Unanswered Questions in Schizophrenia Clinical Trials

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The treatment of schizophrenia remains an enormous challenge. Patients with this illness present with a wide variety of signs and symptoms. Response to treatment and illness course vary considerably. At the same time, we do not have the benefit of established neuropathological, neurophysiological, or neurochemical measures to inform phenotypic classification, and as a result we rely on the clinical evaluation of an array of signs and reports of subjective experience in order to establish diagnoses. The care and thoroughness with which the differential diagnostic process is carried out varies enormously from one clinical setting to another and from clinical practice to clinical research. In addition, mental health care is fragmented, and records are often poor or not readily obtainable and as a result gathering an accurate history of previous symptoms, course, treatments utilized, and response (either therapeutic or adverse) can be very difficult. Patients are not generally in a position to provide the desired historical details.

It is in this context that clinicians make day-to-day decisions as to how to treat their patients. Clinicians will rely on a number of sources of information in developing a treatment plan but will also be influenced by a variety of other factors. It is difficult to rank order these influences; however, personal training and experience, the influence of current colleagues and “institutional traditions,” pharmaceutical detailing and marketing, lectures and continuing medical education activities, journal articles (ranging from reports of individual trials to reviews and meta-analyses) published guidelines, algorithms or expert consensus reports, cost, access, patient preference, and perceived “hassles” are the most salient.

It is with this background that we wish to review the role of the clinical trial in providing appropriate influence in this process. The clinical trial is a mainstay of evidenced-based medicine. In psychiatry, we should be particularly sensitive to the need for appropriate strategies to eliminate, or reduce to the extent possible, subjectivity and bias. It is only after well-controlled studies are conducted that we can draw meaningful conclusions about a treatment’s effects. Though unreplicated trials, uncontrolled systematic descriptions, case reports, etc. can be critical in the process of developing new knowledge, the randomized clinical trial provides the most important evidence and remains the gold standard. It is also true that no single trial, no matter how large, can address the multiple questions that might be relevant in a complex disease like schizophrenia. In addition, small trials might have insufficient statistical power to allow firm conclusions, but meta-analysis has become an increasingly valuable (though not without its own pitfalls) strategy to combine results from all available trials to provide further critical knowledge on treatment effects and characteristics (see Adams, this issue).

In order to discuss the unanswered questions in schizophrenia, it is important to recognize different possibilities as to why questions are unanswered. First, it is possible that a relevant trial was never done. Second, (although less likely now) such a trial was done, but never reported or reported in a foreign language and not widely disseminated. Third, a trial was done, but inconclusive or unreplicated. Fourth, the trial though conducted and published was methodologically flawed, inadequately or inappropriately analyzed and/or reported, not readily generalizable, etc.

Another factor is the sponsor and purpose for which trials are conducted. The overwhelming majority of clinical trials in schizophrenia are sponsored by the pharmaceutical industry. Many of these trials are designed for regulatory purposes, in other words as part of the clinical drug development process required for regulatory approval to market the compound. This is a daunting task in and of itself, but a process that has specific goals and parameters. It is not required by regulatory agencies or necessarily appropriate that everything a clinician might possibly want to know about a drug or drugs will be available prior to marketing. A number of industry-sponsored studies are also conducted postmarketing, but these tend to have a focus and a rationale which might be oriented toward expanding indications, continued
safety assessment, or potential commercial advantage. Studies are also funded by foundations and governmental agencies, and these should be less influenced by the regulatory and commercial issues discussed previously. It is also important to recognize that clinical trials are expensive and there is enormous competition for federal and foundation funding for a wide variety of worthwhile investigations.

