

# Clinical trial methodology to assess the efficacy/effectiveness of long-acting antipsychotics: Randomized controlled trials vs naturalistic studies

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## Abstract

Schizophrenia presents unique difficulties in clinical trial design associated with the condition's variable presentation and clinical course, and multiple features influencing affect, cognition, volition and perception. Randomized controlled trials (RCTs) are explanatory studies using a carefully selected patient population, predefined assessment intervals and, generally, symptom-focused endpoints. Naturalistic studies are pragmatic, with no active intervention, and outcomes that are generally those used in clinical practice (e.g. hospitalization, relapse rate). Both naturalistic studies and RCTs have pros and cons, making it difficult for physicians in clinical practice to apply research findings to their own treatment decisions. The choice of clinical trial design can have a significant impact on the comparative effectiveness or efficacy of drugs. This is particularly true for studies comparing long-acting injectable (LAI) antipsychotics with oral antipsychotics in schizophrenia, in which RCTs generally show no benefit for LAIs over oral drugs, whereas observational studies do. The more pragmatic the study design, the more likely it is to show a benefit for LAIs versus oral therapy. This article reviews the pros and cons of different study types, using published examples. Criteria are outlined to help physicians design appropriate prospective studies in schizophrenia including the relevant pragmatic and/or explanatory features, as required.

## 1. Introduction

The introduction of lithium into clinical psychiatry in 1949 marked the beginning of a new phase of active psychopharmacological drug development, and consequently clinical research (Brunoni et al., 2010). However, the assessment of drug efficacy in psychiatry presents several challenges, in particular the fact that there are no strictly objective measures available to assess outcomes (Kane, 2002). Regulatory authorities, such as the European Medicines Agency, have defined criteria for the assessment of psychotropic drugs in schizophrenia in order to prove a clinical benefit necessary for drug approval (European Medicines Agency, 2012). Such registration studies usually require a randomized, double-blind, parallel-group design in which the novel drug is compared with an existing drug with proven efficacy, as well as placebo (European Medicines Agency, 2012).

While all of the psychiatric conditions are objectively challenging, schizophrenia presents unique difficulties in clinical trial design due to the condition's variable presentation and clinical course, and multiple features influencing affect, cognition, motivation and perception (Kane, 2002). The randomized controlled trial (RCT)

is considered to be the ‘gold standard’ for clinical trial design, but this type of study has a number of limitations. The naturalistic clinical study design approaches have also been developed and tested in schizophrenia. Because the naturalistic studies use ‘real world’ patients, they eliminate the potential for selection bias but they have their own weaknesses.

Long-acting injectable (LAI) antipsychotics were developed to overcome major challenges with oral antipsychotics and show benefits including stable blood levels, treatment adherence and improved bioavailability and pharmacokinetic profile at lower doses (Kane and Garcia-Ribera, 2009, Kane et al., 2013b, Spanarello and La Ferla, 2014). It is becoming increasingly apparent that the choice of clinical trial design can have a significant impact on the comparative effectiveness or efficacy of LAI antipsychotics versus oral antipsychotics in schizophrenia (Kirson et al., 2013). Observational studies show benefit of LAIs over oral treatment (Kirson et al., 2013, Kishimoto et al., 2013, Kishimoto et al., 2014, Lafeuille et al., 2014), but although some RCTs do show a benefit of LAIs over oral antipsychotics (Fleischhacker et al., 2014, Robinson et al., 2004), generally RCTs show little benefit.

The objective of the current review is to describe the different study designs employed in comparisons of LAI and oral antipsychotics, their pros and cons, and the criteria that should be employed by clinical researchers when designing studies of these agents in order to answer specific clinical questions.

## 2. Clinical trial terminology

The RCT employs rigorous controls to reduce variation and bias, including careful patient selection criteria, randomization (to balance potential confounders between treatment groups) and blinding (to limit selection bias) and use evidence-based medicine assessment (Hotopf et al., 1999). However, within the framework of a RCT, several aspects of clinical trial design can be individualized (Table 1) (Gray, 2006). RCTs conducted to meet regulatory requirements are most often explanatory, i.e. a carefully selected and therefore homogeneous patient population are assessed at regular predefined intervals using standardized measures (Alphs et al., 2014). Endpoints are generally symptom-focused and use validated assessment tools.

Table 1. Types of clinical trials.

