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Practical Clinical Trials in Psychopharmacology: a Systematic Review

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Abstract

Practical clinical trials (PCT) are randomized experiments under typical practice conditions with the aim of testing the “real life” benefits and risks of therapeutic interventions. Influential PCTs have been conducted in cardiology, oncology, and internal medicine. Psychotropic medications are widely and increasingly used in medical practice. This review examines recent progress in conducting PCTs in psychopharmacology. The January 2000 – October 2014 MEDLINE, Scopus, and ClinicalTrials.gov databases were searched for peer-reviewed publications of PCTs with at least 100 subjects per treatment arm. Most PCTs in psychiatry evaluated mental health services or psychosocial interventions rather than specific pharmacotherapies. Of 157 PCTs in psychiatry, 30 (19%) were in psychopharmacology, with a median of 2 publications per year and no increase over the period of observation. Sample size ranged from 200 to 18,154; only 11 studies randomized 500 patients or more. Psychopharmacology PCTs were equally likely to be funded by industry as by public agencies. There were 10 PCTs of antidepressants, for a total of 4,206 patients (in comparison with at least 46 PCT of antihypertensive medications, for a total of 208,014 patients). Some psychopharmacology PCTs used suicidal behavior, treatment discontinuation, or mortality as primary outcome, and produced effectiveness and safety data that have influenced both practice guidelines and regulatory decisions. PCTs can constitute an important source of information for clinicians, patients, regulators, and policy makers, but have been relatively underutilized in psychopharmacology. Electronic medical records and integrated practice research networks offer promising platforms for a more efficient conduct of PCTs.

Keywords
Practical trials; large simple trials; psychopharmacology

Introduction

Practical (or pragmatic) clinical trials (PCTs) are randomized studies conducted in practice settings to evaluate the effects of interventions delivered under typical community conditions rather than in tightly controlled research settings.1 PCTs complement and extend
the information provided by efficacy clinical trials, which test interventions under ideal experimental conditions by carefully selecting suitable patients, adopting a placebo control, and using intensive assessment batteries to detect statistically meaningful differences.

“Phase III” efficacy trials have a major role in demonstrating the intrinsic pharmacological effects of medications, thus providing the data necessary for their registration and marketing approval. However, the same stringently controlled experimental conditions that maximize assay sensitivity limit the generalizability of the results to the patient population likely to receive the intervention in the community. In fact, only a fraction of patients typically referred for treatment are eligible for participating in efficacy trials, the majority being excluded for a variety of reasons, such as comorbid conditions, duration of illness, or symptom severity. In the case of antidepressants, for example, there are indications that placebo-controlled clinical trials, which are conducted on highly selected samples, tend to overestimate the effectiveness of these medications in clinical practice.²,³

Most clinical practice guidelines are still based on weak levels of evidence, and there is a recognized need to strengthen the evidence for clinical decisions.⁴ PCTs are meant to inform decision-making in clinical care by addressing the uncertainty that clinicians face at critically important decision points.¹ Thus, the key features of a PCT include: a clinical dilemma for which there is genuine uncertainty on the best course of action (equipoise); a precisely formulated research hypothesis that directly addresses a practical medical decision; an easily measurable outcome of clinical significance (e.g., functional recovery, hospitalization, death, suicide attempt); randomized design; broad entry criteria to capture the typical clinical population likely to receive the intervention in usual care; practice setting; minimal clinician and patient research burden; and a sample size large enough to account for the heterogeneity of the participants.⁵ A PCT is designed to answer a single, clearly formulated research question by focusing on a major outcome of direct clinical relevance. While many patients are enrolled to ensure representativeness and statistical power, only few assessments are collected on each patient. Thus, successful PCTs tend to be “large simple trials”, a concept that applies to studies with many hundreds, if not thousands, of patients.