**Choice of Drug**

The clinical trial data comparing medications are often conducted by industry for regulatory purposes. In early studies, an active comparator is included to determine the “assay sensitivity” of the trial. If a new or experimental medication failed to show superiority over placebo, it might be that the new medication was ineffective or that the particular population included in the trial was unresponsive or that the placebo response was such that it was difficult to establish a drug effect (so-called “failed studies”). The presence of an active comparator along with placebo enables a more meaningful interpretation of the results. At the same time, these are often short-term trials, and there is most often only one dose of the comparator. It is very rare to conduct a study with multiple doses of the comparator as well as multiple doses of the experimental drug, but this is what would be necessary to draw clearer conclusions about the relative merits of specific compounds at various doses. Otherwise, determinations of which dose to use in a trial can be influenced by efficacy or tolerability factors, each of which might lead to different dose selection.

In postmarketing studies, there are often head-to-head comparisons, but the sponsor will often choose doses based on the goals of the study. As we will discuss subsequently, it can be difficult to identify an optimal dose even after years of trials and clinical experience given the complexities of the illness and the varying side-effect profiles of specific medications.

In recent years, there have been studies funded by sources other than the pharmaceutical industry (including multiple medications) with the hope of being able to generate data on their relative merits. It is beyond the scope of this article to review all the issues and controversies surrounding the design, conduct, and interpretation of these studies. It is safe to say that all clinical trials regardless of the sponsor have their limitations in design, execution, and generalizability. It is wrong to assume that all industry-sponsored studies are inherently biased and all nonindustry-sponsored studies manage to avoid bias. But it is fair to say that a major lesson reemphasized by these trials is that there are no clear winners when it comes to the complex evaluation and weighing of risks and benefits in choosing amongst even a multiple array of medications to treat schizophrenia. It is difficult for the experts in this area to derive clear-cut conclusions, not alone the average clinician who is bombarded with various claims, counterclaims, etc. There are many factors that will influence the choice of medication in a previously treated patient including past history (to the extent that it can be obtained), patient preference etc. In a first-episode patient, there are different contributing factors compared with a similar decision in a multiphase patient. First, there is no prior history of response to treatment (either therapeutic or adverse) to inform treatment decisions. Second, there will often be more reluctance on the part of the patient at this phase of illness to accept the diagnosis and need for treatment. Third, first-episode patients can be more sensitive to side effects, in terms of both their incidence and also their salience and impact on subsequent attitudes toward medication and adherence. Therefore, it might be particularly important to avoid adverse events in patients at this stage of treatment.

As a result, a key unanswered question is what is the optimal drug on which to start a first-episode patient? Although there are some large-scale, head-to-head comparisons of different medications, there are no clear winners. There is no obvious answer because we do not have good predictors of therapeutic response or vulnerability to adverse effects. Hopefully, pharmacogenomics will eventually provide important guidance, and early results are beginning to emerge; however, as yet there are insufficient data to make specific recommendations. But currently the choice of drug is only based on pragmatic criteria such as previous response, side-effect profiles, and patient preference.

**Optimum Dose**

When medications are developed and approved, enough information should be available to provide guidance to physicians as to how the medications should be used. As a result, studies are done exploring different dosages so that some recommendations can be made. These guidelines, though potentially based on data from studies involving hundreds of patients, are by no means definitive. If we examine the original dosage recommendations of the second-generation medications, almost all of them are not consistent with current guidelines and/or practice patterns. Even with a medication like haloperidol which was a market leader for many years, there continued to be debate about optimum dosing and the study alluded to previously which involved 3 different doses of haloperidol, 3 different doses of sertindole and placebo, represents the largest fixed dose study of haloperidol since its introduction into clinical practice several decades earlier.

During the 1970s and 1980s, there was a flurry of activity surrounding the role of antipsychotic drug blood levels in determining optimum dosing. Although significant relationships were found with many drugs, clozapine is the only one for which blood levels are
generally recommended by experts, but even then, only when there is a lack of response to an initial trial. Given the fact that there is wide interindividual variability in bioavailability and metabolism, we should ask ourselves to what extent the appropriate use of blood levels could enhance overall effectiveness. Or even should guidance be provided as to what extent body weight could influence milligram dosage?