Randomized controlled trials (RCTs) (Gray, 2006)	Naturalistic studies (Song and Chung, 2010; Thiese, 2014)
<p><b>The following features of RCTs can be varied:</b></p> <ul style="list-style-type: none"> <li>● <b>Comparison:</b> <ul style="list-style-type: none"> <li>a. Single control group (placebo or standard therapy)</li> <li>b. Multiple comparisons</li> <li>c. Factorial comparison (A vs B vs A+B)</li> </ul> </li> <li>● <b>Blinding:</b> <ul style="list-style-type: none"> <li>a. Double-blind (investigators and patients unaware of treatment allocation)</li> <li>b. Single-blind (investigators or patients, but not both, unaware of treatment allocation)</li> <li>c. Open-label (both investigators and patients are aware of treatment allocation)</li> </ul> </li> <li>● <b>Randomization:</b> <ul style="list-style-type: none"> <li>a. Individual (each patient randomized)</li> <li>b. Cluster (groups of patients randomized)</li> </ul> </li> <li>● <b>Design:</b> <ul style="list-style-type: none"> <li>a. Parallel (treatments taken concurrently by different groups)</li> <li>b. Crossover (group takes treatment then switches to an alternative treatment)</li> </ul> </li> </ul>	<p><b>Case series</b></p> <ul style="list-style-type: none"> <li>● Observation of a group of patients</li> <li>● under treatment <b>Mirror-image studies (also called case crossover studies)</b></li> <li>● Comparison of before vs after initiation of a new treatment <b>Cohort studies</b></li> <li>● Two groups of patients on different treatments observed prospectively or retrospectively <b>Case-control studies</b></li> <li>● Patients with a particular outcome are identified and compared with patients who do not have outcome – always retrospective <b>Cross-sectional studies</b></li> <li>● Identify prevalence of particular condition in a group of people at a single point in time</li> </ul>

In contrast, naturalistic or observational studies are pragmatic, where the researcher studies the patients but does not deviate from their usual preferences or practice patterns. Outcome measures in pragmatic studies are generally those used in clinical practice (e.g. hospitalization, relapse rate) rather than symptom rating scales (Hodgson et al., 2007). There are different types of naturalistic studies like case series, mirror-image studies, cohort studies and cross-sectional studies (Table 1) (Song and Chung, 2010, Thiese, 2014). A case series investigates outcomes (prospectively or retrospectively) in a group of patients with a similar characteristic (e.g. on the same treatment). In cohort studies, researchers identify patients with a particular characteristic (e.g. taking LAIs) and a similar group of patients who are controls (e.g. taking oral antipsychotics) and prospectively or retrospectively compare them with regard to particular outcomes (Haddad et al., 2015). Case series are sometimes erroneously called cohort studies but a cohort study includes a control group, whereas a case series does not (Song and Chung, 2010). Mirror-image studies compare the effects of one treatment with another in the same group of patients. In comparisons of LAI and oral antipsychotic treatment, mirror-image studies compare periods of oral antipsychotic versus LAI treatment in the same patients (Haddad et al., 2015). This eliminates the need for a control group because patients act as their own control. Cross-sectional studies examine the prevalence of an outcome (e.g. hospitalization) in a broad population at one point in time and compare different risk factors or interventions in those groups. As they do not have a temporal dimension, they are unsuited to studying cause and effect relationships and are best suited to identifying the prevalence of a particular condition at a single time point (Song and Chung, 2010, Thiese, 2014).

Other forms of naturalistic studies exist but are less frequently used when examining drug effectiveness. For example, case-control studies are principally used in epidemiological research, rather than treatment outcomes research, because this form of study involves the selection of cases on the basis of outcome (e.g. an adverse event) from the start of the research (Song and Chung, 2010). Each case is matched to a control patient who has similar demographic characteristics but did not develop the outcome (Song and Chung, 2010, Thiese, 2014).

Overall, the RCTs provide information on the efficacy of a drug in the treatment of a particular disease/disorder while naturalistic studies provide more real-world data on the effectiveness of a particular drug in the treatment of a specified disease/disorder. Large simple trials (LSTs) are a type of RCT that may be used to study the effect of a drug in a real-world setting. LSTs are a hybrid between an observational study and an RCT where a large number of patients are randomized to a particular treatment and followed-up as per clinical practice (Califf, 2014). These trials are referred to as simple trials as there is little or no interference with the conduct of the study. Since these studies are a hybrid between RCTs and naturalistic studies, they are considered to maximize the generalizability and validity of a particular treatment (Califf, 2014). While these trials are ideal to prove the effectiveness of treatments for common diseases, they are still relatively uncommon (Califf, 2014, Roehr, 2013).