First advocated about 30 years ago, the PCT methodology has been widely applied to several areas of medicine.⁶ Highly influential PCTs have been conducted in cardiology, oncology, and internal medicine, addressing the management of myocardial infarct, stroke, hypertension, and breast cancer.⁷–¹² The impetus to conducting PCTs in medicine continues, as the public health relevance of this type of research is being increasingly recognized.⁴,¹³

The application of the PCT methodology to psychiatry has been slow and more limited. A noteworthy example of PCT in psychopharmacology was reported in 1996,¹⁴ but it was not until the late 1990s that the need for PCTs in psychiatry began to be recognized.⁵,¹⁵–¹⁶ PCTs are especially relevant to psychiatry because of common conditions, such as depression or anxiety, affecting millions of people, availability of a variety of treatments, both pharmacological and psychosocial, all with relatively small effect sizes, and uncertainty of treatment choice.
In particular, pharmacotherapy has been an increasingly common treatment modality in mental health care. As clinicians have a number of treatment options, decision making should rely on empirical evidence. The difference between two active treatments is usually small, but even a modest difference can be clinically important for major outcomes such as suicide, occupational dysfunction, or hospitalization. As pointed out by Peto and colleagues, the “medical importance of treatment effects that are only moderate in size implies the need for large-scale randomized evidence”.

This systematic review was conducted to examine the extent to which the PCT methodology has been applied to psychopharmacology. The aims were to identify PCTs with acceptable statistical power to detect treatment effects of psychiatric medications, and describe the PCT characteristics with respect to medications studied, sample size, outcome measures, and funding sources.

**Methods**

The Medline and Scopus databases were systematically searched for English language publications in the period January 2000 – October 2014, using the following key words: *practical or pragmatic or large simple trials and psychiatry or mental health; effectiveness and randomized and psychiatry or mental health; primary care and mental health and treatment and randomized; practice setting and psychiatry and treatment and randomized.* The search used *clinical trial* as a filter. In addition, the ClinicalTrial.gov database was searched using the key words *psychiatric interventional randomized*, and the bibliographic references of relevant publications were manually examined.

After removal of duplicates, the publication titles and abstracts were visually inspected, and articles were selected for further review. Reports were selected based on the following criteria: a) addressing a treatment of a mental health disorder or condition; b) assessing the treatment effect of a psychiatric medication or specified pharmacotherapy strategy; c) using a randomized design; d) including at least 100 randomized patients in each treatment arm; and e) meeting the key elements for a PCT design.

There is a continuum between purely efficacy and fully pragmatic clinical trials, with some studies having elements of both. For this review, the key PCT elements required for inclusion: 1) addressing a clinical issue of direct and practical importance for decision making in usual patient care; 2) using broadly inclusive entry criteria to ensure generalizability to the targeted clinical population; 3) following a simple protocol with minimal research burden for patients and clinicians; 4) testing interventions easily implementable in usual care; 5) using an easily measurable outcome of direct relevance to clinicians and patients; and 6) maintaining conditions of usual patient care. To be included, trials also had to have a sample size of at least 100 patients randomized to each study treatment arm, as smaller studies would not have sufficient statistical power to detect even a medium treatment effect size.

Excluded were: a) clinical trials of treatments of alcohol and substance abuse (including nicotine use), pain management, dementia, Parkinson, or other neurological disorders (but...
studies testing treatment of psychiatric disorders, such as depression or psychosis, in the context of these conditions were included; b) clinical trials in which the specific effects of a pharmacotherapy could not be assessed because medications were part of a treatment “package”, together with other non-pharmacological interventions, and compared to usual care, so that the treatment effects of medication could not the disentangled from the overall effect of the “package”; and c) primary prevention clinical trials (studies of interventions to prevent relapse or recurrence were included).

Ten percent of the publications identified through the electronic search were independently inspected by another expert in clinical trials in order to assess inter-rater reliability. There was full agreement in 97% of the cases. Throughout the review process, in case of uncertainty in classifying a study as PCT, the publication was reviewed independently by the two experts (BV and JS) and, if needed, further discussed in order to achieve resolution. Trials conducted at university clinics were included if they had the key features of a pragmatic trial, with participation of community care settings, such as the Clinical Antipsychotic Trials of Intervention Effectiveness, which was conducted at 45 sites including private practices, Veteran Administration centers, and university clinics.20

For the purpose of comparison, selected recent meta-analyses of antihypertensive medications and relevant bibliographical references were searched in order to identify PCTs of antihypertensive medications with at least 100 patients randomized to each treatment group and conducted during the period 2000–October 2014.

Standard descriptive statistical methods were applied to the data.

