What does CATIE tell us about Tardive Dyskinesia?

By Neil S. Kaye, MD, DFAPA, for the Neuropsychiatry Committee:

The clinician and forensic psychiatrist are both faced with interpreting the results of the Clinical Antipsychotic Trials of Interventions Effectiveness study (1). The media quickly reported that perphenazine was as effective and as safe as the newer atypical antipsychotics in the study, and many legislative bodies and some managed care companies began to murmur that with these findings, it was only prudent to begin with perphenazine and this obviously would allow significant cost savings. Many of us have been called upon as experts and forensic scientists to discuss the CATIE findings. What follows are some talking points:

CATIE is the NIMH funded study of 1493 subjects. The admission diagnosis was pure schizophrenia (no schizoaffective or bipolar disorder), in adults (ages 18-65), with a known response to one of the included medications (perphenazine, risperidone, olanzapine, quetiapine or ziprasidone) (1). As in all studies, CATIE has some methodological flaws.

The best studies are prospective, double blind, randomized, placebo controlled and parallel in design. CATIE is not. Because perphenazine is known to carry a higher risk rate of tardive dyskinesia (TD), 231 subjects were not randomized to perphenazine, based on their histories of movement disorder. To expose high risk subjects to perphenazine would have been unethical. In addition, in an effort to minimize the risk of TD, the dosing of perphenazine was limited. The mean modal dose of perphenazine in the first arm of CATIE was 20.8 mg with a maximum allowable dose of 32 mg. Many of us who used this medication to treat schizophrenia frequently used doses between 32 and 64 mg qd. Only 40% of subjects in CATIE treated with perphenazine actually received the maximum allowed dose of 32 mg (1).

CATIE assessed extrapyramidal side effects (EPS) using the three standardized and accepted movement disorder rating scales: the Abnormal Involuntary Movement Scale (AIMS); the Simpson Angus Extrapyramidal Symptoms Scale (SA); and the Barnes Akathisia Rating Scale (BARS). CATIE reported that there was no significant difference in the rates of EPS between the five medications based on the above scales. Nonetheless, more patients discontinued perphanzine due to EPS than any other medication. This finding suggests that many patients perceive a difference or a side effect of a medication that may not actually be captured on a rating scale used in a scientific study. Many clinicians are not surprised by these results, as in general, they confirm what we as psychiatrists have long held as true; classic antipsychotics have higher rates of EPS and TD than do the second generation antipsychotics.

CATIE is a prospective study, with a maximum duration of 18 months. Unfortunately, 74% of subjects never complete the study. As we also believe that duration of exposure is a factor in the development of TD, the relatively short duration of exposure during the subject also makes drawing conclusions about relative risks of TD rather risky.

In short, CATIE doesn't tell us much about the real risks of TD with any of these medications. To draw conclusions that suggest the risks are the same or different between any of these medications, based on the CATIE data itself, is not supported by appropriate evidenced based medicine criteria. CATIE simply is neither designed nor powered to answer this question.

CATIE also doesn't address the standard of care. The standard of care is to use atypical antipsychotics first line, particularly because of the known higher risk of TD associated with classic medications (2). As forensic psychiatrists, being aware of this standard of care is crucial to the discussion now taking place in the public forum. There certainly is still a role for classic antipsychotics, and it is clear that the newer agents pose risks of their own, particularly in the metabolic area.

Only by knowing the real data are we able to provide the best answers to our patients when having informed consent discussions. AAPL members can learn more about CATIE and it's findings by attending the Annual Meeting this October, where the Committee on Psychopharmacology and the Law will be joining with the Neuropsychiatry Committee to discuss CATIE and what it all means. We hope to see you there.

1. Lieberman, J. et. al.: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. NEJM: 2005; 353: 1209-23

2. Kaye, N. Tardive dyskinesia: tremors in law and medicine. JAAPL: 1999: 27, 2, 315-33