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POSITION PAPER

Use of Placebo in Clinical Trials of Psychotropic Medication

Mehrul Hasnain, MBBS, DABPN[1]; Abraham Rudnick, MD, PhD, FRCPC[2]; Weldon S. Bonnell, MD, MSc, FRCPC[3]; Gary Remington, MD, PhD, FRCPC[4]; Raymond W. Lam, MD, FRCPC[5]

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Introduction

New medications are needed for people with mental disorders, and placebo-controlled randomized controlled trials (RCTs) are still the most common method to evaluate new medications. However, the use of a placebo in medicine, particularly in mental health disorders, remains a controversial topic. A 1997 position paper from the Canadian Psychiatric Association (CPA) summarized the arguments for and against the use of placebos, and concluded that placebo use was ethically and scientifically justified under certain conditions.[1] With the ongoing debate[2,3] regarding the ethical, scientific, and clinical dilemmas associated with placebo use in clinical trials, and the recent revision of the Declaration of Helsinki code of ethics,[4] we now provide an update to the 1997 CPA position paper. We first briefly summarize the ethical aspects of placebo use, the positions of major funding and regulatory agencies, and the scientific and clinical issues in establishing efficacy and safety of new treatments. Then, we provide guidance and give clinical examples of ethical and scientific placebo use.

Ethical Aspects

Bioethical principles dictate that people should not be denied effective health care solely for research. Hence, the use of a placebo in clinical research rests on the notion

[1] Associate Professor, Discipline of Psychiatry, Memorial University of Newfoundland, St. John's, Newfoundland
[2] Professor, Section of Psychiatry, Northern Ontario School of Medicine, Lakehead and Laurentian Universities, Thunder Bay and Sudbury, Ontario; Vice-President and Chief of Psychiatry, Thunder Bay Regional Health Sciences Centre, Thunder Bay, Ontario; Chief Scientist, Thunder Bay Regional Health Research Institute, Thunder Bay, Ontario
[3] Associate Professor, Discipline of Psychiatry, Memorial University of Newfoundland, St. John's, Newfoundland
[4] Professor, Departments of Psychiatry and Psychological Clinical Science, Faculty of Medicine, University of Toronto; Chief, Schizophrenia Division, Centre for Addiction and Mental Health (CAMH), Toronto, Ontario
[5] Professor and BC Leadership Chair in Depression Research, Department of Psychiatry, University of British Columbia; Director, Mood Disorders Centre, Djavad Mowafaghian Centre for Brain Health, Vancouver, British Columbia

of clinical equipoise.[5] Clinical equipoise refers to a "genuine uncertainty on the part of the expert medical community about the comparative therapeutic merits of each arm of a clinical trial."[6] A placebo is therefore acceptable only when there is no established, evidence-based treatment for a condition, according to the relevant professional community. However, when an established treatment exists, an experimental treatment should be compared to the established treatment to minimize harm to research participants.

The Declaration of Helsinki, the code of ethics developed by the World Medical Association, was recently revised from its last clarification in 2002. The 2013 revision recommends that "the benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s)."[4] The use of a less effective intervention is allowed in exceptional situations "where no proven intervention exists" or "where for compelling and scientifically sound methodological reasons, the use of any intervention less effective than the best proven one, the use of placebo, or no intervention, is necessary to determine the efficacy or safety of an intervention."[4] A precondition for both scenarios is that the patient will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best-proven intervention.

Stance of Funding and Regulatory Agencies

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) brings together regulatory authorities and pharmaceutical industry to determine the scientific and technical aspects of drug registration. ICH guidance emphasizes the importance of sound research methods, including randomization, blinding, and various control conditions (including placebo controls), to establish the efficacy and safety of new medications before they are approved for marketing.[7]

In Canada, Health Canada regulates new drugs and is committed to the adoption and implementation of ICH guidance.[8] In contrast, the Canadian Institutes of Health Research (CIHR) established an independent policy, the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans (TCP1).[6] Although the National Placebo Initiative (NPI) attempted to consolidate the guidelines of these 2 agencies,[9,10] Health Canada and CIHR diverged in acceptance of the final report:[11] Health Canada was concerned that implementation of the NPI policy would further restrict the use of placebo, thus opening the door to more large-scale adverse events with new drugs, whereas CIHR endorsed the main NPI recommendations in 2004. The CIHR placebo policy was also recently revised in 2014[12] (Table 1).

Table 1. Tri-Council Policy Statement (TCP2)[12] on Use of Placebo in Clinical Trials (Excerpt).

a) A new therapy or intervention should generally be tested against an established effective therapy.
b) As with all alternative choices of a control, a placebo control is ethically acceptable in a randomized controlled clinical trial only if:
   - its use is scientifically and methodologically sound in establishing the efficacy or safety of the test therapy or intervention; and
   - it does not compromise the safety or health of participants; and
   - the researcher articulates to the Research Ethics Board (REB) a compelling scientific justification for the use of the placebo control.
c) For clinical trials involving a placebo control, the researcher and the REB shall ensure the general principles of consent are respected and that participants or their authorized third parties are specifically informed:
   - about any therapy that will be withdrawn or withheld for purposes of the research; and of the anticipated consequences of withdrawing or withholding the therapy.

Scientific and Clinical Issues

Any new treatment must demonstrate efficacy (i.e., how a treatment performs under controlled conditions) and safety before it is approved for clinical use. Currently, comparing a new medication (or other type of treatment) to placebo (or sham treatment) using an RCT design is the most common and rigorous method for establishing efficacy and safety. Studies with noninferiority designs,[13] in which a new medication is compared only to an active, established treatment, generally require much larger sample sizes and are not as definitive for safety and tolerability as similar placebo-controlled studies.[14,15]

However, a placebo is not simply an inert substance. The patient assigned to placebo also benefits from nonspecific therapeutic effects of a clinical trial, including education, regular visits, psychosocial interactions with study staff, among other benefits. Thus, it is not surprising that placebo response is high in psychiatric and other chronic conditions where symptoms may fluctuate, and outcomes are based on patient interview or self-report.

