VIEWPOINT

Are Placebo-Controlled, Relapse Prevention Trials in Schizophrenia Research Still Necessary or Ethical?

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Randomized, placebo-controlled trials have been the gold standard for evaluating the safety and efficacy of new psychotropic drugs for more than half a century. Although the US Food and Drug Administration (FDA) does not require placebo-controlled trial data to approve new drugs or marketing indications, they have become the industry standard for psychotropic drug development.

Placebos are controversial. The FDA guidelines state "when a new treatment is tested for a condition for which no effective treatment is known, there is usually no ethical problem with a study comparing the new treatment to placebo."[1] However, "in cases where an available treatment is known to prevent serious harm, such as death or irreversible morbidity, it is generally inappropriate to use a placebo control."[1(p15)] When new antipsychotics are developed for schizophrenia, it can be debated which guideline applies.

In schizophrenia research, 1 study design, the placebo-controlled, relapse prevention trial, is especially problematic. These studies, designed to demonstrate prophylactic or maintenance treatment efficacy, enroll stable patients receiving antipsychotic medication and randomize them to placebo or active drug. Participants are followed up for 6 months to 2 years, with return of psychotic symptoms being the primary end point.

While the ethics of placebo-controlled trials have been discussed extensively, relapse prevention trials have received less attention and, despite expressed concerns, continue to be routinely conducted.[2,3] We suggest that researchers, pharmaceutical companies, and the FDA reconsider the scientific, practical, and ethical justification of placebo-controlled, relapse prevention studies in schizophrenia for the following reasons.

Scientific Considerations

Past studies of schizophrenia addressed questions including how to measure symptom improvement and treatment outcomes, how to dose antipsychotic drugs, how to measure their adverse effect liabilities, and how long antipsychotics should be continued. Studies published in the past decade have examined the effects of various drugs and formulations within specific populations, attempting to parse which effects are specific to a drug and which are a general class effect shared by all drugs with similar mechanisms (comparative effectiveness studies). While the latter continue to be of value (although infrequently conducted), the former mainly produce redundant data whose primary purpose is to obtain labeling language for relapse prevention.

Since the 1950s, a huge body of data has been generated showing that drugs acting through D2 antagonism improve psychotic symptoms, which would seem to obviate the need for more studies of drugs that act through the same mechanism. None of the 60 D2 antagonists that have been developed and have shown short-term treatment efficacy has ever been ineffective for relapse prevention.[4]

Additionally, longitudinal studies suggest that longer duration of untreated psychosis and having more psychotic episodes are associated with disease progression and increased morbidity.[5,6] Thus, removing prophylactic treatment in patients and permitting psychosis to recur could facilitate illness progression, diminish treatment response, and increase risk for complications such as suicide, substance abuse, or violence.

Much remains to be discovered about schizophrenia, including questions about pathophysiology, how treatments affect functional outcomes, and the long-term effects antipsychotics have on the brain.[6] Nevertheless, a compelling body of evidence supports the favorable benefit to risk ratio of antipsychotic drug treatment in terms of prophylactic and long-term effects.[5] Consequently, we believe placebo-controlled, relapse prevention trials are no longer ethically justified for answering these questions.

Practical Considerations

A major advantage of placebo-controlled studies is that they require smaller sample sizes to demonstrate superiority of the experimental drug, whereas active-control studies require larger samples to show noninferiority or superiority vs the active comparator. Thus, placebo-controlled studies contain cost, reduce study duration, and minimize the number of participants potentially exposed to ineffective treatment. Additionally, placebo controls contribute to the "assay sensitivity" of the study by demonstrating the consequences of forgoing effective pharmacologic treatment.

At the same time, placebo-controlled, relapse prevention trials face special challenges inasmuch as different trials have reported markedly different relapse rates. This raises questions of whether studies have problems with internal and external validity, or applicability.

In addition, placebo conditions can potentially compromise the study blind if 1 arm has adverse effects, worsening symptoms, or treatment response. Methods to protect the blind, such as assigning distinct roles to study personnel as independent raters or using centralized raters, may protect the blind but also increase complexity and costs.

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Ethical Considerations

Utilitarian arguments underlie all placebo-controlled trials, with advocates acknowledging that trial participation does place some number of participants at risk for receiving suboptimal treatment but distributing an inadequately tested drug or delaying the use of an effective drug could place many more people at risk. This reasoning is most compelling when a state of equipoise exists (genuine uncertainty about whether a treatment is superior to placebo), but equipoise is hard to claim when the new drug is a D2 antagonist.[7] While it might be true that a new antipsychotic has never been tested against placebo in a relapse prevention trial, 40 years of data have consistently shown that D2 antagonists are superior to placebo for relapse prevention in maintenance treatment.

Beneficence arguments support schizophrenia research in general because there is an urgent need for improved treatments. However, research can take many forms, and placebo-controlled, relapse prevention trials are not the only way to advance knowledge. Active comparison trials and observational data from large cohorts can also provide data about efficacy, safety, and adverse effects. If disallowing placebo-controlled, relapse prevention trials would truly impede progress in schizophrenia research, then beneficence arguments might prevail. But if trials only provide redundant knowledge used to obtain labeling language, then beneficence arguments are weakened.

On an individual level, optimizing patient care and reducing risks are perennial clinical goals that are in tension with placebo-controlled, relapse prevention trials. Patients who participate in placebo-controlled, relapse prevention trials are rolling the dice on the possibility of their illness worsening or incurring other complications to their lives. Ethical concerns are mitigated when participants provide informed consent (based on full and accurate understanding about the long-term risks and benefits of studies) and act with autonomy. This is a high bar because there are special challenges in seeking informed consent from persons with schizophrenia. They are a vulnerable population and might have impaired insight about their chances of relapsing or may not fully understand the potential consequences of a relapse. Additionally, when study recruitment takes place in locations that have limited mental health resources, concern for exploitation grows.

Conclusions

More than 60 D2 antagonists have been developed and tested, and 20 are currently FDA approved and marketed for treatment of schizophrenia. In the course of testing these drugs to determine their efficacy for relapse prevention, a large and consistent body of evidence has accumulated, showing D2 antagonists are effective at preventing relapse in schizophrenia. At the same time, compelling evidence that longer or more numerous psychotic episodes can worsen patients' prognoses and outcomes has emerged. Given the extent and consistency of these data, and a growing awareness of the potential harms, the scientific value of placebo controls in relapse prevention trials of new antipsychotics with D2 targeted mechanisms of action has decreased, and the risks to patients have increased. Consequently, we believe the time has come to cease the use of placebo in relapse prevention studies and encourage the use of active comparators that would protect patients from relapse and provide information on the comparative effectiveness of the drugs studied. We recommend that pharmaceutical companies not seek maintenance labeling if it would require placebo-controlled, relapse prevention trials. However, for putative antipsychotics with a novel mechanism of action, placebo-controlled, relapse prevention trials may still be justifiable.

ARTICLE INFORMATION

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