### **3. Randomized controlled trials**

#### **3.1. Randomized controlled trials in psychopharmacological research**

RCT is a commonly used study design in clinical studies of different drugs used in the treatment of psychiatric disorders in order to comply with the strict drug regulatory guidelines before approval. An example of the typical (explanatory) form of RCT in psychopharmacological research is a phase III study investigating the

efficacy of injectable aripiprazole once-monthly (Kane et al., 2014). In this study, patients (n=340) were specifically selected based on clear inclusion and exclusion criteria and were randomized to double-blind treatment with LAI aripiprazole or placebo and followed up for 12 weeks. Because the placebo and drug suspensions were not identical, a non-blinded drug manager administered the injections at each site to ensure that the physicians remained blinded to the patient's treatment assignment. The study only included patients who were living in a stable environment, were not treatment-resistant and had demonstrated a previous good response to antipsychotic therapy in the past 12 months. Therefore, this was a cohort likely to be adherent and responsive to treatment. A 7-d washout period was used in previously treated patients to prevent any crossover effects from prior antipsychotic therapy. The study was 12 weeks long and the primary endpoint was the Positive and Negative Symptom Scale (PANSS) score, a 30-item questionnaire that measured the prevalence of positive and negative symptoms in schizophrenia, measured at 10 weeks.

Because many RCTs are undertaken for registration purposes, there is a need to demonstrate results quickly; as a result RCTs are often of relatively short duration compared with observational studies which may affect the choice of efficacy endpoints (Hodgson et al., 2007). This explains the use of pragmatic endpoints in many RCTs like the PANSS rating scale which is a commonly used endpoint as it is sensitive enough to detect differences between treatments. However, such scales are seldom used in clinical practice and provide limited information that is meaningful in clinical practice (Correll et al., 2011, Hodgson et al., 2007).

An analysis of clinical trial quality in psychiatry over time has shown significant improvements in the rigor of RCTs, probably as a result of the CONSORT initiative to improve the quality of clinical trial reporting (Brunoni et al., 2010). Some of the specific improvements noted over time were having structured criteria for patient enrolment and severity classification instead of using physician judgment; using a pre-trial calculation of sample size to ensure adequate power; including a washout period to establish baseline; using intention-to-treat (ITT) analysis; and including unbiased methods of randomization (Brunoni et al., 2010).

The ITT population of a trial includes all patients who were randomized to treatment, regardless of whether they completed the study, adhered to treatment or violated the protocol (Gupta, 2011). ITT analysis is recommended in the CONSORT guidelines (Schulz et al., 2010), while both US and European regulatory guidelines recommend analysis of RCT results in the ITT population and in the population of patients who completed treatment (European Medicines Agency, 1998, Food and Drug Administration, 1988). Using the ITT analysis is likely to underestimate the overall treatment effect as it may include patients who did not complete the study treatment or patients who did not adhere to the study treatment or violated the study protocol and therefore may provide a conservative estimate of efficacy, such as might be seen in clinical practice with the usual mix of adherent and non-adherent patients (Gupta, 2011).

### **3.2. Methodological pros and cons of RCTs**

RCTs have several methodological advantages and disadvantages (Table 2). Since patient cohorts in RCTs are carefully selected to ensure a homogeneous patient group and patients with comorbidities or taking concomitant medications are often excluded, some patient subgroups in clinical trials (e.g. elderly patients) may be under-represented (Hodgson et al., 2007). The need for informed consent also diminishes the ability of RCTs to study acutely unwell patients in need of emergency treatment (Hodgson et al., 2007). Therefore, many patients who are typically prescribed LAI antipsychotic therapy in clinical practice are unlikely to meet the strict inclusion criteria used in explanatory RCTs (Patel et al., 2013). Also, many RCTs are double-blind

which minimizes bias from researchers and patients as to the expected treatment effect (Haddad et al., 2015), although in the case of oral versus LAI treatments, double-blind assessment means that patients randomized to the oral treatment arm are subjected to placebo injections.

Table 2. Advantages and disadvantages of randomized controlled trials (Correll et al., 2011).

Advantages	Disadvantages
High internal validity	Limited external validity
Allows specific signal detection in carefully selected patient population Can support regulatory submissions and evidence-based assessments Randomization controls for group differences	Expensive and time-consuming to conduct Selection bias limits generalizability to a wider clinical patient population and may provide relevant dosing information for a more heterogeneous population
May require smaller patient populations than observational studies because of the more homogeneous patient groups Reliable results based on: <ul style="list-style-type: none"> <li>Clearly defined study procedures and outcome assessments means data collection is standardized and often more complete compared with observational studies</li> <li>Specific assessment of measurable outcomes using validated and reliable scales administered by well-trained personnelAllows prospective collection of cost and tolerability/adverse event data</li> </ul>	May be challenges in maintaining blinding in the face of specific adverse events Patients may be more motivated to comply with medication than in clinical practice which can produce disconnect between efficacy as demonstrated in the trial and effectiveness in clinical practice Frequent assessments required – increased burden for patients and health professionals Potentially difficult or slow to recruit patients depending on the selection criteria May be limited to specialized sites with the equipment, infrastructure and personnel to participate <ul style="list-style-type: none"> <li>Need for multiple research sites</li> <li>Need to standardize conduct/control for variation between sites</li> </ul> Low signal to detect rare adverse events or outcomes

