Clinical Development of Atypical Antipsychotics: Research Design and Evaluation

Collaborative Working Group on Clinical Trial Evaluations

Clinical trials support the efficacy and safety of new drugs on the market. They provide the United States Food and Drug Administration with the information needed to approve an Investigational New Drug application and are the basis for package inserts provided by the manufacturers that guide clinicians in the use of a new drug. Because clinical trials are vital to the effective and safe use of new drugs, it is important to understand who participates in them, what questions are answered by clinical trials, and what questions are raised. The reader who asks the proper questions about issues such as methodology, affiliations of the investigators, statistical analyses performed, location of study centers, and study populations will derive the most information from the report of a clinical trial.

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Clinical trials are the means by which information is gathered to support the approval of a new drug by the United States Food and Drug Administration (FDA). Once the drug is approved, clinical trials data are disseminated, via package inserts, to clinicians who will use the drug with patients in everyday clinical practice. Because clinical trials are vital to the effective and safe use of new drugs, it is important to understand what issues are raised by these trials, who participates in them, and what questions the trials answer.

Before an Investigational New Drug application has been entered by the manufacturer of a new drug in the United States, clinical trials are conducted to test the agent's efficacy and safety. There are 4 phases in clinical testing. In phase 1, a drug is tested on a small number—usually 20 to 100—of healthy volunteers. Researchers, in this phase, examine the tolerability and pharmacokinetics of the drug. Phase 2 involves the study of efficacy and identifies a general dose range; a larger patient population, up to several hundred patients, may be used in this phase. Phase 3 trials can study populations ranging in size from several hundred to several thousand. Adverse effects and dosages are evaluated. This phase also generates much of the information that will be included in the package insert of a drug. Information relevant to the risk:benefit ratio of the drug under investigation is developed. Most Phase 3 studies are industry-supported. The authors are often academics, and sometimes the authors are employees of a pharmaceutical company. Arvanitis,[1] Beasley,[2–4] Tran,[5] and Tollefson,[6] for example, are all employed by the companies manufacturing the drugs that were evaluated in trials they conducted of atypical antipsychotics. Kane,[7,8] Small,[9] Peuskens,[10] and Peuskens and Link[11] are among those authors employed by hospitals, whether independent or affiliated with a medical school. Phase 4 studies are conducted after the drug has been approved by the FDA and marketed. This phase examines the performance of the drug in special populations or considers new applications for the drug.[12]

Table 1[1–11,13–17] compares methods and results from studies that examined atypical antipsychotics. The head-to-head comparison of clinical trial results is not necessarily straightforward. Studies that use several dose ranges of the trial drug, for example, may use a single dose range of the comparator drug, which may be less than optimal. An equal number of groups and dose ranges for both drugs is more valid. Dosing and other issues are important to consider when comparing trial data.

INTERNATIONAL REGULATORY DIFFERENCES

Clinical trials are becoming increasingly international in scope, due in part to the necessity of bridging the varying requirements of European and United States regulatory agencies. Although the differences in diagnostic criteria between the United States and Europe are largely

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Table 1. Core Clinical Studies of Atypical Antipsychotics*