Many pharmaceutical companies would like to suggest that dosing is relatively simple and will try to identify a specific dose that can be recommended for the “average” patient. This can easily lead to less thoughtfulness than might be desired in establishing an appropriate starting dose for a given individual. In addition, patients at different phases of illness might have different dosage requirements. For example, first-episode patients generally respond to lower doses than more chronic patients.

There is rarely any systematic attempt to elucidate when and if changing the dose is appropriate. In order to determine, for example, if raising the dose is a useful strategy, studies need to be done controlling for the passage of time by having one group randomly assigned to stay on the original dose and another assigned to a higher dose. If one wishes to establish the value of blood levels, the first step is to correlate blood levels in a fixed dose trial with clinical response measures. However, an important validation trial (which is rarely done) would be to prospectively treat a cohort of patients, determine who among the nonresponders had blood levels out of the putative therapeutic range, and then randomly assign them to either continue on the original dose or have the dosage changed to produce a blood level within the therapeutic range. Issues such as adherence and duration of the trial are also important considerations. The focus in most industry-sponsored trials is initial response and tolerability. There is far less attention given to what to do if response is inadequate. The use of these 2 terms “response” and “inadequate” also raise important issues in exploring what clinicians need to know.

How Should Clinicians Measure Response?

Response in many clinical trials is defined by a percent improvement over baseline and is highly dependent on baseline severity and not necessarily meaningful to practicing clinicians. (These issues are discussed in more detail by Leucht et al.)

The most meaningful response measure should be remission of signs and symptoms. Considerable debate could revolve around the definition of remission. An expert panel has recommended that 8 positive and negative symptoms only be present to a mild or less degree concurrently for 6 months in order for a patient to be considered in remission. The severity component of that definition is probably a more meaningful target, even during short-term treatment, than a specific percent improvement (though they are not mutually exclusive). Estimates suggest that approximately one-third of patients can achieve this low level of symptomatology within 4–6 weeks of acute treatment. Clinical trials need to provide more meaningful measures of response than percent improvement or the difference in change scores on a rating scale between drug and placebo. These measures have little meaning for clinicians. There have been some attempts to equate rating scale scores with changes in clinical global impressions, which is more analogous to how clinicians think about improvement in clinical practice.

It is also important to recognize that the measurements currently employed in clinical trials are not necessarily ideal. Negative signs and symptoms for example remain an enormous unmet treatment need, yet the instruments to assess negative symptoms would benefit from further development and validation. Measures of agitation in clinical trials have generally been tested on only mildly or moderately agitated patients because those with severe agitation are unlikely to participate in a trial requiring informed consent. The field would also benefit from better measurement of the patient’s experience and point of view.

Another problem that needs to be addressed in this context is the lack of quantitative measures in routine clinical practice. Psychiatric treatment does not have the availability of laboratory tests or physiologic measures to guide the evaluation of treatment effects. In our clinical practice, we generally rely on our subjective assessment of a patient’s behavior coupled with information gleaned from the patient’s self-report of his/her own subjective experience. Unfortunately, the assessment and tracking of these phenomena are usually conducted in a less than systematic and reliable fashion. The use of some quantitative assessments in clinical practice would be a valuable step in facilitating more measurement-based decision making. This issue becomes particularly relevant in discussing the next question.

How Long Should a Trial of an Antipsychotic be Before it is Viewed as Ineffective?

