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Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) What Does It Mean for Practice and Policy?

Background and Study Design

CATIE is the largest, longest, and most comprehensive independent trial ever conducted to study medication treatments for schizophrenia. It is an independent study sponsored and funded by NIMH. Pharmaceutical companies whose drugs were included donated drug supplies. The study design attempts to compare the efficacy and cost-effectiveness in treating schizophrenia of four of the second-generation atypical anti-psychotics; olanzapine (Zyprexa), risperidone (Risperdal), quetiapine (Seroquel), and ziprasidone (Geodon) and one first-generation typical antipsychotic perphenazine (Trilafon). It is a double-blind prospective study that intends to be more like every day practice as compared to the initial trials of new medications. Subjects do not include persons having their first episode of illness or who had a history of being a treatment non-responder. All are reasonable candidates for medication change due to lack of efficacy or tolerability issues and 28% of the patients had an exacerbation of their illness in the previous three months. The trial does include persons with substance abuse problems, anxiety, depression and medical illnesses that are usually excluded in other trials. Patients could be prescribed other psychotropic medications as needed during the study except for anti-psychotics.

The study is designed to have three phases. In the first phase, lasting 18 months, patients are randomly assigned to one of the five antipsychotic medications and remain blind to which medication they are receiving. The medication is provided as a single dosage tablet. Patients and their treating psychiatrist can decide on taking from one to four tablets a day in order to allow for dosage adjustment. Patients remain on this medication until either they or their psychiatrist decide to switch to a different medication for any reason. The primary outcome measure is how long patients stay on the medication before switching. [The NEJM article of September 2005 reports only on the first phase clinical results.] Patients enter the second phase when they are switched to a different medication. In the second phase they are blindly randomized to either one of the four second-generation atypical anti-psychotics that they did not receive in the first phase, or to clozapine. Doses are adjusted with the same for tablet methodology as in the first phase. Results of Phase 2 are expected to be released in March 2006. In the third phase the medication choice is no longer blind and use of two anti-psychotics simultaneously is also an option.

Separate analyses and publications addressing neurocognitive effects, work and functioning, movement disorders, use of adjunctive medication, interaction with substance abuse, cost-effectiveness and cost-benefit are currently underway.

Initial Results of CATIE Phase 1

Overall 74% of patients discontinued their initial medication prior to 18 months time. By physician decision, 24% discontinued due to lack of efficacy and 15% discontinued due to side effect intolerability. The majority of these two groups continued in the study and were switched to a second random medication. Another 30% switched as a result of the patient's decision to do so. In this group half the patients left the study and half were switched randomly to a second medication. There is no information regarding the patients' reasons for discontinuation. 16%

were hospitalized at some point. Comparing the five different anti-psychotics revealed few differences. The time of discontinuation /switching was modestly longer for olanzapine than for the other medications (9.2 months vs 3.5-5.6 months), and the rate of hospitalization was slightly less (11% vs 15-20%). However, olanzapine has a higher incidence of weight gain (2lb/month) and metabolic problems. Perphenazine was associated with more discontinuation for extrapyramidal effects.