Results

The initial search yielded a total of 2984 publications; an additional 19 were identified through manual reference review or other sources. After exclusion of duplicates, 2585 publications were screened, and 1981 excluded as not meeting initial selection criteria (Supplemental Figure 1). Of the remaining studies, 230 were excluded for lacking key elements of a PCT and 217 for having a sample size per treatment group below 100. Of the remaining 157 PCTs, 72 (46%) tested services interventions (e.g., collaborative care models in primary care) rather than a specific treatment, 52 (33%) tested psychosocial interventions, and 3 (2%) tested other non-pharmacological interventions (i.e., physical exercise, massage therapy) (Supplemental Figure 2). The remaining 30 (19%) PCTs were in psychopharmacology (Table 1, Supplemental Table 1).20–49

The number of PCTs in psychopharmacology published ranged from 0 to 5 (median 2) per year, with no increase over the period of observation (Figure 1). Medications studied included antipsychotics (16 studies), antidepressants (10 studies), mood stabilizers (3 studies), and an antianxiety agent (1 study). Cumulatively, a total of 32,556 patients were randomized in the 30 PCTs. Study sample size ranged from 200 to 18,154, with a median of 387. Only 10 PCTs enrolled 500 or more patients. The time needed for trial completion ranged from 6 to 72 months, with a mean of 29.1 months and a median of 32 months (Table 1).

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Of the 30 PCTs, 16 tested antipsychotic medications, having a sample size between 215 and 18,154 (median 524, mean 3,214 ± SD 7,535), for a total of 27,315 randomized patients; 3 PCTs had a sample size above 1,000. Ten PCTs tested antidepressant medications, having a sample size between 208 and 727 (median 401, mean 420± SD 185), for a total of 4,206 randomized patients; none had a sample size above 1,000. As a comparison, primary reports of 46 PCTs of antihypertensive medications published in 2000–2014 were identified by searching recent meta-analyses. These 46 PCTs had a sample size between 250 and 33,357 (median 1,700, mean 4,728±SD 5,985), for total of 208,014 randomized patients; 33 (72%) had a sample size above 1,000.

A wide range of comparison groups were used in the 30 psychopharmacology PCTs, most commonly another medication, but also psychotherapy or combination of medication and psychotherapy trials. A few studies also included placebo to mask treatment assignment and ensure assay sensitivity of the trial. Most (N=20) PCTs were open-label, meaning that both clinicians and patients were aware of the treatment condition. A few studies used masked raters to assess outcome as a way of minimize ascertainment biases.

For 15 PCTs (50% of the cases), the primary outcome was the incidence or time to a specific event that was deemed to be clinically significant, including remission, treatment discontinuation, need for a treatment change, falling asleep, emergence of delirium, death, suicidality episode, or hospitalization. In the other cases, the primary outcome was symptomatic improvement measured with a disorder-specific clinical rating scale (e.g., Hamilton Depression Rating Scale), global improvement (e.g., using the Clinical Global Impression Scale), or change in quality of life (Table 1).

Of the 30 psychopharmacology PCTs, a statistically and clinically significant difference between treatments was reported in 16 studies, allowing a conclusion of superiority of one treatment over the other to be drawn. In the other 14 studies, no difference was detected, leading the authors to conclude that there was no advantage, or disadvantage, of one treatment over the other.

Most of the 30 PCTs were conducted in either the U.S.A. or the U.K. PCTs were equally likely to be funded by industry (12 studies) as by public agencies (11 studies) (Table 1).

Discussion

The concept of PCT was first introduced into psychiatry about 15 years ago as an important source of practical information to complement and expand the data from traditional efficacy trials. This systematic review identified 157 psychiatric PCTs, with a minimum sample size of 100 patients per treatment group, reported between January 2000 and October 2014. Of these, 30 (19%) were in psychopharmacology. Most PCTs in psychiatry tested the effectiveness of mental health services or psychosocial interventions, rather than specific pharmacological agents. This may not be surprising as a number of decision points in clinical practice relate to choice of services. No trend towards an increase in the number of psychopharmacology PCTs was detected. Thus, despite the widespread use of psychotropic medications, the application of the PCT methodology to addressing pharmacotherapy...
decision-making remains rather infrequent. Furthermore, of the identified 30 PCT, only one third had a total sample size of 500 or more, indicating that psychopharmacology has had very few “large simple trials”.