High rates of placebo response are commonly found among patients with mental disorders. For example, antidepressant and antipsychotic trials in major depressive disorder (MDD) and schizophrenia have shown mean placebo response rates (ranges) of 31% (13%

to 52%) and 25% (0% to 41%), respectively.[16-18] Hence, placebo response varies widely among studies. In addition, over the past 3 decades, antidepressant-placebo differences have declined markedly,[19] with similar findings reported from trials of antipsychotics for patients with schizophrenia.[20,21]

Because of the high placebo response, even "established" treatments may not demonstrate efficacy against a placebo. In a review of data from 45 studies submitted to the European regulatory authorities, 38% of antidepressant trials and 16% of antipsychotic trials were recorded as failed; i.e., when both the investigational and "established" reference medication did not separate from placebo.[22] Similarly, in an analysis of clinical trials of approved antidepressants submitted to the US Food and Drug Administration, only 53% of 81 trials found the active drug superior to the placebo.[23] Placebo response was even higher than "treatment as usual" conditions in MDD.[16]

The presence or absence of a placebo in clinical trials may also influence both the response and dropout rates of active medications. For example, the degree of improvement with antipsychotics in active-controlled schizophrenia trials was nearly double that seen with the same drugs and dosages in placebo-controlled studies.[24] In studies of MDD, the response to an active antidepressant increases when there is less expectation to receive a placebo: response rates for active antidepressants are significantly higher in studies comparing 2 or more active medications without a placebo arm (65.4%) than in similar studies with a placebo (57.7%), and are lowest in studies comparing only one active medication with a placebo (51.7%).[25] Similarly, the dropout rates for active medications are higher in placebo-controlled antipsychotic trials than in trials with only active medication comparisons.[26] Because of these findings, noninferiority, active-control study designs may sometimes not be as valid as placebo-controlled designs in examining efficacy and safety.

The placebo-informed efficacy evidence also may not generalize to subgroups of patients with a particular diagnosis. Placebo-controlled trials of psychotropics are typically conducted in a narrow patient population with many exclusion criteria; but the findings are often generalized to other populations in "real life" clinical practice, such as different age groups or patients with comorbidities. Subsequent studies in patient subgroups may not support efficacy or may raise concerns about safety. For example, placebo-controlled studies of antidepressants for MDD in children and adolescents have smaller effect sizes and increased risk of suicidality when compared with similar studies in adults.[27] Hence, it may be scientifically and clinically important to establish efficacy using a placebo in subgroups of patients based on age, comorbidity, ethnicity, previous treatment nonresponse, and other characteristics.

Discussion

The ethical dilemma we face is that enrolment of patients in a clinical trial may hinder our fiduciary responsibility by potentially exposing them to ineffective treatments, both the experimental drug and placebo, thus delaying their active treatment. On the other hand, without properly controlled clinical trials, we risk introducing ineffective and perhaps unnecessarily harmful treatments into the market, thus sabotaging our fiduciary responsibility on a larger scale. A noninferiority study design comparing an experimental drug to an "established" medication would potentially expose many more participants to ineffective or unsafe treatments than a placebo-controlled study. This dilemma seems to be at the core of the disagreement between regulatory and research funding/ethics agencies.

These opposing views deter us from making a clear statement about the use of a placebo that applies to all situations. Instead, each proposed clinical trial and population must be evaluated individually by research ethics committees to minimize risk to participants, irrespective of whether a placebo is used. For example, including the use of a placebo is not acceptable when there is grave risk of clinical deterioration in severely affected individuals. Some clinical examples include acute suicidality, severe acute psychosis, anorexia nervosa with physical deterioration, and severe psychotic mania.

For conditions or patient subgroups where there is no established or approved psychotropic treatment, the use of a placebo is ethically and scientifically justified and permitted. Some examples include major depressive episodes with mixed features, persistent depressive disorder, treatment-resistant psychosis, paraphilic disorders, and bulimia nervosa.

For conditions where there is an established treatment, trial designs without a placebo, such as active control, treatment as usual, or noninferiority designs, must be considered. A placebo condition can only be considered when there is compelling scientific justification. In some cases, the use of a placebo may be scientifically justified, even when clinical equipoise is not present, by the high placebo response and narrow drug-placebo differences in a particular population (e.g., moderately severe MDD and anxiety disorders) and by the low risk of clinical deterioration.

Whenever a placebo is used in a clinical trial, there must be adequate measures to ensure informed consent, including disclosure of established or available treatments (including nonpharmacological treatments, if applicable), and the potential risks and benefits of experimental and placebo conditions. Additionally, there must not be a risk of serious or irreversible harm from delaying treatment. There should also be clear protocols for dealing with worsening symptoms and severe adverse events.

Conclusions

Ethically, we have fiduciary responsibility to ensure that our patients are treated with effective and safe medications and are not exposed to unnecessary risks when participating in research studies. High rates of placebo response, the diminishing response of active medications compared with placebo, and the limitations in generalising the efficacy results to "real-world" clinical practice make the evaluation of psychotropic medications particularly challenging. In this context, placebo controls are ethically justified when there is no established treatment, or when there is a compelling scientific justification for a placebo and its use will not expose research participants to excessive risks of harm. Each clinical trial must, therefore, be evaluated individually for ethical and scientific approval for placebo use.

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