RCTs provide detailed information on the overall efficacy of novel drugs in the treatment of a particular disease/disorder in a selected patient population (Suvarna, 2010). Because of the controls inherent in the RCT to reduce variation and bias (randomization to separate treatment groups, blinding, placebo control [if ethical]), these trials have high internal validity and the results can be considered reliable (Correll et al., 2011). The Paliperidone Palmitate Research in Demonstrating Effectiveness (PRIDE) study which compared the efficacy of a LAI antipsychotic (paliperidone) with daily oral antipsychotic drugs in the treatment of schizophrenia in patients at a higher risk of relapse was a randomized, open-label study designed to reflect real-world management of schizophrenia (Robinson et al., 2004). The primary efficacy end point used in this study was time to first treatment failure which was determined using the Kaplan Meier method. The results of this trial showed that LAI treatment of schizophrenia was superior to oral antipsychotics in delaying the time to treatment failure.

A homogeneous patient group allows the RCT to demonstrate a statistically significant effect within a relatively narrow cohort of patient type and the use of explanatory endpoints may allow a relatively short duration of follow-up (Correll et al., 2011). However, statistical significance could be achieved in a heterogeneous group which is a closer representation of the patient population in the real-life setting, provided the study was carried out on a much larger cohort. Cost is a major limiting factor and contributes to restricting the size of the study population as well as the duration of RCTs. RCTs are expensive to conduct and often require multiple specialized sites with carefully trained personnel (Correll et al., 2011). It should also be noted that since RCTs use highly selected patient populations, their external validity and generalizability is considered low (Correll et al., 2011).

Perhaps a key disadvantage of the RCT is that the protocol-driven assessment and monitoring processes tend to make patients more adherent to treatment during the trial than they normally would be in clinical practice. While blinding minimizes bias, it may also distort the usual clinical schedule of visits: patients randomized to oral therapy are seen more frequently than they would be during normal clinical practice because they are seen as frequently as patients randomized to LAI treatment (Haddad et al., 2015). Sackett and Wennberg (1997) summed up the difficulty for clinicians: “Randomised controlled trials carried out in specialised units by expert care givers, designed to determine whether an intervention does more good than harm under ideal

conditions, cannot tell us how experimental treatments will fare in general use” (Sackett and Wennberg, 1997). Also, attrition bias (differences in the number of patient withdrawal from each treatment group) is a major disadvantage of randomized controlled trials (Dumville et al., 2006).

#### **4. Naturalistic studies**

##### **4.1. Naturalistic studies in psychopharmacological research**

Primarily, two types of naturalistic studies are used to evaluate antipsychotic drug effectiveness: mirror-image studies and cohort studies (Haddad et al., 2015). Mirror-image studies have been used in the assessment of LAI antipsychotics since 1975 and they have invariably compared LAI use after oral antipsychotic use (Kishimoto et al., 2013). This probably results in more favorable outcomes for LAI antipsychotics because of expectation bias and regression to the mean (Haddad et al., 2015, Kishimoto et al., 2013).

An example of a cohort study used in psychopharmacological research is one by Patel and colleagues, which examined patients who were receiving treatment for schizophrenia under a compulsory treatment order (CTO) at a large mental health trust in South London between 3 November 2008 (when CTOs became legally available) and 31 October 2009 (Patel et al., 2013). The study prospectively examined outcomes for 12 months after the CTO was initiated, comparing outcomes in patients who were receiving LAI and oral antipsychotics, thereby examining the effects of routine clinical decisions. Selection bias was minimal because all patients who had a CTO during the study period were included. The study found no difference between LAI and oral antipsychotics in the time to first hospitalization or the incidence of re-hospitalization after CTO. However, the study did not include a control group of patients who would have been eligible for a CTO but did not receive one, so the potentially confounding effect of the CTO itself on treatment outcomes was not determined (Patel et al., 2013).

Another retrospective cohort study by Marcus and colleagues examined the adherence to medication and re-hospitalization in schizophrenia patients treated with LAI versus oral antipsychotics after discharge from hospital (Marcus et al., 2015). The study was an observational study and used 2010–2013 data from the Truven Health Analytics MarketScan Medicaid research claims database; patients included were those receiving either oral or LAI antipsychotics within 30 days after a schizophrenia-related hospitalization who had a history of non-adherence to treatment. The results of the study showed that more patients on oral medication were non-adherent to the antipsychotics, discontinued the treatment or were hospitalized for the treatment of schizophrenia compared with patients on LAI antipsychotics. Furthermore, the study showed that patients treated with second-generation LAI antipsychotics displayed better outcomes compared with patients treated with first-generation LAI antipsychotics. Overall the study highlighted the effectiveness of second-generation LAI antipsychotics in the treatment of schizophrenia in real-world clinical practice.

