Comments on implications of CATIE Phase I results for the IPAP Schizophrenia Algorithm

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January 9, 2006

CATIE (**Clinical Antipsychotic Trials of Intervention Effectiveness**) is an NIMH sponsored study in which 1,493 patients, age 18-65, from 57 sites were randomly assigned to treatment with olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone.1 Ziprasidone was added as an option in 2002 after 40% of patients were enrolled, following its U.S. approval. The goal of the CATIE study was to compare the second-generation antipsychotics' effectiveness and side effects to determine their risk/benefit ratio compared to a representative first-generation medication. An 18-month period of continuous treatment with the same medication was considered a bench mark, producing time to discontinuation, for any reason, as the primary outcome measure of overall effectiveness. Discontinuation for lack of efficacy, 'patient choice,' or side effects were equally weighted in the primary analysis. Separate analyses were conducted for ziprasidone because of its late introduction. Patients with tardive dyskinesia (TD) were excluded from the perphenazine group out of concern it might worsen TD, leading to separate analyses for patients with and without TD. Here are the main results for effectiveness and side effects. For the sake of brevity, we have reported the ziprasidone analysis results as though they were part of the major analysis.

- Patients were flexibly dosed up to maximum limits set in consultation with the manufacturers of the atypical antipsychotic drugs and this resulted in the following mean doses (mg/day): olanzapine 20 (max 30), perphenazine 21 (max 32), quetiapine 540 (max 800), risperidone 3.9 (max 6), ziprasidone 110 (max 160).
- Olanzapine was significantly more effective than all other treatments by the primary outcome measure which was time to discontinuation for any reason. Patients stayed on olanzapine for a median of 9.2 months. Patients assigned to the others stayed on them for from 5.6 months (perphenazine median – the second longest) down to 3.5 months (ziprasidone – the shortest). 64% of olanzapine-treated patients discontinued it before the end of the study. The discontinuation rates for the others ranged from 74 to 82%. After correction for multiple comparisons, olanzapine was superior to quetiapine and risperidone but not perphenazine or ziprasidone. There were no significant differences among the other drugs.
- Discontinuations due to lack of effectiveness: olanzapine 15%; the others 24-28%. Olanzapine was superior to quetiapine, risperidone and perphenazine, but not ziprasidone, after correction for multiple comparisons
- Discontinuations due to intolerability: olanzapine 19%; the others 10% (risperidone) - 16%. The higher rate for olanzapine was mainly due to greater weight gain.
- Discontinuations due to EPS: perphenazine 8%; the others 2-4%; $p<0.002$). The use of anticholinergic drugs minimized EPS with perphenazine. Fewer patients treated with quetiapine required use of anticholinergic drugs. There were no significant differences in the incidence of EPS, akathisia or movement disorders as reflected in rating scale measures of severity.
- Rehospitalizations: olanzapine 11%; the others 15-20% ($p <0.001$; quetiapine = 20%) (uncorrected for duration on drug).

- Weight gain > 7%: olanzapine 30%; p<0.001; the others 7% (ziprasidone) -16%. Patients in the olanzapine group gained an average of 2 lbs. per months.
- As noted in this and the next bullet, olanzapine had effects consistent with the potential development of the metabolic syndrome. Triglycerides in mg/dl: olanzapine +43 mg/dl; quetiapine, 17 mg/dl; risperidone, 3 mg/dl, perphenazine, 2 mg/dl and ziprasidone, a decrease of 18 mg/dl). There was an overall group difference (p<0.001) These levels are the average of the two highest values before discontinuation and are not necessarily peak increases or comparable across drugs. Cholesterol changes were small compared to triglycerides with olanzapine showing the largest increase (8.5 mg/dl) and ziprasidone and risperidone, showing small decreases.
- Glycosylated hemoglobin: olanzapine +0.41%; the others –0.1 (ziprasidone) to +0.1% (perphenazine). There were no significant changes in blood glucose.
- Prolactin in ng/dl: risperidone +15; the others –6.1 (olanzapine) to +0.4 (perphenazine)