Study	N	Drug	Dose (mg/d)	Design	Duration	Assessment	Results
Kane et al.[7]	268	Clozapine Chlorpromazine	≥ 900 ≥ 1800	Flexible-dose	6 wk	BPRS, NOSIE, CGI-S	Clozapine > chlorpromazine
Kane et al.[8]	319	Clozapine Chlorpromazine	≥ 900 ≥ 1800	Flexible-dose	6 wk	BPRS, CGI-S	Clozapine > chlorpromazine
Marder & Meibach[15]	388	Risperidone Haloperidol	2, 6, 10, 16 20	Fixed-dose, placebo-control	8 wk	PANSS	6, 16 mg/d risperidone > placebo or haloperidol
Chouinard et al.[14]	135	Risperidone Haloperidol	2, 6, 10, 16 20	Fixed-dose, placebo-control	8 wk	PANSS, CGI	Risperidone ≥ haloperidol, > placebo; optimum risperidone dose = 6 mg/d
Peuskens et al.[10]	1362	Risperidone Haloperidol	1, 4, 8, 12, 16 10	Fixed-dose	8 wk	PANSS	4, 8, 12, 16 mg/d risperidone, haloperidol > 1 mg/d risperidone; optimum risperidone dose = 4 or 8 mg/d
Beasley et al.[2]	152	Olanzapine	1, 10	Fixed-dose, placebo-control	6 wk	BPRS, PANSS	10 mg/d olanzapine > placebo
Beasley et al.[3]	431	Olanzapine Olanzapine Olanzapine Olanzapine Haloperidol	1 5 ± 2.5 10 ± 2.5 15 ± 2.5 15 ± 5	Flexible-dose	6 wk	CGI-S, BPRS, PANSS	Olanzapine > 1 mg/d olanzapine, increasing dose-response curve
Beasley et al.[4]	335	Olanzapine Olanzapine Olanzapine Haloperidol	5 ± 2.5 10 ± 2.5 15 ± 2.5 15 ± 5	Flexible-dose, placebo-control	6 wk	BPRS	Olanzapine ≥ haloperidol; olanzapine, haloperidol > placebo
Tollefson et al.[6]	1996	Olanzapine Haloperidol	5–20 5–20	Flexible-dose	6 wk	BPRS, PANSS	Olanzapine > haloperidol
Tran et al.[5]	339	Olanzapine Risperidone	10–20 4–12	Flexible-dose	28 wk	PANSS, BPRS, SANS, CGI-S	Olanzapine = risperidone, SANS: olanzapine > risperidone
Arvanitis et al.[1]	361	Quetiapine Haloperidol	75, 150, 300, 600, 750 12	Fixed-dose, placebo-control	6 wk	BPRS, CGI, SANS	150–750 mg/d quetiapine > placebo, = haloperidol
Borison et al.[13]	109	Quetiapine	75–750	Flexible-dose placebo-control	6 wk	BPRS, CGI-S	Quetiapine > placebo
Peuskens & Link[11]	201	Quetiapine Chlorpromazine	50–750 100–750	Flexible-dose	6 wk	BPRS, CGI-S	Quetiapine ≥ chlorpromazine
Small et al.[9]	286	Quetiapine	≤ 250, ≤ 750	Flexible-dose, placebo-control	6 wk	BPRS, CGI-S	Quetiapine > placebo, optimum dose > 250 quetiapine
van Kammen et al.[16]	205	Sertindole	8, 12, 20	Fixed-dose, placebo-control	40 d	PANSS, BPRS, CGI	20 mg/d sertindole > placebo
Zimbroff et al.[17]	497	Sertindole Haloperidol	12, 20, 24 4, 8, 16	Fixed-dose, placebo-control	8 wk	PANSS, SANS, BPRS, CGI	Sertindole = haloperidol, > placebo

*Abbreviations: BPRS = Brief Psychiatric Rating Scale; NOSIE = Nurses' Observation Scale for Inpatient Evaluation; CGI = Clinical Global Impressions scale; CGI–S = Clinical Global Impressions–Severity of Illness scale; PANSS = Positive and Negative Syndrome Scale.

disappearing, discrepancies remain. For example, France has its own set of diagnostic criteria, distinct from that of other European countries. The stringent regulatory atmosphere of the United States and of the United Kingdom is reflected in the relatively low drug recall rates in these countries (3% and 4% respectively).[18]

Regulatory differences may influence such decisions as what is used as the comparator drug in a clinical trial. While a United States manufacturer must prove only that a drug for which it seeks approval is safe and effective, in European countries and Australia, the drug must be demonstrably cost-effective in order to gain the approval of pricing authorities.[19] Standards regarding what constitutes superiority differ from country to country. In such an atmosphere, the choice of the comparator drug is hardly straightforward.

Differences among countries in attitudes and expectations can also be informative. When different fixed doses are used in studies, the conclusions reached by the investigators concerning adequate dose may vary. Also, fixed-dose studies may not truly reflect the clinical situation, leading to subsequent changes in the adequate dose recommendation. In the risperidone trials, for example, North American researchers—Marder and Meibach[15] and Chouinard et al.[14]—used placebo as the comparator, as required by the FDA. In the European study, Peuskens et al.[10] chose to use 1 mg/day of risperidone as an anchor instead of placebo, mostly because of regulatory differences in the participating countries.

