CATIE Trial Review of Phases 1 and 2

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Introduction

The CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) program was conducted in order to evaluate the effectiveness of antipsychotic drugs in typical settings and populations. This trial promised a "real world" approach, differing from previous industry-sponsored antipsychotic trials which typically have strict entry and exclusion criteria, are conducted at only a of couple sites, and narrowly focus on comparing 1 or 2 drugs with placebo. CATIE's design consisted of three main phases. This review will focus on the first two phases of the CATIE trial.

- Phase 1: Phase 1 was a double blind randomized clinical trial comparing treatment with the second-generation antipsychotics (olanzapine, quetiapine, risperidone, ziprasidone) to perphenazine, a mid-potency first generation antipsychotic.
- Phase 2: If a patient discontinued the phase 1 medication and wished to continue with the trial, enrollment in one of two phase 2 pathways was an option: (1) Randomization to open-label clozapine or a double-blinded second generation drug that was not assigned in phase 1; or (2) Double-blinded randomization to ziprasidone or another second generation drug that was not assigned in phase 1.

The primary outcome measure was discontinuation of treatment for any cause, selected due to the frequency of stopping or changing antipsychotic medication in the clinical setting. Secondary outcome measures included specific reasons for discontinuation such as inefficacy or intolerability due to side effects.

The purpose of this evidence-based evaluation of CATIE's first 2 phases is to determine if the results are a valid and useful addition to a healthcare provider's resources when treating schizophrenia.

Summary of Author's Results and Conclusions:

Phase 1:

- The authors concluded that olanzapine was the most effective in terms of the rates of discontinuation; however, it was also associated with the greater weight gain and increases in measures of glucose and lipid metabolism.
- They also concluded that the efficacy of the conventional antipsychotic perphenazine appeared similar to that of the atypical antipsychotics.

Phase 2:

- For the phase-2 efficacy pathway, the authors concluded that in the group of patients who had just discontinued a course of treatment with a newer atypical antipsychotic, treatment with clozapine was significantly more effective than switching to another of the newer atypical antipsychotics.
- It was determined that the results of phase-2 were consistent with previous studies finding clozapine more effective than conventional antipsychotics.
- The authors of the phase 2 tolerability arm concluded that olanzapine and risperidone were more effective than quetiapine and ziprasidone as reflected by longer time until discontinuation for any reason. It was also concluded that olanzapine was the most effective medication for those patients who discontinued their previous treatment due to inefficacy, although not for those who discontinued due to intolerability.
- Their original hypothesis that ziprasidone would be most effective was not confirmed.

Reviewer's Conclusion:

The CATIE trial was meant to be a realistic and practical approach toward the evaluation of antipsychotics in the treatment of schizophrenia. In contrast with previously conducted industry-sponsored clinical trials, the CATIE trial incorporated a large number of subjects in numerous clinical settings and followed them for an extended duration of time. In addition, rather than focusing on one or two drugs as compared to placebo, these trials evaluated all available atypical antipsychotics and one first generation drug. In order to be as "real world" as possible, the trial enrolled patients with stable co-morbid disease, substance-use disorders, and those taking concomitant non-antipsychotic-related medication. While such an approach is supposed to increase the external validity of the study by making the results more applicable to the general population of schizophrenic patients, it may also decrease internal validity. Confounding factors have the potential to influence outcomes so that the results cannot necessarily be attributed to the drugs under study. However, keeping these factors in mind, one must acknowledge that the CATIE trial was meant to evaluate the *effectiveness* of antipsychotic medications; in other words, whether or not a drug works under the usual conditions of care. *Usual conditions of care* unavoidably include such confounding factors as concomitant medications and co-morbid conditions. It is evident that the CATIE study was flawed in a number of ways as presented in this review; however, it is a trial that takes a novel approach toward evaluation of antipsychotic effectiveness in a more representative population than has previously been studied. While the aforementioned threats to internal validity of the study are important to keep in mind, CATIE results may be useful in that