##### **4.2. Methodological pros and cons of naturalistic studies**

Since naturalistic studies are pragmatic, they more accurately reflect real-world clinical practice. On the other hand, patients are not randomized to treatment in naturalistic studies, so bias is inherent in the study design and is one of the major drawbacks to this type of study (Hodgson et al., 2007). In addition to bias in patient selection, there is a tendency for investigators to encourage patients to continue with the treatment despite

a lack of positive outcomes, which they may not have done outside of the context of a clinical study. For pharmaceutical companies, there is limited incentive to conduct this type of research because drug regulators often do not accept them as they are less likely than an RCT to demonstrate a clear efficacy difference between treatments (Kane, 2002). Moreover, in an unselected patient group with comorbidities, there is greater risk that patients will develop an adverse event and it may be difficult to accurately attribute such events to the correct medication (Kane, 2002).

Confounding is a phenomenon observed in naturalistic studies whereby the observed effect of the treatment is mixed. Similarly, selection or information bias in naturalistic studies is the bias introduced in the results due to procedures used in patient selection and measurement error. Biases and confounding in naturalistic studies can result in a heterogeneous treatment effect within the studied populations, which makes naturalistic studies more likely to yield an erroneous/null average treatment effect compared with RCTs (Velentgas et al., 2013). For example, patients may be taking concomitant medications, including other psychoactive agents, which may affect treatment outcomes. Use of concomitant oral antipsychotics is high in patients receiving LAI therapy – more than 75% in one US analysis of recently hospitalized patients (Doshi et al., 2015) – and patients on LAI antipsychotics tend to be more likely to use concomitant psychotropic agents than those taking oral therapy (Sneider et al., 2015).

Both retrospective and prospective naturalistic studies are also subject to prescribing bias, where the clinician's preference for one form of treatment over another impacts their assignment to treatment. This may influence studies of LAIs more so than oral therapies, since there is evidence of physician reluctance to prescribe injectable therapy in psychiatric patients, even if they perceive them as effective (Weiden et al., 2015). Prescribing bias is influenced not only by physician preference, but by the patient's previous response as well as where they live (Geerts et al., 2013). In the study by Tiihonen and colleagues, which compared re-hospitalization rates and adherence during treatment with oral and LAI antipsychotics in Finnish patients after their first hospitalization for schizophrenia, prescribing bias was present, but it was not influenced by the patient's previous response because the study included only patients who were being hospitalized for the first time (Tiihonen et al., 2011). In observational studies, a heterogeneous treatment effect can be the result of bias or chance (Velentgas et al., 2013); however, the study by Tiihonen and colleagues (Tiihonen et al., 2011) provides an example of how careful study design can minimize some of the sources of bias within a pragmatic design.

The key advantages of mirror-image studies are that patients act as their own control, thereby reducing variation; however, mirror-image studies may have a number of disadvantages as well (Table 3). A key disadvantage is that one portion of the study is retrospective and the other prospective. This introduces a number of biases, including recall bias during the retrospective portion and selection bias during patient recruitment. Selection bias may favor the second treatment if patients are chosen because they have not done well on the first treatment (Haddad et al., 2015) as they were in the earlier example by Rosa and colleagues (Rosa et al., 2012). Another potential type of bias in mirror-image studies is expectation bias, whereby clinicians, patients and families are aware that patients are on an LAI and this may affect their subsequent treatment decisions (Kishimoto et al., 2013). In addition, during the prospective portion of the study, patients receive more active surveillance and attention (Haddad et al., 2015), which makes the investigators more aware of their outcomes. Unfortunately, in mirror-image studies comparing LAIs with oral antipsychotic treatment, medical records are notoriously unreliable (due to their subjective nature), and the LAI portion has always been the prospective portion, which favors the LAI (Kishimoto et al., 2013).

Table 3. Advantages and disadvantages of mirror-image studies (Haddad et al., 2015, Kane et al., 2013a, Kishimoto et al., 2013, Thiese, 2014, Velentgas et al., 2013)

Advantages	Disadvantages
Study real-world patients, limiting selection bias and improving generalizability Include pragmatic outcomes (e.g. hospitalizations, all-cause treatment discontinuation)	Can be confounded by factors that vary over time. For example, outcomes (e.g. admission rates) may be affected by independent events (e.g. health policy changes or insurance coverage) and without a separate control group this type of confounding cannot be controlled for
Patients act as their own control – reduces the potential for variation and confounding and requires fewer patients because no control group is recruited	One phase is usually retrospective and one phase prospective, so prospective phase may be influenced by greater surveillance and scrutiny
Less expensive to conduct compared with RCTs Can easily incorporate large samples When the treatment switch is not triggered by a health event such as lack of efficacy, but a logistic change (e.g. insurance coverage) the outcome information can be unbiased	If switch is prompted by failure of initial treatment, the subsequent treatment is going to look more favorable because of regression to the mean and expectation bias Subject to recall bias Subject to selection bias (may favor the second treatment if patients are chosen because they have not done well on the first treatment or have been on the second medication for a certain length of time)

