Schizophrenia Research 156 (2014) 228–232

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

How study designs influence comparative effectiveness outcomes: The case of oral versus long-acting injectable antipsychotic treatments for schizophrenia

Larry Alphs [a,*], Nina Schooler [b], John Lauriello [c]

[a] Janssen Scientific Affairs, LLC, 1125 Trenton-Harbourton Road, Titusville, NJ, USA
[b] Department of Psychiatry & Behavioral Sciences, State University of New York Downstate Medical Center, Brooklyn, NY, USA
[c] Department of Psychiatry, University of Missouri, Columbia, MO, USA

ARTICLE INFO

Article history:
Received 20 December 2013
Received in revised form 17 April 2014
Accepted 23 April 2014
Available online 17 May 2014

Keywords:
Pragmatic
Explanatory
Effectiveness
Long-acting

ABSTRACT

This article reviews key methodological considerations for clinical trials that utilize explanatory and pragmatic trial designs and relates these contrasting approaches to the interpretation of results from comparisons of oral versus long-acting injectable (LAI) antipsychotics in schizophrenia. Explanatory randomized controlled trials (RCTs) generally measure the efficacy of a treatment in a homogeneous population with intensive, frequent, and often clinical trial-specific assessments. In contrast, pragmatic trials measure effectiveness in routine clinical practice and frequently aim to inform choices between treatments. Comparative effectiveness outcomes with pragmatic designs in naturalistic settings for schizophrenia treatments are of increasing interest to healthcare providers because outcomes of treatment (both efficacy and safety) may vary significantly when identified in an explanatory setting compared with a naturalistic pragmatic setting. Indeed, it has been suggested that the inconsistent outcomes observed in trials comparing oral and LAI antipsychotic medications may be a function of the use of explanatory or pragmatic trial designs.

In practice, clinical trial designs are seldom purely explanatory or pragmatic. To identify the predominant orientation of a trial, one must consider multiple features. This paper reviews the relative impact of these features when comparing LAI and oral antipsychotic treatments and makes recommendations for improving these comparative designs.

1. Introduction

The question of whether long-acting injectable (LAI) antipsychotics offer meaningful advantages over oral antipsychotics in the treatment of individuals with schizophrenia has been addressed in recent studies with inconsistent results (Chue et al., 2005; Bai et al., 2006; Emsley et al., 2008; Weiden et al., 2009; Gaebel et al., 2010; Macfadden et al., 2010; Rosenheck et al., 2011; Schooler et al., 2011; Weiden et al., 2012; Zhornitsky and Stip 2012; Barrio et al., 2013). Meta-analytical reviews of these studies have been similarly inconsistent (Leucht et al., 2011; Fusar-Poli et al., 2013; Kirson et al., 2013; Kishimoto et al., 2013, 2014). Consequently, whether treatment with oral or LAI formulations of antipsychotics produces meaningfully different outcomes remains a matter of debate.

Pharmacological differences are unlikely to explain potential differences in treatment outcomes between LAI and oral formulations because the medications in both groups have similar (Weiden et al., 2009; Gaebel et al., 2010; Macfadden et al., 2010; Schooler et al., 2011; Weiden et al., 2012; Zhornitsky and Stip 2012; Barrio et al., 2013), sometimes identical (Chue et al., 2005; Bai et al., 2006; Emsley et al., 2008), pharmacological mechanisms. Rather, potential differences in effectiveness between LAI and oral antipsychotics are most likely attributable to the fact that, in clinical practice, administration of an LAI guarantees medication adherence during the postinjection treatment interval. In addition, failure to receive a follow-up injection signals the onset of nonadherence. In contrast, adherence to oral treatment is nearly always uncertain.

Explanatory randomized controlled trials (RCTs) of pharmacological treatments are designed to study the efficacy and safety of molecules under well-controlled circumstances. Subjects selected must understand and consent to both treatment and assessment procedures and are expected to adhere to the protocol. Further, a great deal of attention is paid to ensuring and reinforcing protocol compliance. Such care may

* Corresponding author at: Janssen Scientific Affairs, 1125 Trenton-Harbourton Road, Titusville, NJ 08560, USA. Tel.: +1 609 730 3693; fax: +1 609 730 3232.
E-mail addresses: lalphs@its.jnj.com (L. Alphs), nina.schooler@gmail.com (N. Schooler), laurielloj@health.missouri.edu (J. Lauriello).

http://dx.doi.org/10.1016/j.schres.2014.04.024
0920-9964/

preclude detection of differences between LAI and oral medication formulations that are present in actual practice. Pragmatic studies, in which differences in adherence are less constrained, seem more likely to mirror real-world practice and may offer advantages.

The aims of this article are (1) to review in detail differences between explanatory and pragmatic trial designs, (2) to show how these design considerations may impact interpretation of disparate findings from studies that have compared LAIs versus oral medications, and (3) to offer recommendations for such studies going forward.

2. Design considerations

2.1. Specification of study objectives

Studies designed to address one objective may not be appropriate for addressing others, even if the objectives are related. Indeed, if an inappropriate study design is selected, results may be misleading. The specific study objective and design characteristics must be aligned (American Psychological Association, 2010).