Element	Criteria	Comments	THREAT
Study Design Assessment	Is the design appropriate to the research question?	Phases-1 and 2, with the exception of those patients assigned to clozapine, were double-blinded randomized control trials designed to assess differences in effectiveness between antipsychotics. Clozapine was open-label due to complexities involving weekly blood drawing for hematological monitoring. Perphenazine was the only first generation antipsychotic used for comparison with the second generation drugs, chosen because of its lower potency and decreased risk of extra pyramidal side effects and sedation. This presents a problem due to the tremendous variability in efficacy and tolerability within the first generation antipsychotic class. The primary endpoint of all-cause treatment discontinuation was chosen because it is a distinct measure that reflects both efficacy and side effects. Discontinuation of medication is a major problem in the treatment of schizophrenia and the authors decided that the effectiveness of therapy would be best measured by an outcome that encompasses a variety of causal factors. It was determined to be a clinically meaningful outcome that reflects the input of both the patient and the clinician.	***THREAT:*** Open label trials can lead to a significant bias and misrepresentation of outcomes measured. ***THREAT:*** Use of a first generation antipsychotic that is not representative of the class may lead to inappropriate application of results to the entire class. Specifically, the perphenazine results may not apply to the entire class. ***THREAT:*** A major problem with this outcome is its inability to pinpoint the specific cause of treatment discontinuation. Secondary endpoints do include specific causes; however, analyses of these outcomes were considered descriptive in nature and lacked the statistical power used for primary outcome analysis.
Internal Validity Assessment	Can bias, confounding or chance explain the study results? Might there be another factor associated with the study variable that may account for the conclusion **instead** of the variable under study (i.e. confounders)?	The authors mentioned that the FDA approved dosage regimens for quetiapine and ziprasidone may be suboptimal. In addition, the recommended dose of 6mg per day for risperidone was chosen to decrease the risk for extra- pyramidal symptoms; however, this dosage may not be optimal. While the doses used in the study were on average higher than those used in the community setting, such differences in dose optimization may confound outcomes. Broad inclusion and few exclusion criteria were used in order to make the results of the trial "generalizable" and representative of the broad group of chronic schizophrenia patients. See performance bias for specifics.	***THREAT:*** Suboptimal dosing for quetiapine, ziprasidone, and risperidone may have resulted in better outcomes for olanzapine which was more optimally dosed. This is a highly significant threat since a) the purpose of this study is to compare agents — thus, the deck is potentially stacked in favor of one agent; and b) a dosing differential could easily have an effect on continuation and discontinuation — each of which is a potentially separate question. Discontinuation was the primary outcome in this study and if more comparable doses of study drugs were used it is quite possible that the study outcomes would have differed. ***THREAT:*** While the sample of patients in the CATIE trial may be more representative of the real world, there is the risk that certain baseline characteristics, such as stable co-morbid disease or substance-use upon enrollment, may confound results. *continued*

they challenge the current mode of thinking that atypical antipsychotics are the primary therapy for psychoses. However, given that perphenazine was the only conventional drug used in the study, it does not follow that all other conventional antipsychotics will be as effective. Other studies will have to be performed in order to measure these other agents in a similar manner. In addition to challenging the current mode of thinking, CATIE also provides us more information with regard to the adverse effect profiles of the individual agents. This may be useful when weighing the risks and benefits of antipsychotic therapy. While the authors of this review disagree about the usefulness of the results of this study, the CATIE trial has created a dialog that tests the current mode of thinking regarding antipsychotics. However, as with many other psychological conditions, we are still in the dark as to which therapy is "best" for schizophrenic patients. The CATIE study has shed some light for us, if only illuminating the sign on the door.

Overall Grade: B-U = Possible to uncertain usefulness (J. Erickson, Pharm. D.)