Both prospective and retrospective cohort studies have advantages and disadvantages (Table 4). Like mirror-image studies, cohort studies have the advantage that they study real-world clinical patients and therefore may provide more generalizable findings than RCTs can. Retrospective studies are less expensive to conduct than prospective studies, but may not allow complete and accurate collection of data because they rely on existing medical records (Song and Chung, 2010). Prospective cohort studies are subject to attrition bias, which can negatively affect the internal validity of the study if too many patients are lost to follow-up (Song and Chung, 2010). On the other hand, retrospective studies may be subject to recall bias. An exception may be if the outcome measure is derived from a clinical database. For example, the retrospective study by Tiihonen and colleagues discussed above (Tiihonen et al., 2011) avoided recall bias by using hospital admission as an outcome measure. However, it should be noted that hospital admissions is not a very reliable outcome measure because hospitalization may occur for reasons unrelated to drug treatment.

Table 4. Advantages and disadvantages of cohort studies (Haddad et al., 2015, Hodgson et al., 2007, Song and Chung, 2010, Velentgas et al., 2013)

Advantages	Disadvantages
Study real-world patients, limiting selection bias and improving generalizability	Results may be affected by selection or prescribing bias, e.g. increased use of LAIs in more severe patients
Include pragmatic outcomes (e.g. hospitalizations, all-cause treatment discontinuation) Clear timeline for determining the relationship between exposure and outcome Can assess causality Can calculate rates of outcomes in different groups over time (e.g. relative risk)	Because there is no randomization, results may be impacted by confounders Bias inherent in an open-label design Likely to produce a homogeneous result because of the broad study population included
Retrospective studies are inexpensive Can easily incorporate large samples Can assess multiple exposures and outcomes Ability to control for some confounders	Retrospective cohort studies are subject to recall bias Prospective studies can require long study durations while waiting for events to occur
	Maintaining follow-up during prospective studies can be difficult, especially if a long follow-up is required because the incidence of the outcome is low Prospective studies may be susceptible to attrition bias if patients withdraw or are lost to follow-up Prospective studies can be expensive Both prospective and retrospective studies are time intensive Retrospective studies may be hampered by incomplete, inaccurate or inconsistently measured data

## 5. Randomized controlled trials or naturalistic studies?

Since both naturalistic and RCTs have pros and cons, it very difficult for physicians in clinical practice to apply clinical research findings to their own treatment decisions. Data from RCTs may provide robust evidence of benefit, but the findings may not be generalized to a diverse clinical practice population and pragmatic endpoints often have limited applicability in a routine practice setting. On the other hand, naturalistic studies may provide generalizable evidence of benefit in a diverse clinical trial population using explanatory and clinically applicable endpoints, but the results are often subject to confounding and bias.



There is no ‘ideal’ study design, but researchers should choose the type of study based on the specific question they need to answer (Sackett and Wennberg, 1997). In general, naturalistic studies can be conducted in any setting (community, inpatient, outpatient), but RCTs generally require a specialized setting where there is the personnel and infrastructure to support the requirements of the study protocol (Table 5). This too may limit the generalizability of RCT data to patients treated in similar well-resourced or specialized treatment centers.

Table 5. Comparison of naturalistic studies and randomized controlled trials (RCTs) (Alphs et al., 2014, Hodgson et al., 2007)

Feature	RCT (explanatory)	Naturalistic (pragmatic)
<b>Objective</b>	Efficacy and safety in a controlled environment	Efficacy and safety in a real-world clinical environment
<b>Number of patients</b>	Modest	Large
<b>Patient population</b>	Homogeneous; extensive exclusion criteria	Heterogeneous; includes any patients who meet basic inclusion criteria; minimal exclusion criteria
<b>Setting</b>	Controlled clinical environment with experienced practitioners	Any relevant settings that provide treatment to the target population
<b>Duration</b>	Modest	Long
<b>Drop-out rate</b>	High	Lower
<b>Results</b>	Statistically significant	Clinically meaningful
<b>Dosing</b>	Structured regimen	Naturalistically selected
<b>Treatment assignment</b>	Randomization	Naturalistic
<b>Validity</b>	Maximizes internal validity	Maximizes external validity
<b>Bias and variability</b>	Minimized	Present
<b>Adherence</b>	Artificially enhanced by frequent contact	Not mandated, ‘real’ patients
<b>Assessment</b>	Efficacy	Effectiveness
<b>Concomitant medications</b>	Excluded or limited	Allowed
<b>Outcome measures</b>	Generally explanatory and symptom-focused – complex applied scales	Pragmatic – used in everyday practice; may include costs, adherence, resource use

In the last decade, a new type of clinical trial design has evolved to try and overcome the limitations of the RCT and combine some of the best features of both naturalistic studies and RCTs, namely the pragmatic RCT (Bossie et al., 2015). Such studies still use randomization to allocate patients to treatment (and ideally blinding), but employ less restrictive selection criteria so that the patient cohort is more representative of those in real-world clinical practice, with all the attendant comorbid psychiatric diagnoses, substance abuse issues and general medical illnesses that such diversity carries with it (Stroup et al., 2003). The most relevant comparator in pragmatic RCTs is ‘usual care’, but this needs to reflect good clinical practice and should be defined a priori in the trial protocol (Hotopf et al., 1999).