An important question facing clinicians every day is how long to wait if a newly hospitalized or acutely relapsed patient is not responding. The findings from clinical trials sponsored by industry and the large practical trials sponsored by governmental agencies provide no relevant data. There are some guidelines, algorithms, and expert consensus panels that provide recommendations, but they are not data driven. The American Psychiatric Association Practice Guidelines for the Treatment of Patients with Schizophrenia states that “an initial trial of 4–6 weeks generally is needed to determine if the patient will have any symptomatic response.” Does this mean...
that clinicians should wait 4 weeks if they see no initial response before changing the treatment? The Texas Medication Algorithm project provides recommendations for various stages of treatment, but no real guidance as to how long a trial is recommended at each stage. The Schizophrenia Patients Outcomes Research Team Guidelines provide no statement as to the duration of an adequate trial except in the case of clozapine (8 weeks). The UK National Health Service National Institute for Clinical Excellence Clinical Guideline 1 Schizophrenia recommends a minimum of 6 weeks. The Expert Consensus Guideline Series in Optimizing Pharmacologic Treatment of Psychotic Disorders suggest waiting a minimum of 3 weeks and a maximum of 6 weeks before making a major change in treatment regimen.

There is remarkably little guidance from clinical trials to inform routine practice in this regard. In the real world there is enormous pressure to reduce length of hospital stay and to justify continued hospitalization based on “aggressive treatment.” This has led to clinicians changing treatment regimens very quickly, raising doses to high levels, adding other medications (antipsychotic and/or mood stabilizers), or switching from one antipsychotic to another.

In order for clinical trials to be informative on this issue, it is important to have appropriate control groups. Switching from one drug to another, polypharmacy, or raising the dose need to be compared in a randomly assigned design to a control group staying on the original treatment.

Guidance regarding the length of an adequate trial also should be informed by what is intended. Is the trial duration that which is expected to bring about “initial” response, “clinically meaningful” response, or full possible response? Clearly, different time frames and designs would be required to address these issues.

To some extent, the recommendations regarding duration of an adequate trial are influenced by early notions that it took several weeks for antipsychotic drugs to begin to show clinically meaningful antipsychotic activity, in other words a delayed onset of effect. Recent data have called into question this concept and have led to a rediscovery of older data, which also suggested earlier response.

Agid et al reported the results of an extensive meta-analysis, suggesting that the greatest proportion of ultimate acute antipsychotic response occurs within the first 2 weeks. Leucht et al replicated this finding utilizing individual patient data from several multicenter trials. These investigators also found that symptom reduction in both total scores and psychotic subscales were greater in weeks 1 and 2 than in weeks 3 and 4. May et al suggested that the degree of early response (or lack thereof) might be predictive of subsequent response; however, these data had little impact on clinical practice. More recently, this topic has received renewed attention. Correll et al reported on data from a trial involving newly admitted patients with schizophrenia spectrum disorders treated with 20 mg of fluphenazine for 4 weeks. Employing a 20% improvement in brief psychiatric rating scale total scores at 1 week, they reported high specificity (100%) for prediction. Those who showed minimal response at 4 weeks (<20% improvement) were all classified as nonresponders after 1 week. However, sensitivity was low with only 35% of patients who were responders at week 4 meeting response criteria at week 1. These data suggest that those individuals who are unlikely to respond to a particular antipsychotic might be identified sooner than waiting several weeks.

Chang et al applied a different statistical approach combining patterns of response in the first 2 weeks of treatment to predict response (and nonresponse) at weeks 4 and 6. They reported both high sensitivity (80%) and high specificity (83%). Leucht et al analyzed a large data set of 1708 patients and reported that those individuals who showed no improvement in symptoms or worsened during the first 2 weeks of treatment were unlikely to respond at 4 weeks and suggested that they might benefit from a change in treatment.

Kinon et al have also reported relevant data. They analyzed data from 5 randomized, double-blind trials comparing olanzapine with other atypical antipsychotics. One thousand and seventy-seven subjects were included in the data set. Early response was defined as equal to or greater than 20% improvement on the positive and negative syndrome scale (PANSS) scale at 2 weeks. Ultimate response was defined as ≥40% improvement in the PANSS total after up to 3 months of treatment. Eighty percent of subsequent nonresponders by 3 months were classified correctly as early nonresponders at 2 weeks (high specificity), and 84% of early nonresponders at 2 weeks were subsequent nonresponders at the end of the trial (high negative predictive value).