Element	Criteria	Comments	THREAT
Selection Bias	Are groups truly randomized (concealment of allocation strategies, similar group characteristics, avoids potential for anyone affecting assignment to study arm, etc.)?	CATIE subjects were originally randomized to phase-1 treatment groups and then re-randomized upon entrance to phase-2. For phase-1 of CATIE, subjects had no choice as to which drug they were assigned. However, subjects **were** allowed to choose which study arm of phase-2 they wished to enter (clozapine/"efficacy" or ziprasidone-"tolerability"). In addition, enrollment in the clozapine arm was relatively low with a total of only 99 patients. (See assessment bias for effects of small sample sizes.) The broad inclusion and narrow exclusion criteria of the CATIE trial allowed for enrollment of subjects with medical co-morbidities in addition to those patients with substance-use disorders and concomitant medications (other antipsychotics were not allowed). Adjustments for these factors were not mentioned, nor were they stratified for at baseline randomization. Patients receiving ziprasidone or other second generation drug in phase-2 were limited to those re-randomized after not choosing to take open-label clozapine.	***THREAT***: No details of randomization are provided. Baseline characteristics, however, seem balanced between groups for demographics and disease dimensions, which is suggestive of successful randomization. However, not being able to evaluate randomization methods is of concern. ***THREAT***: Unclear if concealment of allocation was carried out in order to preserve true randomization and minimize direction of participants into a particular group. ***THREAT***: Treatment allocation based on preferences or patient choice can bias results in favor of one drug over another. For example, those patients who chose clozapine may have had preconceived ideas about its efficacy and/or side effects, which may have led them to continue taking the drug for a longer period of time. ***THREAT***: Re-randomization after initial randomization and loss of subjects may create a selection bias.
Performance Bias	Has double blinding been successfully employed? Are there any other performance biases such as differences between groups, except for what is under study?	Efforts were undertaken to increase medication adherence through education, counseling, etc. While these services may have been offered to all subjects, they may not have been used by all.	***THREAT***: As mentioned above, the clozapine subjects of this study were NOT double blinded. Lack of blinding can significantly distort study results. ***THREAT***: Protective concomitant medication use and co-interventions were not adjusted for and therefore had the potential to affect outcomes. ***THREAT:*** While the authors report efforts to increase adherence and describe methods to evaluate adherence, there is no actual reporting of adherence. This can result in bias overall and a difference between groups.
Attrition Bias	Are there any missing data points?		***THREAT:*** Significant loss of data points which is likely to affect reported results—see Assessment Bias below.

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Guest Editors' Opinion & Comments: Overall Grade: U = Uncertain validity and clinical usefulness.

The CATIE Trial is a highly complex trial that has created controversy. Critical appraisal requires judgment, and so reasonable reviewers may come to different conclusions on possibly any study — this is even more expected with a clinical trial as complicated as this. Firstly, the outcome measure of "time-to-discontinuation" is a novel one, which, thoughtfully was designed to address efficacy, effectiveness, safety and tolerability issues. However, in that it is novel — and in that drug dosing was not comparable — has generated controversy. For example, can we really

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Assessment Bias	Are assessors blinded? What is the likelihood of findings due to chance? Is there statistical significance? Do confidence intervals support conclusions? Intention-to-treat analysis? Modeling?	For those patients receiving clozapine, investigators were not blinded. Randomized patients who received at least one dose of study medication made up the "intention-to-treat (ITT) population." However, ITT requires that all patients who are randomized be included in the analysis. The authors state that 4% were excluded from the analysis - which is a number that is not likely to produce significant bias. Modified, intention-to-treat (reported as ITT by authors) was employed for primary analyses of both primary and secondary effectiveness outcomes, with the objective of determining if the atypical treatments maintained patients on original therapy for a longer period than the conventional therapy. In fact, the authors actually used Kaplan-Meier survival curves to estimate the time to the discontinuation of the treatment. Survival curves are an estimation method — or model — in which patients are removed when a study outcome occurs or when the subjects are censored (i.e. removed) from the denominator at various points in the study. Missing data is replaced using data from patients who remain in the study and may be different from censored patients. Censored patients may not be included in the 4% of excluded patients mentioned above. Finally without knowing the assumptions used in the formation of the curves and without more information about the censoring, it is not possible to evaluate how likely the model may have approximated a likely truth. It is also important to note that approximately 50% of patients who discontinued their phase 1 study medication did not continue on to phase-2. These patients were not given any study medication and were followed naturalistically on the treatment of their choice, which could include no treatment at all. These subjects were included in the intention-to-treat analyses.	***THREAT***: Assessment of outcomes with clozapine treatment may have been biased as a result of preconceived opinions about clozapine. ***THREAT***: No confidence intervals provided. ***THREAT***: Excluding the first 26% of patients enrolled in phase-2 ziprasidone pathway introduces assessment bias and decreases the validity of the intention-to-treat analysis. ***THREAT***: Insufficient information to evaluate survival curves used for results reporting. Survival curves, depending upon assumptions used in the model, may distort results by more than a relative 50%. ***THREAT***: Including such a large number of patients who completely discontinued the study in the analysis of primary and secondary effectiveness outcomes presents a serious threat to the validity of results. This group of patients could have been taking any number of antipsychotic medications over which the investigators had no control, introducing significant assessment bias into the CATIE study.
Usefulness Assessment	Is there a clinically significant area and sufficient benefit size?	Authors used Kaplan-Meier (KM) curves to measure the primary outcome measure, time-to-discontinuation of treatment in this 18 month study ($P<0.001$). Results: 64% discontinuation for olanzapine, 75% for perphenazine, 79% ziprazidone, 74% risperidone, 82% quetiapine. The times to discontinuation because of intolerable side effects were similar among the groups, but the rates differed ($P=0.04$); olanzapine was associated with more discontinuation for weight gain or metabolic effects, and perphenazine was associated with more discontinuation for extrapyramidal effects.	***THREAT***: Reported results may be misleading because the study has significant threats to validity, which can distort study results.