The underutilization of PCT in psychopharmacology is most evident in the case of antidepressants. Depressive disorders are the leading cause of burden of disease in middle- and high-income countries, followed by ischemic heart disease and cerebrovascular disease. Still, there were 20 PCTs of antidepressants for a cumulative number of less than 5,000 patients vis-à-vis at least 46 PCTs of antihypertensive medications for a cumulative number of more than 200,000 patients. More than two-thirds of the antihypertensive PCTs had a sample size greater than 1,000 as compared with none of the antidepressant PCTs.

On a more positive note, the review shows that psychopharmacology PCTs can be successfully conducted and provide important information. Some of the identified PCTs have addressed critical issues of psychiatric care, such as the choice of antipsychotic or antidepressant medication, prevention of suicide, or major safety concerns. The largest PCT enrolled more than 18,000 patients with schizophrenia, a sample size comparable to that of the PCTs conducted in cardiology and oncology. This study was requested by the Food and Drug Administration to inform on the safety of ziprasidone, and the finding that this medication did not increase mortality had important both clinical and regulatory implications. It is noteworthy that most pragmatic trials evaluated the effectiveness and safety of antipsychotic medications, which are typically used to treat most severe forms of mental illness.

It seems critical that future PCTs should include enough patients to ensure adequate statistical power to address the study hypothesis in a definitive way. Given that, by definition, PCTs have broadly inclusive entry criteria in order to represent the diversity of community patients, and that the difference between treatments is likely to be of a small effect size, large sample sizes are necessary. This is especially relevant to interpreting studies that do not show the superiority of one treatment over another. In fact, lack of a difference in a study designed as a superiority trial (i.e., an experiment attempting to reject a null hypothesis of no difference) does not demonstrate equivalence (i.e., it can only reject but not accept the null hypothesis). “Negative trials” (i.e., trials with no treatment difference) and “failed trials” (i.e., trials without assay sensitivity as indicated by lack of effect of the active comparator) are extremely common in psychopharmacology, accounting, for example, at least half of the antidepressant placebo-controlled trials. It is critical that PCTs avoid this unfortunate situation. A large sample size and, when appropriate, a non-superiority or equivalence design may be the best approach to protecting the interpretation of the results.

Looking to the future, a number of developments seem to favor the expansion of PCTs. Following dissatisfaction with traditional clinical trials, which are seen as lengthy, costly, and of uncertain ecological validity, there is increased interest in the PCT as an essential tool to advance evidence-based medicine, including psychiatric care. Attention has been brought to the need to decrease the administrative and regulatory complexities the slow the conduct of clinical trials. For example, the current bioethical framework for clinical
trials was set up to address traditional efficacy trials, which are conducted in research settings and evaluate novel treatments. For this type of studies, a rigorous separation between research and clinical care functions has been advocated under the tenet that research is essentially aimed at generating new generalizable knowledge and not at improving the condition of the individual research participants. But PCTs are conducted in practice settings and compare interventions of known efficacy that are delivered by clinicians, thus blurring the difference between research and clinical care. Thus, a different framework is needed to ensure appropriate protection of research participants in a context of a close interface, rather than separation, of clinical and research components.

From the funding perspective, the recently constituted Patient Oriented Outcome Research Institute (PCORI) in the U.S.A., has the mission of funding clinical research of direct relevance to patient care and will provide an important resource for conducting PCTs in medicine, including psychiatry. In particular, the development of PCORnet and psychiatric research networks, such as the Mental Health Research Network, provide infrastructure for large PCTs. Currently, the only psychiatric component of PCORnet is the Mood Patient Powered Research Network that is planning to launch PCTs in patients with major depressive and bipolar disorders. Electronic medical records are becoming more common and can facilitate the collection and transfer of clinical data thus making easier and less expensive to conduct PCTs.