Study Issues under Discussion

- A. *Dosage Levels.* The dosage levels used for olanzapine and perphenazine were the same as originally proposed by the investigators and are consistent with current general clinical practice. The dosage for olanzapine allowed for doses up to 30 mg which is higher than the FDA indicated range. The dosage levels for the other three medications were recommended for a higher dosage range by the researchers but were set lower as a result of advocacy by their manufacturers. It has been speculated that these medications may have proven more effective than perphenazine had they been given at higher dosages. However, higher dosages usually also result in more side-effects.
- B. *Randomization Bias.* Persons with tardive dyskinesia (231 persons out of 1432 total) were excluded from randomization to perphenazine. Some of the general discussion occurring in the field has asserted that this biased the outcome of the study. However the persons with pre-existing tardive dyskinesia who were excluded from perphenazine were also excluded from statistical analysis when on another drug if they were being compared to the perphenazine group. Thus the CATIE results when involving perphenazine only address patients for whom there was no pre-existing tardive Dyskinesia. CATIE provides no information about comparisons between perphenazine and newer anti-psychotics in these patients.
- C. *Study Underpowered for Comparisons Involving Ziprasidone.* Ziprasidone became available and was added after the study was started, and the size of its treatment group is only approximately 60% of the other second-generation atypical treatment groups. Some of the statistical analyses done for other groups were not possible due to the smaller size of this group.
- D. *Limited Applicability To Overall Practice.* The study is limited to persons with schizophrenia. The majority of antipsychotic use is not associated with schizophrenia. While this is certainly true, there is also less evidence supporting the use of anti-psychotics in other disorders other than bipolar disorder. The CATIE design is significantly closer to usual practice than other prospective, double-blind, random studies of anti-psychotics.
- E. *Lack of Subgroup Analysis.* While groups of patients may show little difference in efficacy between older and newer anti-psychotics, some individual patients show near miraculous improvement on a particular one of either old or new anti-psychotics. However, it is not possible to predict which particular patient will do better on which particular anti-psychotic.
- F. *Differences in New Anti-psychotics.* The new anti-psychotics are not a uniform group and they all have unique mechanisms of action. The new atypical anti-psychotics have at least a half-dozen receptors at which they are substantially active and across which they vary greatly. It is unclear how these are linked, if at all, to anti-psychotic action.
- G. *Tardive Dyskinesia.* CATIE does not tell us anything about long-term side effects. Tardive dyskinesia is often not apparent until after years of treatment. Obesity, insulin resistance, diabetes, metabolic syndrome or cardiovascular consequences are also not predictable when

starting an antipsychotic. Both the new and the old anti-psychotics have significant negative consequences when used over long periods of time

Contrasting With Other Studies

New research should always be interpreted and understood through comparing and contrasting with prior research. The initial FDA licensing trials of the new generation anti-psychotics also had significant methodology and analysis design issues. In their initial trials the second-generation atypicals were usually compared to haloperidol (Haldol), a high potency anti-psychotic with higher rates of extrapyramidal side effects than moderate and low potency typical anti-psychotics. Haldol was most often given at a moderately higher dose than is usually used in initial treatment, making side effects more likely to occur. The FDA at that time required a show of clear superiority in either efficacy or tolerability. The higher doses were used to assure that Haldol had “a fair chance” in the comparison. Patients were usually not given medication to prevent/treat extrapyramidal side effects until after they had emerged. New drug trials usually exclude all other medications unless absolutely necessary. These several factors probably contributed to earlier discontinuation of Haldol than the atypical anti-psychotic being studied. The method of analysis required by the FDA was “last observation carried forward” which assumes that degree of improvement seen on the last day of treatment would have been the same as if the person had continued through the entire study period. Initial licensing trial studies are usually 12 or 16 weeks duration and anti-psychotic effects often do not become apparent until after four to six weeks of medication. So early discontinuation analyzed using a LOCF methodology appears the same as lower efficacy. Thus the choice of methodology and analysis favored the new atypical medications. Overall, this was not a true comparison to current practice which is to give moderately low doses of moderate potency anti-psychotics simultaneously with medication to prevent extrapyramidal side-effects. The CATIE design was chosen to address the shortcomings in earlier studies. Independent meta-analysis have concluded, with the exception of clozapine, that there is not consistent evidence of superior efficacy for second-generation anti-psychotics except in reduced negative symptoms.

Anti-psychotics, new and old, can be compared across three broad domains, efficacy, tolerability, and cost. The overall evidence around efficacy even prior to CATIE failed to show any clear superiority except in the case of clozapine. The currently available CATIE results challenge the prior generally accepted view that the newer anti-psychotics are clearly superior in terms of tolerability. While acquisition costs for medications are easily determined, overall cost effectiveness is more difficult and has not consistently favored the newer anti-psychotics. More data on this issue from CATIE should be available soon.