Collectively, these data suggest that early response could be a valuable predictor and that waiting 2–4 weeks to see an initial response or considering an adequate trial to be up to 6 weeks are not necessarily clinically appropriate. Clinical trials are needed to further test this hypothesis and determine what alternative treatment strategies are most likely to be effective for patients identified as probable nonresponders to the initial treatment. Here again appropriate controls are necessary with random assignment to alternative treatments or staying on the original treatment.

Once an optimum alternative is established by conducting appropriate trials, the next question will be what to do if that fails. The medication with the greatest likelihood of being efficacious when other drugs have failed is clozapine. Both the CATIE and the CUlLASS 2 trials again demonstrated superiority for clozapine over alternative medications; however, clozapine continues to be markedly underutilized in routine clinical practice.
What Medications Are Most Effective in Treating Severe Agitation?

This question arises in emergency rooms and acute care hospitals every day, yet methodologically appropriate trials are generally lacking. Those patients who are most agitated or even violent are not likely to sign consent to participate in a randomized trial; therefore, most of the data that are available involve patients with mild to moderate agitation. Short-acting intramuscular antipsychotics and or benzodiazepines are frequently used; however, debate remains as to which specific antipsychotic or even class of antipsychotic is most effective.

The TREC studies are an example of how such clinical trials might be done. Large numbers of patients in real world settings were included because institutional review boards allowed family members to provide informed consent.

How Many Treatments Should be Tried Before Initiating a Trial of Clozapine in Treatment Refractory or Poorly Responsive Patients?

Here as well, we do not have a clinical trial database to inform this decision. Guidelines generally recommend trials of at least 2 other agents before going to clozapine. In order to address this question, prospective random assignment comparisons would need to be conducted. In other words, patients who failed a first trial would be randomly assigned to stay on the original treatment, switch to clozapine, or switch to another agent considered to be the second best choice. At the same time, it is not primarily the lack of such data that explains the underutilization of clozapine. There are still large numbers of patients who have failed trials of multiple other medications who are not offered a trial of clozapine. This is largely due to physician reluctance, anxiety, and the perceived added burden associated with clozapine use. Although there is progress in identifying genetic risk factors for clozapine-induced agranulocytosis, the data are still insufficient to allow any reduction in blood monitoring.

Is Polypharmacy Helpful?

A substantial proportion of patients are receiving multiple antipsychotics or combinations of antipsychotic and mood stabilizers. Unfortunately, despite a number of clinical trials in this area, it is difficult to draw meaningful conclusions. The meta-analyses that have been conducted did not strongly support the efficacy of these agents (e.g., on benzodiazepines, beta-blockers, carbamazepine, electroconvulsive therapy, lithium); however, this does not mean that some patients would not derive benefit. The problem currently is that the degree of polypharmacy being practiced seems far in excess of the supporting data. (Polypharmacy is being employed to mitigate adverse effects as well, and this issue requires specific trials with appropriate designs.)

What is the Appropriate Duration of Maintenance Treatment in First-Episode Patients?

The placebo-controlled maintenance treatment trials in first-episode patients have all involved conventional antipsychotics, and none has lasted longer than 2 years. The reported rates of relapse vary considerably among the studies. Relapse rates on active medication versus placebo were 0% vs 41%, 46% vs 62%, 0% vs 57%, and 43% vs 64%. As with more chronic patients, all these studies show significant superiority for active medication over placebo; however, some studies are relatively small, so the confidence intervals around the estimates can be large. In addition, criteria for entry in terms of the level and duration of remission or stability vary as do the definitions of relapse. Clearly, not all patients on placebo relapse, and the question remains as to how long should a first-episode patient stay on medication?

Naturalistic studies generally find relapse rates in the 70%–80% range within 5 years. Robinson et al. reported data suggesting that most subjects experienced multiple relapses during the first years of illness. By 5 years of follow-up, 82% of subjects had experienced 1 relapse, 78% of those who recovered from their first relapse had a second, and 86% of those who recovered from their second had a third. A survival analysis using medication status as a covariate indicated that those patients who discontinued medication had a relapse rate 5 times higher than those who continued medication.