Pragmatic RCTs may also include pragmatic rather than exploratory outcome measures. One of the first pragmatic RCTs to be conducted was the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study that compared different atypical antipsychotics with first-generation antipsychotics (perphenazine) in patients presenting with schizophrenia in usual clinical practice, with few exclusion criteria (Stroup et al., 2003). The primary outcome in CATIE was all-cause treatment discontinuation (Stroup et al., 2003), a pragmatic outcome measure. The primary results of this study showed no significant difference in the rate of treatment discontinuation between a range of second-generation antipsychotics and perphenazine after adjustment for potential confounders (Lieberman et al., 2005). The European First Episode Schizophrenia Trial (EUFEST) was another pragmatic open-label RCT that compared the effectiveness of low-dose haloperidol with different second-generation antipsychotic drugs in the treatment of first-episode schizophrenia and used all-cause treatment discontinuation as the primary study outcome (Kahn et al., 2008). The results of EUFEST demonstrated that all second generation antipsychotics in the study, both individually and as a group, were superior to haloperidol with the pragmatic primary outcome measure; however, there were no significant difference in the efficacy of the compared treatment regimens (a secondary outcome of the study).

More recently, the QUALity of Life with AbiliFY Maintena (QUALIFY) study included both pragmatic and explanatory study features to compare the effects of two LAI antipsychotics with different mechanisms of action (Naber et al., 2015). Key features of the QUALIFY study were minimal patient exclusion criteria (ensuring a patient cohort that was representative of the range of patients with stable schizophrenia seen in clinical practice), randomization to treatment (limiting prescribing bias), a quality of life measure (QLS and IAQ scales) as the primary endpoint (rather than symptom-focused measures of efficacy) and rater blinding for the primary endpoint assessment to minimize bias. In this way, the QUALIFY study combined many of the best features of the randomized and the naturalistic study (Naber et al., 2015). Similarly, another randomized, prospective, active-controlled, open-label study that compared the efficacy of paliperidone with oral antipsychotics utilized a pragmatic approach by including a more naturalistic study population than most RCTs (Schreiner et al., 2015).

Interestingly, there is evidence of differential outcomes between explanatory and pragmatic research comparing LAI and oral antipsychotics (Bossie et al., 2015, Haddad et al., 2015, Kirson et al., 2013, Kishimoto et al., 2013, Kishimoto et al., 2014). Bossie and colleagues conducted an analysis of studies comparing oral and LAI antipsychotic therapy, assessing their relative pragmatic and explanatory features (Bossie et al., 2015). They identified 11 studies published between January 1993 and December 2013 which included more than 100 patients and had a follow-up duration of at least 6 months (Bitter et al., 2013, Gaebel et al., 2010, Grimaldi-Bensouda et al., 2012, Kane et al., 2010, Keks et al., 2007, Macfadden et al., 2010, Olivares et al., 2009, Rosenheck et al., 2011, Tiihonen et al., 2011, Tiihonen et al., 2006, Zhu et al., 2008). They then scored dimensions of the studies' designs using the 6-domain ASPECT-R (A Study Pragmatic: Explanatory Characterization Tool Rating), which applies a rating from 0 (extremely explanatory) to 6 (extremely pragmatic) to the six important domains, namely participant eligibility criteria, intervention flexibility, medical practice setting/practitioner expertise, follow-up intensity and duration, outcomes and participant adherence. The studies which found that LAI antipsychotics were more effective than oral antipsychotics had ASPECT-R total scores ranging from 25 to 36 (Bitter et al., 2013, Gaebel et al., 2010, Grimaldi-Bensouda et al., 2012, Olivares et al., 2009, Tiihonen et al., 2011, Tiihonen et al., 2006, Zhu et al., 2008), indicating more pragmatic features, while the studies in which the finding was reversed (oral agents were more effective than LAI) had total ASPECT-R scores of between 9 and 13 (Kane et al., 2010, Keks et al., 2007, Macfadden et al., 2010, Rosenheck et al., 2011), indicating fewer pragmatic features and more explanatory ones (Bossie et al., 2015).