More speculatively, a methodological challenge is how to enrich the traditional PCT design in order to make it more relevant to the age of personalized medicine while maintaining its key features (i.e., practice setting, broadly, representative sample, and low research burden on patients and clinicians). A limitation of current PCTs is that they inform at the group mean level. By estimating average treatment response rate, they provide generally useful parameters such as the number needed to treat. But they do not contribute to identifying a priori treatment responders or explaining why non-responders did not improve. In fact, PCTs are, by current definition, the very opposite of such “explanatory trials”, as they collect only the data necessary to answer the primary question of the study. Personalized medicine, on the other hand, aims at tailoring of treatment to the specific characteristics and needs of individual patients. To this end, the research approach of personalized medicine is to target the treatment to the precisely identified pathophysiological processes that underlie the clinical manifestations of the disease. Technological advances may bridge this gulf between PCTs and personalized medicine. Collection of genetic material can be easily accomplished in practice settings. Availability of electronic medical records linked to PCT participants can provide access to detailed information without requiring intensive data collection in the PCT. It may not be inconceivable to foresee “large complex trials” in a not too distant future.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.
Acknowledgments

The opinions and assertions contained in this report are the private views of the author and are not to be construed as official or as reflecting the views of the Department of Health and Human Services, the National Institutes of Health, or the National Institute of Mental Health.

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Figure 1.
Practical clinical trials in psychiatry 2000–2014 by publication year

Through October 2014; not included in this figure are 3 trials testing alternative interventions (2 physical exercise in 2012 and one massage therapy in 2007)
**Table 1**

Characteristics of Identified Psychopharmacology Practical Clinical Trials (PCTs)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total N of PCTs</td>
<td>30</td>
</tr>
<tr>
<td>Sample size (total N):</td>
<td></td>
</tr>
<tr>
<td>lowest-highest</td>
<td>200–18,154</td>
</tr>
<tr>
<td>median</td>
<td>387</td>
</tr>
<tr>
<td>Total sample size (N of PCT with)</td>
<td></td>
</tr>
<tr>
<td>N=200–499</td>
<td>19</td>
</tr>
<tr>
<td>N=500–1,000</td>
<td>8</td>
</tr>
<tr>
<td>N&gt;1000</td>
<td>3</td>
</tr>
<tr>
<td>Study design: N of PCTS</td>
<td></td>
</tr>
<tr>
<td>open-label</td>
<td>20</td>
</tr>
<tr>
<td>double-blind</td>
<td>9</td>
</tr>
<tr>
<td>single-blind</td>
<td>1</td>
</tr>
<tr>
<td>Primary outcome:</td>
<td></td>
</tr>
<tr>
<td>specific event(^a)</td>
<td>15</td>
</tr>
<tr>
<td>symptom improvement</td>
<td>7</td>
</tr>
<tr>
<td>global improvement</td>
<td>5</td>
</tr>
<tr>
<td>others(^b)</td>
<td>3</td>
</tr>
<tr>
<td>Duration of PCT (months)</td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
<td>29.1 ± 17.5</td>
</tr>
<tr>
<td>median</td>
<td>32</td>
</tr>
<tr>
<td>Geographical area</td>
<td></td>
</tr>
<tr>
<td>Americas</td>
<td>12</td>
</tr>
<tr>
<td>Europe</td>
<td>12</td>
</tr>
<tr>
<td>India</td>
<td>3</td>
</tr>
<tr>
<td>Intercontinental</td>
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</tr>
<tr>
<td>Medication studied (N of trials)</td>
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<tr>
<td>antipsychotic</td>
<td>16</td>
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<tr>
<td>antidepressant</td>
<td>10</td>
</tr>
<tr>
<td>mood stabilizer</td>
<td>3</td>
</tr>
<tr>
<td>other</td>
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</tr>
<tr>
<td>Reporting a statistically significant difference between treatments</td>
<td>Yes 16</td>
</tr>
<tr>
<td>No</td>
<td>14</td>
</tr>
<tr>
<td>Funding source (N of trials)</td>
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</tr>
<tr>
<td>Industry</td>
<td>12</td>
</tr>
<tr>
<td>Public</td>
<td>11</td>
</tr>
<tr>
<td>Private non-profit(^c)</td>
<td>5</td>
</tr>
<tr>
<td>Mixed</td>
<td>2</td>
</tr>
</tbody>
</table>

\(^a\) Specific event included: treatment discontinuation (3), illness remission (3), need for treatment change (2), falling asleep (3), delirium (1), mortality (1), suicidal episode (1), hospitalization/crisis (1).

\(^b\) Quality of life (1), metabolic status (1), total time free of symptoms (1).

\(^c\) Including institutional academic or hospital funds.