Although there have been efforts to study so-called targeted, intermittent or guided discontinuation, the results suggest that this is a feasible strategy only for the small minority of patients. Without reliable predictors to identify suitable candidates, there is the risk of allowing numerous preventable relapses to occur with potentially significant sequelae.

Despite the data reviewed here and elsewhere, most guidelines are rather ambiguous in their recommendations for maintenance treatment for longer than 1 or 2 years following recovery from a first episode.

Can and How Much Should Antipsychotic Dose be Reduced in the Maintenance Phase of Treatment?

Because of the risk of neurologic side effects, particularly tardive dyskinesia, a series of studies were conducted to attempt to identify minimum dosage requirements for maintenance treatment with the conventional antipsychotics. Interestingly, most of these studies involved long-acting injectable antipsychotics, and as a result we have much more information regarding dose–response relationships for relapse prevention with these formulations than we do with oral medications. This makes
sense because potential nonadherence would severely compromise the ability to establish dose–response/relapse relationships in long-term treatment. There are hardly any data with the second-generation medications addressing this issue. This might be due to the fact that these drugs were initially perceived to be better tolerated; therefore, there was less of an apparent need to establish minimum effective dosage. The extent to which metabolic side effects are dose related should be considered, and even though the newer medication appears to have a lower risk of tardive dyskinesia, the risk is not absent and might be dose related. For both metabolic adverse events and neurologic adverse events, pharmacogenomics might help to identify at-risk individuals for whom special efforts at prevention could be implemented.

To What Extent Can Long-Acting Injectable Medication Reduce Rates of Relapse and Rehospitalization Compared to Usual Care?

Numerous random assignment, double-blind trials have been conducted comparing long-acting injectable medication to oral medication; however, the generalizability of these results remain an issue. First, to what extent are nonadherent patients or those at high risk for nonadherence likely to participate in controlled trials? This question is even more relevant when "double dummy" medication designs are employed (ie, participants have to receive both injections and oral medication, one of which is a placebo), placing even more burden on a reluctant participant. Second, is the relatively short (1 year or less) duration of most trials comparing oral and depot medication given the likely duration of maintenance treatment.

If one assumes for the moment that such studies might be biased in favor of including relatively more adherent (at least currently) subjects, and tries to model the time course of the subsequent development of nonadherence and the time course of the potential consequent relapse, one can appreciate that a 6- to 12-month time frame is likely to underestimate the potential difference. Interestingly, the one such study reported to date which lasted 2 years reported no difference between oral and depot medication in the first year but apparent separation in the second year (though not statistically significant due to small sample size).

This is clearly an area where large effectiveness trials are needed. As of now clinicians (especially in the United States) are reluctant to use long-acting injectable medication and, if they use them at all, it is only after several relapses have been attributed to nonadherence. Ideally, trials would be conducted in relatively early phase illness where the potential impact of more successful relapse prevention on psychosocial functioning, family burdens, and pharmacoeconomic parameters might be more informative.

How Should Patients Who Relapse Despite Adequate Dosages and Adherence to Medication be Treated?

There are remarkably few data to address this question. We are only aware of a small pilot study (n = 32) that found no difference between adding fluphenazine or placebo to drug treatment. First, the issue of relapse despite adherence is a difficult one to evaluate with certainty. Unless someone is taking a long-acting injection, it is often impossible to be certain that nonadherence was involved. But among patients receiving long-acting injectable medications, there has never been a clinical trial to address what to do when a relapse occurs. Should the dosage be raised or would a different medication be more effective? Or is this a psychosocial phenomenon or stress reaction that needs to be managed in a nonpharmacologic fashion? Unfortunately, we know remarkably little about the cascade of events leading to a psychotic relapse.