Marder and Meibach[15] evaluated risperidone versus haloperidol and placebo in 388 schizophrenic patients. This study examined the efficacy of risperidone at dosages of 2, 6, 10, and 16 mg/day. Clinical improvement, defined as a 20% reduction on the Positive and Negative Syndrome Scale (PANSS), was shown in 35% of patients taking 2 mg/day of risperidone, 57% of patients taking 6 mg/day of risperidone, 40% of patients taking 10 mg/day of risperidone, 51% of patients taking 16 mg/day of risperidone,

30% of patients taking 20 mg/day of haloperidol, and 22% of those taking placebo. Negative symptoms were reduced significantly only in patients taking 6 ($p < .001$) or 16 ($p < .001$) mg/day of risperidone. The incidence of extrapyramidal symptoms (EPS) increased with the risperidone dose. EPS were significantly higher ($p < .05$) in patients treated with 16 mg/day of risperidone, compared with those taking a placebo, while patients taking 6 mg/day of risperidone experienced EPS at a rate no higher than patients taking a placebo. The investigators concluded that 6 mg/day of risperidone was the optimal dose because it was effective against both positive and negative symptoms and had a low incidence of EPS.

In the Canadian arm of the study, which used the same fixed doses, Chouinard et al.[14] also found 6 mg/day of risperidone to be optimal. Risperidone was superior to haloperidol and placebo in the treatment of positive symptoms in a controlled, double-blind study evaluating the responses of 135 patients. The authors noted that patients treated with 6 mg/day of risperidone evinced significant improvement in both positive and negative symptoms without an increase in EPS.

However, in the international study, a lower dose of risperidone was reported to be effective, probably because lower doses were tested. Peuskens et al.[10] conducted a double-blind trial to evaluate the safety and efficacy of 1, 4, 8, 12, and 16 mg/day of risperidone compared with 10 mg/day of haloperidol. In this 8-week study, response was defined as a 20% reduction in the PANSS score. Response rates were 63.4% and 65.8% respectively for patients taking 4 and 8 mg/day of risperidone; 58.7% of patients taking haloperidol were responders. The authors noted that patients taking doses of 4 or 8 mg/day of risperidone had a lower incidence of side effects than patients taking haloperidol and suggested 4 to 8 mg/day as the optimum dose of risperidone.

The results of fixed-dose studies sometimes fail to be reflected in clinical practice. The Marder and Meibach[15] and Chouinard et al.[14] findings were reflected in the package inserts for risperidone. But, as the use of risperidone increased in the United States, many treating physicians observed that patients often responded to extremely low doses of risperidone. Thus, as a result of both the international trial and clinical experience, risperidone package inserts in the United States have recently been changed to reflect a lower recommended dosage, down from 4 to 6 mg/day[20] to 1 to 2 mg/day.[21] In addition, risperidone was approved in October 1997 for once-a-day dosing. This change in dosage points out the need both for long-term studies to complement the initial short-term studies of a drug and for testing low dosages in clinical trials. Judgments about effective dosage levels change over time and with clinical experience; the proper maintenance dose for a drug may not become apparent during short-term studies. Patients are more likely to discontinue taking medication during the long term, not during the first few weeks of a treatment phase.

METHODOLOGY

Examining the methodology of a clinical study will make some questions easier to answer and some harder. The design of a study focuses the researchers' attention. Each potential design has advantages and drawbacks. Methodology will identify, for example, inclusion and exclusion criteria for the study population, outcome measures, and statistical analyses and their rationale.

Study Population

Schreiber et al.[22] looked at patients who had been selected from referrals for subsequent admission to a National Institute of Mental Health clinical research unit. Of 399 patients selected from referrals received between February 1983 and December 1986, only 53 (13.3%) were ultimately admitted to the unit. Patients were excluded for behavioral reasons (substance abuse or destructive behaviors) as well as for medical problems, diagnostic uncertainties, and age. Trials regularly exclude patients who are substance abusers or who are or might become pregnant. In addition, comorbid medical conditions may exclude otherwise viable candidates who require medication for these conditions. A pool of 100 potential subjects may yield only 2 or 3 qualified participants, a fact that raises the issue of generalizability of results.

