased risk of severe suffering or long-term morbidity following exposure to placebo; 2) the belief that clinical measures put in place (frequent and careful monitoring for early indicators of worsening and the use of sensitive relapse criteria) would effectively detect early symptoms and prevent serious relapse, and 3) the likelihood that fewer relapses would be necessary to detect a positive outcome with placebo rather than with an active comparator (Beasley et al., 2003).

The European Medicines Agency recently introduced a Guideline on Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia. The document recognises the need for placebo to ensure assay sensitivity, even in well designed and conducted RCTs, but emphasises that these studies need to be conducted in highly controlled settings, with appropriate safeguards. In this context it is considered that the benefits of a placebo arm will generally override ethical reservations in short-term trials. However, long term exposure to placebo is not only ethically problematic but also scientifically unsound due to high rates of withdrawals which make interpretation of the data difficult. Yet, it is stated that, for demonstrating maintenance of effectiveness of treatment over time the inclusion of a placebo arm is possible and appropriate in a randomised withdrawal study as long as it is appropriately designed and conducted. Patients who relapse should receive immediate active treatment, and there should therefore not be ethical problems (European Medicines Agency Committee for Medicinal Products for Human Use, 2012).

A draft guidance addressing enrichment strategies for clinical trials of the United States Food and Drug Administration describes the randomised withdrawal design as a way to establish long-term effectiveness of drugs when protracted use of a placebo would not be acceptable. In this design the study population is on active treatment for an extended period and those who respond enter a blinded, randomised treatment withdrawal phase for a short duration. Patients are withdrawn from the study in the case of symptom recurrence, thereby minimising exposure to placebo treatment (U.S. Food and Drug Administration Center for Drug Evaluation and Research, 2012).

2.2. The case against placebo

On the other hand, there is a concern that, particularly in relapse-prevention RCTs, exposure to placebo is associated with a risk of undue suffering or harm. Inclusion of a placebo-arm appears to be in conflict with clinical equipoise, considered to be the moral foundation of the RCT, which requires the use of best available treatment as the control in RCT. This is consistent with the principle of beneficence which requires that a physician should act in the best interest of each patient. Furthermore, scientific criticisms of the use of an active control with a non-inferiority study design may not present an insurmountable barrier to their use as an alternative to placebo-controlled RCTs (Weijer, 1999; Fleischhacker et al., 2003). Meta-analyses indicate that a therapeutic dose of SGA is very likely to be statistically superior to placebo in an adequate trial, and that despite an increasing effect, the average improvement of schizophrenia symptoms in a placebo arm will be small. There are few efficacy differences between SGAs, and expected differences are in their safety profile or their influence on quality of life. Therefore, hypothesis testing is often limited to the problem of confirming that the new drug is not inferior to a comparator antipsychotic with respect to its efficacy (Fleischhacker et al., 2003). An additional point is that high dropout rates have been reported in clinical trials utilizing placebo controls (Kemmler et al., 2005), thereby reducing the statistical power of these studies.

A final point to consider concerns our ability to recognise early signs of recurrence, and the effectiveness of rescue interventions in preventing serious relapse. Such a strategy would comprise frequent monitoring and careful assessment of patients for early warning signs of relapse. While success has been reported in identifying early signs of relapse by means of an instrument specifically designed to detect early warning signs a specifically designed scale (Birchwood et al., 1989), this may not always be the case. Other studies suggest that early warning signs are relatively unreliable predictors of relapse (Gaebel et al., 1993; Norman and Malla, 1995; Gaebel and Riesbeck, 2007) and it has been reported that in many cases recurrence symptoms do not return gradually, but rather abruptly, with rapid return to levels of previous psychotic episodes (Emsley et al., 2012a, 2013). These findings are consistent with those of a previous study in which it was found that