What is the Best Way to Manage Sleep Abnormalities in Schizophrenia?

Insomnia, excessive sleepiness, and lack of energy are common symptoms in schizophrenia. Sleep-onset insomnia and maintenance insomnia are problems in both medicated and never-medicated patients with this illness. A meta-analysis of sleep architecture studies in individuals suffering from schizophrenia found reduced duration of stage 4 sleep and reduced rapid eye movement (REM) latency although duration of REM sleep was not abnormal. These abnormalities appear to be associated with the illness itself and not a particular phase or treatment status. (However, sleep problems, particularly insomnia, are often seen as part of the prodrome of a psychotic exacerbation.)

Patients with schizophrenia are often treated with sedating antipsychotics or sedative hypnotics in response to sleep complaints; however, the evaluation of the underlying sleep dysfunction is often cursory at best. There are few trials that provide guidance on evaluating and managing sleep in schizophrenia patients. The extent to which medications intended to facilitate sleep are necessary, helpful, or even detrimental is far from clear.

How Best Should Negative Symptoms be Treated?

Although some atypical antipsychotic medications have demonstrated advantages for negative symptoms in some clinical trials, the results are often difficult to interpret because of the potential confounds of concurrent positive symptoms, neuromotor adverse effects, depression, and demoralization. Very few trials have been conducted utilizing strategies that attempt to identify true primary negative or deficit symptoms. Many clinical trials have attempted to simultaneously assess treatment effects in a variety of domains (positive, negative, and cognitive symptoms); however, each one of these domains often
requires specific design features to increase the likelihood of finding reliable and valid treatment effects. Apart from antipsychotic drugs, antidepressants are often used in clinical practice to alleviate negative symptoms. Statistically significant, but not robust, evidence exists that this strategy may be effective.\(^5\)

**Challenges in the Conduct of Clinical Trials**

We have been focusing largely on a series of unanswered questions that need to be addressed in the treatment of schizophrenia. It is also important to recognize the obstacles and challenges in the conduct of high-quality clinical trials. Recruiting appropriate subjects is an enormous challenge. Many potentially eligible subjects are not interested in or willing to participate in clinical research. Numerous settings where patients are treated are not involved in clinical research and do not have the personnel or infrastructure to carry out clinical trials. Because participating sites are most often reimburshed on a per patient basis, there can be misaligned incentives in terms of rigorously adhering to entry criteria (both inclusion and exclusion). For example, if patients are required to have a minimum level of psychopathology as measured by a particular rating scale, raters might consciously or unconsciously inflate item scores to provide an eligible patient. True interrater reliability is rarely achieved in multicenter trials. At best, a few videotapes might be assessed to determine if raters agree with a gold standard; however, this provides no evidence that different raters would conduct the interview in an appropriate fashion, as well as elicit and reliably rate the same elements of psychopathology. The poorer the interrater reliability, the more subjects are needed to demonstrate a specific effect. This can be a particularly important challenge in areas where interrater reliability is even more difficult to achieve, such as negative symptoms. Raters might utilize adverse effects to provide clues as to what treatment the patient is receiving and also might be prone to varying degrees of expectancy bias based on their knowledge of the design of the trial.

Enormous variation in the degree of improvement on placebo is evident even in schizophrenia trials, and this can complicate the detection of a drug effect. Many of these issues have been much more widely studied in depression and anxiety disorders\(^3\) than in schizophrenia, but the failed trials (where proven efficacious medications fail to demonstrate superiority over placebo) are also not unusual in schizophrenia. The challenges of conducting trials in the United States has led to more and more clinical investigation being conducted overseas.

**Conclusions**

We have tried to highlight a series of important and frequent clinical decisions that must be made without the benefit of a systematic evidence base. Attempts to better address these issues are sorely needed and could help to significantly improve the effectiveness of treatment in schizophrenia. The challenge is for the field to develop better mechanisms to facilitate the design and conduct of relevant clinical trials.

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