The issue of selecting clinical trial populations presents a host of other questions. Dosage recommendations derived from trial results may differ from clinical practice depending on the characteristics of the trial population. Kane et al.,[7] for example, studied a population that was 80% male, possibly due to the disproportionate representation of Veterans Administration medical centers among participating institutions. The typical patient in this group was a 35-year-old man with chronic schizophrenia who had been previously treated with neuroleptics. As the number of atypical antipsychotics introduced into the marketplace grows, it becomes increasingly likely that a subject who enrolls in a clinical trial of a new atypical antipsychotic will have failed to respond to trials of some of the earlier drugs. A subject who responds to a drug and is doing well on that drug will generally not enroll in the subsequent trial of a similar drug. A chronic nonresponder who has failed 3 previous trials of atypical antipsychotics may not respond to the trial of a new antipsychotic, while a neuroleptic-naive subject may respond well. It is becoming ever more difficult to find neuroleptic-naive subjects in this country, though international studies offer opportunities unavailable to the researcher who confines study populations to the United States. Many subjects in phase 3 studies are patients who have not done well on previous treatments, again posing questions of generalizability.

In phase 3 trials, the study population is randomly assigned to a treatment group, and neither the physicians nor the patients know to which treatment group a particular patient has been assigned (called a "double-blind" study). The study drug is compared with either placebo or a "gold standard," a drug with long-established efficacy. On the positive side, the randomized control trial eliminates a number of potential biases. Randomization minimizes baseline variability, and blindness controls bias in patients' and raters' evaluations of outcome. In addition, blindness controls bias in how the treatment is administered. On the negative side, the subject pool is limited by nature to patients who are eligible for and agree to participate in a double-blind clinical trial. Further, randomization usually means that the patients are assigned to a drug or dosage group with no consideration of prior history. Finally, patients who might benefit from an adjunctive medication such as a mood stabilizer may not receive it during the trial, so even if they are eligible, they might not enroll.

Phase 4 studies are often open-label trials, in which both the physician and patient know what treatment is being used. An open-label trial is subject to the biases of both patient and clinician. The belief that one drug works better than others will affect how a patient reports subjective progress and how a clinician evaluates that progress (or lack of it). The nature of an uncontrolled trial skews the results: only responders will be reported, as nonresponders will depart the study quickly. Generalizing from open studies can be difficult; many environmental factors can neither be identified nor controlled.

Comparator

Traditionally, clinical studies have been placebo-controlled, but today there are ethical objections to such controls, although even those who raise ethical objections to placebo-controlled studies acknowledge their usefulness. Many of the atypical antipsychotic studies included a placebo-control arm (i.e., Marder and Meibach,[15] Chouinard et al.,[14] Beasley et al.,[2,4] Arvanitis et al.,[1] Borison et al.,[13] Small et al.,[9] van Kammen et al.,[16] and Zimbroff et al.[17]).

Using another drug as the comparator introduces new problems. Haloperidol, for example, has been the comparator in many clinical trials of atypical antipsychotics.[1,3,4,6,10,14,15,17] Because of its well-known side effects, though, it is difficult to find subjects to participate in a long-term study that may require them to use haloperidol. Kane et al.[7] chose to use chlorpromazine over haloperidol in the double-blind phase of their study of clozapine because when chlorpromazine is combined with prophylactic antiparkinson medication, its adverse effect profile is similar to that of clozapine. The atypical antipsychotics may soon become the gold standards as comparators because of their widespread use and attractiveness to patients.

Another methodological issue is choosing the proper dosage of the comparator drug to administer to trial subjects. In 1990, Van Putten et al.[23] reported 20 mg/day of haloperidol to be slightly superior to 5 or 10 mg/day during the first 2 weeks of treatment but not superior afterwards. By the end of the 4-week study, 35% of patients taking 20 mg/day left the hospital against medical advice, versus 4% of patients taking 5 or 10 mg/day of haloperidol. Various researchers since Van Putten et al. have interpreted these findings differently. Lower doses are generally used in Europe and higher doses in North America. Beasley et al.[4] acknowledged the role of Van Putten et al. in establishing the optimal dose of haloperidol, reporting that patients in their study were stabilized on a median haloperidol dose of 15 mg/day. The European risperidone trial[10] used 10 mg/day of haloperidol as the comparator, while the North American researchers[14,15] selected 20 mg/day of haloperidol, which they believed would be more efficacious. Using higher than adequate doses of the comparator drug may bias the study in favor of the new drug.