### **5.1. Criteria for selection of study design**

The type of study design employed in psychopharmacological research is determined by the research question being asked (Sackett and Wennberg, 1997). The research question will determine the setting of the study, which patients are included/excluded, how patients are allocated to treatment, which dose is used, the comparator (active treatment or placebo), how long patients are studied for (acute or long-term effects, maintenance/continuation of efficacy over time) and what the primary and secondary outcome measures are (Kane, 2002, Velentgas et al., 2013). A useful acronym for remembering these considerations is PICOTS, which stands for population, intervention, comparison, outcomes, timeframe and setting.

The US Agency for Healthcare Research and Quality (AHRQ) aimed to identify the best practices and minimal standards for designing observational studies and has identified and defined some of the key steps researchers need to consider when developing a research protocol for trials assessing clinical effectiveness in a real-world scenario (Table 6) (Velentgas et al., 2013). Explanatory RCTs are best suited to phase III

development studies of novel agents, for registration purposes. Pragmatic RCTs are suited to determine which agents are more effective in the context of general clinical practice. Naturalistic studies are poor at determining causal relationships but are excellent at evaluating real-world clinical practice patterns (Rosenheck, 2013). Non-experimental epidemiological studies (e.g. case-control) are suited to identifying rare side effects, and are important for generating hypotheses, but cannot distinguish between true positive and false positive efficacy results (Sackett and Wennberg, 1997).

*Table 6. Conceptual framework for developing a protocol for comparative effectiveness research in schizophrenia. Adapted and reproduced with permission from AHRQ Publication: Smith, SR “Chapter 1. Study Objectives and Questions” in “Developing a protocol for observational comparative effectiveness research: a user's guide” (Velentgas et al., 2013)*

Domain	Relevant questions
Identify decisions, decision-makers, actions and context	What healthcare decision or set of decisions are being considered about the comparative effectiveness, risks or benefits of medical treatment?
Synthesize the current knowledge base	Who are the decision-makers (e.g. prescribers) and in what context is the treatment decision being made?
Conceptualize the research problem	What is known from the available scientific evidence and what is unknown because the evidence is insufficient or absent?
Determine the state of knowledge development	What research questions or series of questions are critical to reduce decisional uncertainty and gaps in the current knowledge base?
Apply PICOTS framework	What stage of knowledge is the study designed to address?
Discuss evidentiary need and uncertainty	For a particular question, what study populations, interventions, comparisons, outcomes, time frame and settings are important to the prescriber(s) in weighing the balance of harms and benefits of action?
Specify the magnitude of the effect	Are some research questions easier to operationalize than others?
	Are intervention effects expected to be homogeneous or heterogeneous between different population subgroups?
	What level of new scientific evidence does the prescriber need to make a treatment decision or take action?
	What is a clinically meaningful difference in the study endpoints from the perspective of the prescriber?
	What is a meaningful difference from the patient's perspective (e.g. symptoms interfering with work or social life)?

PICOTS = population, intervention, comparison, outcome, time frame and setting

In reality, clinical research is best guided, not by definitions of study type, but by the range of features required to answer the question that forms the basis of the research hypothesis (Sackett and Wennberg, 1997). In this way, prospective studies should be seen as a continuum between the purely explanatory and the purely pragmatic, and include features of both as required (Bossie et al., 2015). The more pragmatic a study is, the more applicable the results are to routine clinical practice; each intervention that is included as part of the study design, but which would or could not be used during routine clinical practice, detracts from the applicability and generalizability of the results to usual care (March et al., 2010). In the case of LAI studies, only 13% of patients with schizophrenia have only one episode in their lifetime (Robinson et al., 2004). As such, the variability in the course of schizophrenia can limit the ability to conduct a pragmatic RCT study in this indication.

## 6. Conclusions and recommendations

The literature comparing LAI and oral antipsychotics has identified different effects of these agents in different types of trials (Kirson et al., 2013, Kishimoto et al., 2013, Kishimoto et al., 2014, Lafeuille et al., 2014), highlighting the fact that there is no single ideal clinical trial design for the assessment of new drugs in psychiatry. Both RCTs and naturalistic studies are required to answer questions of clinical efficacy and effectiveness in the range of patients generally seen during routine clinical practice. Using a combination of explanatory and pragmatic features within a clinical trial context can overcome some of the limitations inherent in both RCTs and naturalistic studies, as has been shown by the recent QUALIFY study with long-acting aripiprazole and the PRIDE trial with injectable paliperidone. The AHRQ framework for conceptualizing and developing a clinical research protocol can be a very useful starting point. Clinicians need to remember that schizophrenia is a heterogeneous condition with variability over time. Average effects achieved during

clinical trials can be a useful guide for clinicians to make treatment decisions, but it should be kept in mind that patients in real-life clinical practice may respond differently to different treatments.

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