Conclusions and Recommendations for Commissioners

1. Discontinuation of an individual anti-psychotic should not be seen as equivalent to failing treatment. The majority of patients treated with anti-psychotics experience both moderate improvement and moderate side effects, leading them and their physicians to try multiple anti-psychotics over time.
2. Anti-psychotic medication in general, and the new atypicals in particular, are probably overvalued in terms of their efficacy. CATIE reminds us of the very real benefit limitations of these medications. 75% of people taking them switch to another medication in less than a year and a half and 16% are hospitalized. Very few patients achieve full symptom relief.

3. Do not make policy decisions solely on the currently available CATIE results. Additional information from the other two phases and the other analyses that are a part of CATIE should become available in the near future. This new information needs to be understood in the context of the other older data available.
4. At this time, do not support policy decisions requiring patients to fail first on older first-generation anti-psychotics before having access to second-generation anti-psychotics. The overall current available information still continues to suggest that the new atypical anti-psychotics are somewhat better overall than the older first-generation atypical anti-psychotics. CATIE leads us to revisit the question of just how much better. The initial FDA licensing trials of the new anti-psychotics probably overstated their advantages.
5. Do not support policies that require persons who are doing well to switch their current antipsychotic. All patients who entered CATIE desired a medication change and their physicians concurred. However, once randomized and switched, 75% required continued medication changes. CATIE provides no information regarding the outcomes of switching medications in patients who were currently doing well.
6. Recent and anticipated findings about antipsychotic efficacy from the CATIE studies, increased knowledge about antipsychotic side effects, recovery focused medication approaches, and cost concerns have increased attention on the use of antipsychotic medications. There is an urgent clinical need for updating of clinical guidelines and algorithms to include new findings from the CATIE and other recent studies. These clinical guidelines should address efficacy, side effect concerns and should have a recovery patient choice focus. This guidance will provide the clinical recommendations that policy makers can utilize in addressing cost and formulary approaches.
7. Do support policies that make all anti-psychotics available eventually since some patients do markedly better on a particular anti-psychotic.
8. Do not over generalize the CATIE results. CATIE tells us nothing about the treatment of the first episode of psychosis in persons with schizophrenia. CATIE tells us nothing about the treatment of persons with bipolar illness or other psychiatric disorders where anti-psychotic medication is commonly used. It is not certain that the results regarding low to moderate doses of perphenazine in treatment of schizophrenia can be generalized to all first-generation anti-psychotics.
9. When making policy, bear in mind that treatment must always be individualized. Research results and algorithms do not apply to all patients, and each must be adapted and tailored to the individual patient. Proper use, adaptation, modifications, or decisions to disregard research findings or algorithm recommendations, in whole or in part, are entirely the responsibility of the clinician responsible for treatment.
10. Do not underestimate the emotional component of the policy debate. Most advocates and consumers, and many prescribers remain convinced that newer is better and are unlikely to be convinced otherwise by data no matter how well designed the study.

Issue without consensus-step therapy among the new atypical antipsychotics

The medical directors could not come to consensus regarding the except ability of applying step therapy among the new atypical antipsychotics based on cost. The following recommendation was considered and equal numbers endorsed it, opposed it, or were equivocal. "There is no clear clinical reason to oppose step therapy or an algorithm based approach among the new atypical anti-psychotics based on price for persons who have not taken an anti-psychotic

previously. This is because the overall risk to benefit ratios are roughly equivalent and there is no way to predict with any certainty which patients will do better on a particular anti-psychotic. However, patient specific factors (such as a patient or family history of good response/tolerability to a particular medication) may suggest that one anti-psychotic will be better tolerated than others. If cost based therapy is implemented there should be provision for exceptions based on patient specific factors.”