Dosage and Titration

When comparing 2 drugs in a clinical trial, it is important to remember that response rates of each drug may vary depending on dose; a reported improvement at one dosage level may not be present at other dosage levels. Conversely, results reported for a group taking higher than adequate doses of a drug may obscure significant improvement at an adequate dose level. Rapid dose titration may also show response in favor of one drug. In addition, a brief study duration may distort the comparison.

For example, in a multinational study comparing risperidone and olanzapine, Tran et al.[5] used risperidone doses and a titration schedule that would be considered inappropriate today, although the dosing of risperidone was consistent then with manufacturer-provided labeling. On day 1, patients received 1 mg of risperidone b.i.d. On day 2, patients received 2 mg of risperidone b.i.d. On day 3, patients received 3 mg of risperidone b.i.d. From week 2 to the end of the study, dosage increases of 1 mg b.i.d. were allowed after 7 days at the previous dose; the minimum risperidone dose was 4 mg/day and the maximum dose 12 mg/day. The starting dosage of olanzapine was, however, higher than the 10 mg/day dose recommended by the manufacturer at the time of the study.[20] On day 1 through day 7, patients took 15 mg/day of olanzapine. From week 2 until the end of the study, the dose could be adjusted upward or downward by 5 mg every 7 days. Tran et al. defined the mean modal dose as the most frequently administered daily dose, as determined by the investigator on the basis of optimal patient course. At week 8, the mean modal daily dose of risperidone was 7.3 ± 2.5 mg; at week 28 it was 7.2 ± 2.7 mg. For olanzapine, the mean modal dose at week 8 was 17.0 ± 3.5 mg; at week 28, it was 17.2 ± 3.6 mg.

At week 28, patients taking olanzapine evinced greater improvement (as measured by PANSS total score) than did patients taking risperidone. Of those patients showing improvements greater than or equal to 50%, twice as many were taking olanzapine as were taking risperidone. In fact, only among patients demonstrating improvement greater than or equal to 20% was the number of patients taking risperidone greater than the number of those taking olanzapine. The rapid dose titration and the higher doses of risperidone than are normally used today may have led to discontinuation and hospitalization in some patients. The higher incidence of EPS among patients taking risperidone may have been a reflection of the higher doses than recommended now.

Another issue in the methodology of clinical trials is the use of flexible versus fixed doses. Fixed- and flexible-dose studies answer different questions, but each has advantages and disadvantages. In the studies under consideration here, 3 of 4 olanzapine studies,[3,4,6] the clozapine studies,[7,8] and 3 of 4 quetiapine studies[9,11,13] employed flexible dosing; key studies examining risperidone[10,14,15] and sertindole[16,17] used fixed dosages. Fixed dosing allows for more precise comparisons of specific doses of a drug. Flexible dosing—upward or downward titration of the dosage until the patient responds or adverse events disappear—produces results that are harder to generalize, since each dosage has been tailored to a specific individual. Small et al.[9] conducted a flexible-dosage study of quetiapine. In their comments, they noted that a fixed dosing schedule might have furnished a better comparison of the 250-mg low dose and the 750-mg high dose of quetiapine. On the other side, one might argue that flexible-dosing studies reflect clinical practice and ethical considerations more accurately than do fixed-dose studies. Regardless, clinicians need to be aware that results from fixed-dose studies cannot be compared with results from flexible-dose studies.

Duration of Trial

Most antipsychotic clinical trials are 4 to 8 weeks in duration, following the guidelines of the Third Consensus Conference on the Methodology of Clinical Trials With Antipsychotic Drugs.[24] The risperidone studies[10,14,15] and the Zimbroff et al.[17] sertindole study lasted 8 weeks; most of the other clinical trials of the atypical antipsychotics were 6 weeks in duration.[1–4,6–9,11,13]

The FDA mandates that a manufacturer may not give indications for long-term use of a drug without long-term, placebo-controlled trials of that drug. Many researchers and clinicians are questioning the ethics of a requirement that exposes part of a study group with a particular condition to placebo for a long-term period when there are medications known to be effective in the treatment of that condition. Kane et al.,[7,8] Peuskens et al.,[10] Beasley et al.,[3] Tollefson et al.,[6] and Peuskens and Link[11] declined to include a placebo-control group when designing their studies.