Putting Phase I CATIE Results in Perspective

There are a number of issues that need to be considered before drawing conclusions from what has been published to date from the CATIE data set. This is the first of dozens of publications on this rich data set. We have not yet heard about the effect of the various medications on negative symptoms or cognition, which may be the two most important differences in efficacy between typical and atypical antipsychotic drugs.2

Issue 1. What kind of patient entered CATIE: the issue of treatment resistance

The nature of the patient population who entered CATIE requires careful consideration. Patients who entered the study were moderately ill on average, despite the fact that 72% were taking antipsychotic medication at the time of randomization. CATIE should be seen as a study of a mixture of patients who were not doing well on current medication and hence were willing to enter a randomized trial. Unfortunately, the results for those who were treatment responsive and those who were treatment resistant have not been separately presented. Many of those who entered CATIE had persistent psychosis despite normally adequate doses and would, thus, be considered treatment resistant by previous criteria which emphasize persistent moderate-severe levels of psychosis despite usually adequate treatments. Only those who were severely ill despite treatment were excluded from the study. Many of the patients who entered CATIE had already failed risperidone or olanzapine, the most frequently used drugs prior to study entry, by the lower limit of the criteria used to define eligibility for the US Multicenter Clozapine Trial, namely, moderate level of positive symptoms and poor social function for several years prior to entry.

Three hundred forty of the 1493 (22.8%) of the patients who entered the study discontinued because of lack of efficacy. Most, if not all of these patients, might be considered to be treatment resistant. Inclusion of this many treatment-resistant patients could have affected the comparison between olanzapine, the other atypical antipsychotic drugs, and perphenazine. The relatively higher dose of olanzapine compared to the other atypical drugs in the CATIE trial, could have led to a better response to olanzapine in CATIE Phase I compared to other drugs. The results from CATIE are not helpful for the initial choice of drug or the choice of drugs in those cases

where patients have a satisfactory response in terms of efficacy but not necessarily tolerability or safety.

More evidence that the CATIE patients, overall, represented a less responsive group of patients comes from the data on duration of successful treatment., Successful treatment was defined by a CGI severity score of at least 3 (mildly ill) or by a score of 4 (moderately ill) at baseline with an improvement of at least two point from baseline. The median duration of successful treatment was 3 months for olanzapine and 1 month for all four other treatments. Olanzapine was superior to quetiapine, risperidone and perphenazine in this outcome measure, after correcting for multiple comparisons.

Issue 2: Dosage

The use of flexible doses as was done in the CATIE study, within a limited range, when dose ranges are not known with certainty and not clearly equivalent, is not optimal for comparing across treatments. If, as appears to be the case, a significant proportion of patients who entered CATIE were treatment resistant, there is reason to be concerned that the somewhat superior effectiveness of olanzapine was due, at least in part, to the relatively higher dose of this agent compared with some of the others rather than an intrinsic difference in efficacy. It is unlikely that dosage would be as much of an issue if all the patient sample had been non-treatment resistant. A peak dose of 30 mg with olanzapine was permitted which is higher than the usual clinical upper limit of 20 mg. This higher dose may have led to better efficacy in a subgroup of the treatment resistant patients. Risperidone at 3.9 mg/day is slightly lower than typical use today (4.2-4.5 mg/d).3 There is some evidence to suggest that quetiapine should be given in higher doses than were achieved in this study, particularly in patients who fail to respond to the doses (200-500 mg/day) that have been used in clinical trials which have excluded treatment resistant patients.4 The ziprasidone median dose of 110 mg/day seems to be less than optimal, especially considering that it appears no provision was made for ensuring that it be taken with food, which could cut absorption by 40% according to the Package Insert. This may explain ziprasidone's underperformance in CATIE and in another recent comparison of olanzapine and ziprasidone by Breier et al.5 The dose of ziprasidone has been kept low because of fears of ventricular arrhythmias which have, in fact, never been observed, since it was introduced. The fact that only about 40-45% of patients received the maximum dose of each of the drugs is worrisome. A fixed dose study, with multiple doses of each drug, covering the range from the low end to the high end, is unquestionably a superior design to compare efficacy and tolerability. In light of the concern that most experts believe that adequate dose response data have never been obtained in phase III trials for most atypical antipsychotic drugs, let alone an effectiveness trial which has major differences from phase III trials, this suggestion, although difficult to implement, does not seem unreasonable. While this would have been expensive to do, the fact that it was not employed does place significant limits on the generalizability of the CATIE results