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External Validity	How likely are research results to be realized in the real world?	The CATIE study was meant to be representative of the real world. This was to be accomplished through recruitment of patients using broad inclusion criteria (i.e. 18-65 years of age, adequate decisional capacity, DSM-IV diagnosis, etc.) and few exclusion criteria (i.e. other cognitive disorders, first-episode schizophrenia, history of treatment failure, treatment resistance with previous clozapine administration, etc.).	***THREAT***: While the goal was to have a study population that was highly representative of the real world, this goal was not fully realized. For example, the requirement for adequate decisional capacity may have created a study population with a higher intelligence level than the general population. This higher cognitive ability may have increased medication adherence and continuation, thus influencing the primary outcome measure. In addition, excluding patients with a history of treatment failure or resistance with prior clozapine-use would create a population that was less severe in illness than the general population. These factors create a significant threat to the external validity of the study, making it more difficult to draw conclusions about the applicability of results to the general schizophrenic population. It is also important to realize that various threats to the internal validity of the CATIE study have the impact of indirectly decreasing its external validity. One cannot confidently apply the results of a study with significant threats to internal validity to the population at large.

conclude that discontinuation is due solely to the drug interventions (vs other aspects of care), especially when blinding is not complete? Second, dosing that is not comparable is not necessarily a problem in itself provided that the study is valid and that any conclusions drawn are highly transparent. It is not fair to claim that time-to-discontinuation for olanzapine, per se, was longer when the dosing was higher for olanzapine than the other agents. Provided the study is considered to be sufficiently valid to make any claims, those claims should be constructed to be complete with dosing, formulation and administration information, so as not to mislead readers.

So is this study valid? Given the above, plus an open-label design for Phase 2, use of Kaplan-Meier curves with insufficient reporting, along with a myriad of other problems or lack of details to enable evaluation, we are left uncertain about any conclusions that can be drawn with reasonable comfort. Our bottom line is that we do not feel that this study would be of use in guiding us clinically in treating patients when considering efficacy or effectiveness. If this were the only study on this topic, we would be advising patients that there was not sufficient scientific information to discern the preference of one agent over another.

And what do we think of our differing viewpoints? We think that reviews and discussions of this nature are incredibly important. All too often clinicians, pharmacists, nurses and other healthcare professionals read studies uncritically. The insightful comments in Ms. Ericksen's review, along with other reviewers' and our own comments contribute to engagement in a conversation about the evidence upon which we base important decisions. We consider critical appraisal to be a "team sport" that invites discussion and reflection and continual discovery, insights and learnings. Ultimately what we consider to be the bottom-line is how we allow ourselves to be guided toward different clinical decisions and what information gets communicated to other healthcare providers and patients. Reviews such as this contribute importantly to that guidance.

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