Washout Period

Since most patients who enroll in clinical trials have been previously treated with antipsychotics, the issue of the washout period is important. In the published review of the Peuskens et al. study,[25] D.A.W. Johnson pointed out that a 1-week washout period is of little value in patients who have been continuously treated, particularly with depot injections, for weeks or months. In their discussion, Peuskens et al.[10] acknowledged that a continuing effect was possible, especially in those subjects who had taken depot preparations; they noted that a longer washout period was not permitted for ethical reasons in many of the participating countries. When Peuskens and Link[11] selected a 24-hour washout period for their study of quetiapine versus chlorpromazine, they argued that while a longer washout period might have permitted D_2 receptor occupancy to approach normal levels, it might also have allowed positive symptoms to deteriorate unacceptably.

Dropouts

Dropouts should also be considered when evaluating the results of clinical trials. Placebo-controlled studies will, by nature, have a high dropout rate, as most patients receiving a placebo will be nonresponders. Two olanzapine[2,3] studies included a group taking 1 mg/day of olanzapine, a dose likely to be subtherapeutic and to produce dropouts. In a quetiapine study,[9] 159 of 286 subjects withdrew before trial completion, primarily because of treatment failure. Of these, 57 were taking placebo, 54 were taking a low dose (≤ 250 mg/day) of quetiapine, and 48 were taking a high dose (≤ 750 mg/day) of quetiapine. Subjects are frequently unwilling to continue treatment with an agent they view as ineffective. In the Peuskens et al.[10] study, 154 of 1362 patients withdrew because of insufficient response. A greater percentage of patients in the 2 higher dose ranges of olanzapine completed one study[3]; the authors suggested that the higher dropout rates in the 2 groups of patients taking lower doses may have been related to ineffective treatment.

STATISTICAL ANALYSIS

Readers of clinical trials must also be aware of the statistical analysis used. Last Observation Carried Forward (LOCF) and intent-to-treat analyses are statistical techniques that make it possible to include subjects who have withdrawn from the study in the subsequent computation of results. An intent-to-treat analysis determines how dropouts will be treated in a study. For example, Kane et al.[7] included any patient who had had a baseline assessment and at least 1 assessment following randomization in an intent-to-treat analysis. When LOCF is used,

data from the last assessment for a patient who drops out are carried forward and statistically treated as if the data had been obtained at the endpoint assessment. Such an analysis controls for a high dropout rate, but it can also skew the results. Among the trials considered here, Arvanitis et al.,[1] Borison et al.,[13] Chouinard et al.,[14] Kane et al.,[7] Small et al.,[9] and Tran et al.[5] employed LOCF.

Readers must be vigilant for improvements measured with multiple subscales, particularly when Bonferroni corrections have not been made. A study may reveal, for example, that a certain new drug scored statistically significantly better than its competitors on 3 subscales; it may also be true, though, that there were no statistically significant differences between treatment groups on 25 other subscales. When Tran et al.[5] compared the rating scores of risperidone-treated patients with those of olanzapine-treated patients on 8 scales, between-group differences were statistically significantly different on only 2 of those scales. The improved performance of risperidone in this trial did not emerge as the result of testing an a priori hypothesis but was uncovered in a post hoc analysis. Clinical trials should present a priori theses that the trial will prove or disprove. Any post hoc thesis can focus on unanticipated positive effects of a drug at the expense of negative effects that are equally in evidence.

CONCLUSION

Clinical trials are an indispensable tool in the FDA drug approval process. They also provide invaluable information to the clinician seeking information on drug dosing and indications. The reader must approach the clinical trial report prudently, however, and ask questions about methodology, affiliations of the researchers, statistical operations, location of study centers, and study populations, among others. Approached with the right questions, carried out competently, and correctly analyzed, clinical trials can yield valuable answers.

Drug names: chlorpromazine (Thorazine and generic brands), clozapine (Clozaril), haloperidol (Haldol and generic brands), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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DISCLOSURE OF OFF-LABEL USAGE

The authors of this article have determined that, to the best of their clinical estimations, no investigational or off-label information about pharmaceutical agents has been presented that is outside Food and Drug Administration–approved labeling.