Issue 3: Tolerability

Metabolic Side Effects: The main results have been reported above. They clearly show that olanzapine is more likely to increase the risk of the metabolic syndrome than are the other drugs, with ziprasidone being the least likely. There was a modest signal with triglycerides from

quetiapine. These broad conclusions about rank order are consistent with the rest of the literature and add relatively little new knowledge. The data represent the baseline and the average of the two highest post-baseline samples with adjustment for exposure. How this adjustment was made is not clear. Although patients were instructed to fast, non-fasting samples were not excluded. Until, and if, these weaknesses in methodology are clarified, it is difficult to conclude much from these data. CATIE did suggest that quetiapine produces more weight gain and lipid changes than atypical antipsychotic drugs other than olanzapine. The data support other data that ziprasidone has the lowest risk for metabolic side effects of all of the atypicals. However, comparison with aripiprazole was not part of CATIE.

EPS: The exclusion of patients with tardive dyskinesia from assignment to perphenazine produced a significant bias to the study. This is true with comparison of the drugs for EPS and potential cause for discontinuation. It would have been superior to consider TD as a factor and adjust for it in the analyses. CATIE confirmed that perphenazine treatment led to a higher rate of discontinuation due to EPS compared to the other agents but the use of anticholinergic drugs was no different. This indicated that rather than manage EPS as would be done in clinical practice, patients were switched to an atypical if clinicians assumed that the EPS was due to perphenazine (or possibly risperidone). However, it is noteworthy that perphenazine was no worse than any atypical antipsychotic other than olanzapine with regard to all causes for discontinuation despite the fact that it had a high rate of discontinuation due to EPS. The differences in EPS between atypicals was marginal, which indicates that at the doses used, risperidone does not have an EPS disadvantage. It is also noteworthy that clinical symptoms of hyperprolactinemia did not differ between drugs

Issue 4: Substance Abuse

The inclusion of patients who had significant alcohol and drug abuse problems is a departure from the usual clinical trial results and make results more generalizable to clinical practice. Preliminary secondary analyses suggest this was not a factor in the difference between the atypical antipsychotics and perphenazine but further analysis of this issue is indicated.

Implications of CATIE for the IPAP Schizophrenia Algorithm

The IPAP Schizophrenia Algorithm is designed to apply to a broad range of patients who are in various stages of treatment, from patients about to get their first antipsychotic to those who have had an unsatisfactory outcome after one or more antipsychotic trials. The CATIE study addresses the treatment of a subgroup of patients – those who have had antipsychotics in the past and, for reasons of lack of efficacy, side effects, or other reasons, are not satisfied with their previous antipsychotics. Patients who had responded and tolerated well a previous antipsychotic, presumably would have been unlikely to choose to participate in CATIE. In addition, patients would not qualify for CATIE if they had “persistence of severe symptoms” during an adequate trial of at least one of the study medications, or if they had been treated with clozapine in the past.

The primary end point in this study, all cause discontinuation, quite simply leaves so much to be desired that it is exceedingly difficult to know what to make of it. Patients could discontinue for

the reason that they wished to try another one of the drugs which might be available to them. The decision making that goes into such a choice is not comparable to clinical practice. Side effects that cause discontinuation do not occur at the same time. Metabolic side effects such as those produced by olanzapine and quetiapine are more likely to cause discontinuation later rather than sooner.

The IPAP algorithm recommends a sequence of two monotherapy trials with atypical (preferred) or typical antipsychotics, followed by a trial of clozapine. Patients are to go on to the next trial if "clinical response was inadequate," especially in positive symptoms after an adequate trial [see Node 4]. They would not need persistence of "severe" symptoms. The additional evidence of greater metabolic risk from olanzapine and compared to risperidone and ziprasidone will no doubt increase the reason for clinicians to be more cautious in choosing olanzapine from among the group of atypical antipsychotic drugs.