Careful definition of the study objective is particularly critical when one is looking for potential treatment differences between oral and LAI antipsychotic medications. First, it must be determined if the study focus is to ascertain whether the medication is inherently effective and safe, or whether the medication is effective and safe in naturalistic practice settings (i.e., whether a more explanatory or a more pragmatic design is needed [Section 2.2]). Then, the trial design must be selected according to whether the study is to show equivalence, non-inferiority, or superiority over the comparator treatment. Each approach requires a very different study design and analytical method.

2.2. Pragmatic versus explanatory design

Explanatory clinical trials generally measure efficacy of a treatment in a relatively homogeneous population by performing intensive, frequent, and standardized clinical assessments, whereas pragmatic trials measure effectiveness in more heterogeneous populations in routine clinical practice. Actual clinical trial designs represent a spectrum of pragmatic and explanatory approaches; seldom is a trial purely explanatory or purely pragmatic (Thorpe et al., 2009). Several study design domains are particularly relevant for characterizing a study along the pragmatic–explanatory continuum. These include design choices around (1) patient population selection; (2) site selection and medical practice setting/practitioner expertise found at the site; (3) degree of intervention flexibility allowed during the evaluation; (4) measures of primary and secondary trial outcomes; (5) participant adherence to treatment and to assessment; and (6) whether subjects are randomly assigned to treatment (Table 1).

2.3. Specific study design features relevant to pragmatic–explanatory continuum

2.3.1. Patient population selection

A key consideration in study design involves the definition of the population to be studied. Explanatory clinical trials designed to demonstrate intrinsic efficacy and safety of a treatment seldom randomly sample from the total population of potential patients with the illness that needs to be treated. Indeed, to minimize interpretive confounds from concomitant medications and comorbid conditions, restrictive selection criteria for potential subjects often identify constrained population subgroups for study. Most studies further select subjects who are likely to be adherent with treatment and trial procedures by excluding patients with a history of noncompliance or substance abuse (Thorpe et al., 2009). Additionally, patients enrolled in clinical trials are more likely to adhere to treatment regimens when they are aware that their compliance is being strictly monitored. This is specifically seen in schizophrenia trials (Gutiérrez-Casares et al., 2010; Kirson et al., 2013). Other exclusion criteria in trials investigating the treatment of schizophrenia frequently eliminate participants at highest risk of unfavorable outcomes (treatment resistant) and those with psychiatric and medical conditions that might interfere with assessment of the safety and efficacy of the treatment(s) being evaluated (Bai et al., 2006; Fleischhacker et al., 2012). Although this process is useful in selecting subjects for whom observed efficacy and safety data are most clearly attributable to the study drug, it is unlikely to yield a sample population that is fully representative of patients who will be treated in real-world clinical practice settings.

Pragmatic trials strive to enroll all patients who meet the basic entry criteria for the population of interest defined by the study question (i.e., ideally, no additional restrictions are applied to the predefined population of interest). Thus, with perfect pragmatic designs of adequate size, considerations such as responsiveness, adverse events, and treatment adherence should be fully reflective of the population identified by the study question/hypothesis. However, even prospective trials that aim to be pragmatic are constrained by sample size and selection biases arising from the need for informed consent, the range of patients available at the study site, and the selection biases that draw patients to that site. For example, in comparing LAIs to oral treatments, patient reluctance to receive injections can reduce the likelihood that such patients will enroll in the trials and increase dropout, thus altering the representativeness of the trial population (Kishimoto et al., 2013, 2014). These selection issues represent limitations for nearly all pragmatic clinical trials. Nevertheless, despite their imperfections, well-conducted pragmatic trials better reflect the broad range of patients found in regular clinical practice, and results of pragmatic trials will be more broadly generalizable than those from explanatory trials.

When data from schizophrenia trials comparing LAI and oral treatment outcomes are compared, additional patient characteristics are relevant. These include severity and stability of symptoms, duration of follow-up, and clinical history such as duration of illness and number of prior relapses/hospitalizations. For example, differences in efficacy between LAI and oral treatments may be more evident in recently diagnosed patients, perhaps because they are less likely to be adherent to treatment than more chronically ill patients (Subotnik et al., 2012). Attitudes toward taking medicine and, by implication, adherence to treatment may be affected by local culture, ethnicity, age, and gender and may affect relative treatment response.

2.3.2. Site selection and medical practice setting/practitioner expertise

The representativeness of the skill sets of practitioners and the characteristics of the clinical settings relative to those in which the treatment will be applied also affect the degree to which a trial is explanatory or pragmatic. Local standards of clinical practice, the skill and experience of practitioners, and the availability of concomitant or alternative treatment options may affect treatment outcomes. In explanatory trials, experienced practitioners in optimal clinical settings are usually most desirable. On the other hand, a prototypic pragmatic study selects broadly, although rarely randomly, from the range of relevant clinical practices the settings in which treatment is to be given. Treatment settings and practices also change over time. This is relevant when the results of both explanatory and pragmatic trials that have been completed across an extensive time span are evaluated in meta-analyses. Meta-analyses that compare LAI antipsychotics versus oral medications may be confounded by differences in treatment practice that may have been prevalent when alternative treatment options were prevalent. For explanatory and most prospective pragmatic trials, a standardized protocol and systematic training are used to reduce variability in assessment and experience. However, adherence to these study-specific standards and training reduces their pragmatic character.

To assess the generalizability of clinical trial results with LAI versus oral antipsychotics, it is necessary to understand (1) the heterogeneity of schizophrenia, (2) the varieties of clinical practice applied to