A basic principle of the IPAP algorithm is that patients with even moderate persisting symptoms that are disabling should be offered a trial of clozapine after two other antipsychotic trials. Thus, it appears that many subjects in Phase One of CATIE would have been eligible for clozapine in the IPAP algorithm. This was not one of the options in phase I although results from phase II will address this choice. Considering the generally unsatisfactory results in CATIE, with three quarters of patients failing to stay on the assigned antipsychotic for 18 months, it appears that some CATIE patients might have done better by following the IPAP algorithm. Phase II of CATIE includes an optional study in which open-label clozapine is compared with drugs not taken in Phase I. These results in which are in press suggest that clozapine is superior to the other atypical antipsychotic drugs in refractory patients but the very small number of patients who entered that trial, less than 100, its open-label design and dose restrictions limits the confidence in the data.

We may probe the implications of these Phase One CATIE results by commenting on some specific patient subgroups addressed in the IPAP algorithm.

1. Patients who have not had an adequate trial of any antipsychotic but have failed to tolerate one or more antipsychotics that have been offered in the past.
   These are patients who could be included in the CATIE population. They would be at Node 4 of the IPAP algorithm, where the algorithm recommends returning to Node 3 and giving another monotherapy trial of a different antipsychotic. This process repeats until an adequate trial (4-6 weeks at a dose in the therapeutic range) is completed. The effectiveness and side effect findings in CATIE may be applied in selecting an antipsychotic for these patients. See the discussion below.
2. Patients who have had one adequate trial of an antipsychotic but clinical response was inadequate
   These are patients who could be included in the CATIE population. They would be at Node 6 of the IPAP algorithm. The Node Note states that there are no data which bear upon whether a second antipsychotic drug should be tried after an adequate trial of one atypical has failed to adequately control positive symptoms, although it had been found that after one trial of a typical antipsychotic it was unlikely that another trial of a typical agent will be effective. It was nevertheless the consensus opinion that a second atypical

should be tried. The effectiveness and side effect findings in CATIE may be applied in selecting an antipsychotic for these patients (see below). Phase II CATIE results suggest that a single trial before switching to clozapine might be indicated

3. Patients who have had one adequate trial of an antipsychotic with persistence of severe symptoms of schizophrenia
   CATIE did not include patients of this description. They would also be at Node 6 of the IPAP algorithm. The CATIE effectiveness results may not apply. The side effect data could affect the choice of the antipsychotic for the second definitive trial.
4. Patients who have had two or more adequate trials of antipsychotics with "inadequate" clinical response, but the persisting symptoms are not "severe"
   These are patients who could be in the CATIE population. In the IPAP algorithm, they would be at Node 8 and under consideration for clozapine. The CATIE finding of somewhat greater efficacy for olanzapine compared with the other non-clozapine options are of interest here. If olanzapine was not one of the two antipsychotics tried so far, it might be considered now, as a third antipsychotic trial before clozapine, especially if the patient is considered at high risk for the metabolic or non-metabolic side effects of clozapine or is unwilling to take clozapine for whatever reason. The metabolic risks of clozapine may be higher than those with olanzapine.
5. Patients who have had two or more adequate trials of an antipsychotic with persistence of severe symptoms
   CATIE did not include these patients. They would be at Node 8 and be under consideration for a trial of clozapine.

Choosing among atypicals: balancing benefits and risks

These comments would apply to choosing an antipsychotic for patients in subgroups 1-3 above. These patients would be among those who would be found at IPAP algorithm nodes 3 through 6.

The IPAP algorithm and linked commentaries on choice of antipsychotics indicate a preference for the atypical antipsychotics over the typicals when they are available. This was because of extrapyramidal side-effect (EPS), including tardive dyskinesia, differences, as well as the evidence of greater benefit on cognition with the atypicals. This initial set of CATIE data confirmed that EPS were somewhat more problematic with perphenazine, but did not report on differences in effects on cognition. This will be reported in a later publication. So, for now, it seems that there is no reason to change the present IPAP algorithm language expressing preference for the atypicals.

These CATIE results suggest some moderate effectiveness superiority for olanzapine. Patients stayed on it for significantly longer than the other antipsychotics, typical or atypical. The results also indicate that olanzapine produced significantly more weight gain and more metabolic consequences compared to the others. Previous evidence of a greater risk of metabolic consequences with olanzapine was discussed at length in the IPAP linked essay on metabolic side effects. IPAP said that if these appear, it would "ordinarily be indicated" to switch to a different antipsychotic with less risk. In this statement, IPAP took a stronger position than the American Diabetes Association recommendation, which recommended only to "consider" a switch.7 The CATIE results appear to support the present IPAP language.

IPAP also recommends selecting the initial antipsychotic, and subsequent ones, in Nodes 3-6, based on evaluating the patient's propensity for getting the different side effects of the atypicals. Thus, for example, a patient with a past or family history of diabetes should probably not receive olanzapine at these nodes unless the others have been tried and not tolerated. What is not addressed is the question of whether or not olanzapine is a reasonable early option in those with low apparent risk.8 An editorial by R. Friedman in the issue of NEJM that contains the CATIE study suggests that early use of olanzapine "is a matter of clinical judgment and informed patient preference," but he suggests that it might be tried in anyone who has not had a full remission on a previous medication trial (i.e. - Node 6 of IPAP).9 If the patient develops a significant metabolic syndrome, he proposes a switch because "the positive effects often persist." However, one would like to see some evidence that switching from olanzapine to another antipsychotic in clinically stabilized patients can successfully reverse the metabolic side effects and preserve the clinical effectiveness. There may be some data mining from CATIE that could address this question since about 22% of patients were on olanzapine at baseline before random assignment to the other antipsychotics.

Proposal for sequencing the antipsychotics for the generic patient with no known risk factors for side effects

Patients in CATIE did not stay on any of the medications very long. Even with olanzapine, only 36% stayed on it for the full 18 months and this was a population of relatively cooperative patients willing (and deemed able to) cooperate in a complicated study. These results are not necessarily representative of clinical practice. It may be that the nature of the study was to suggest to patients and clinicians to try another drug to see if it might do better. The issue of expectations becomes paramount in such situations. Because the advantage for olanzapine for efficacy is questionable based on the higher dosage available and because of the higher risk for metabolic side effects, it cannot be recommended as the first choice among the atypical agents for starting a patient on an atypical. We also cannot conclude from CATIE, in the absence of cognition data, that a typical agent is as effective as an atypical; this issue will require review when cognitive data from CATIE are reported. Quetiapine has a metabolic side effect profile that is closer to olanzapine than the others.

With this reasoning, the choice of atypicals in Node 3 might begin with ziprasidone, risperidone or aripiprazole, even if there are no known risk factors for diabetes. Aripiprazole was not used in Phase One of CATIE, but there is evidence from some randomized controlled trials that its efficacy is equivalent to the non-olanzapine group 10,11 and its rate of metabolic side effects seems comparable to ziprasidone and risperidone. Risperidone does cause prolactin elevations which the other drugs do not, but the evidence that this has a long-term adverse effect, which is reviewed elsewhere in the IPAP, suggests that this is not a sufficient reason to rank it lower than aripiprazole or ziprasidone with regard to tolerability and safety.

If aripiprazole, risperidone, or ziprasidone is tolerated and the patient receives an adequate trial, but effectiveness is unsatisfactory, then consider olanzapine next (Node 6) because all of the others have comparable effectiveness to the first medication tried, and olanzapine may have greater effectiveness. It may be necessary to go up to doses as high as 30 mg/day. If olanzapine

then is given in an adequate trial and produces an unsatisfactory outcome, there would have been two adequate antipsychotics trials and clozapine should be considered (Node 8).

If, on the other hand, aripiprazole, risperidone, or ziprasidone cannot be given in an adequate trial due to lack of toleration, try one of the others (Node 4). If neither is tolerated (still Node 4), try perphenazine, or quetiapine which have somewhat more serious side effect problems (movement disorders, less benefit for cognition, greater weight gain) though these problems may be of less concern than the metabolic issues with olanzapine. If these are not tolerated (still Node 4), try olanzapine.

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