

Estimated 10-year Coronary Heart Disease Risk Differs Significantly Between Antipsychotic Agents

The following is an extract of:

Daumit GL, Goff DC, Meyer JM, et al. Antipsychotic effects on estimated 10-year coronary heart disease risk in the CATIE schizophrenia study. *Schizophrenia Research* 2008; (105): 175-187.

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Bottom Line:

- Estimated 10-year Coronary Heart Disease risk differed significantly between antipsychotics, with the highest risk conferred by olanzapine, followed by quetiapine.
- Coronary Heart Disease risk estimates decreased for individuals switched to risperidone, ziprasidone, and perphenazine.
- Analysis based on a research population of outpatients (n=1460) with schizophrenia in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial.

This prospective, randomized study is the first to characterize the effects of individual antipsychotics on overall CHD risk over time. Investigators in the CATIE Schizophrenia Trial found that the impact of antipsychotic agents on CHD risk varies significantly between antipsychotic agents. Lead authors Gail L. Daumit, MD (Johns Hopkins University) and Jeffrey A. Lieberman, MD (Columbia University, New York State Psychiatric Institute) found that olanzapine produced the largest elevation in CHD risk, as determined by the Framingham risk equation, after only a few months of treatment. Quetiapine also elevated risk, but to a lesser extent. Furthermore, the authors found the largest treatment differences among older subjects and those with at least a 10% CHD risk at baseline. These findings have important clinical implications for assessing risk vs. benefits of different antipsychotic medications.

Study Background

Persons with schizophrenia have standardized mortality rates up to three times higher than the general US population. Recent studies suggest that much of this increased mortality is related to cardiovascular disease. Factors associated with elevated CHD risk, including smoking, obesity, diabetes, unhealthy diet, hypertension and elevated total or low HDL cholesterol, are more highly prevalent among those with schizophrenia. Atypical antipsychotics likely contribute to elevated CHD risk by affecting weight gain, glucose dysregulation and lipid abnormalities. The CATIE Schizophrenia Trial was conducted between January 2001 and December 2004 at 57 US treatment sites. In the first phase of the study outpatients with schizophrenia (n=1460) were assigned to one of four different antipsychotics: olanzapine, perphenazine, quetiapine or risperidone. Participants were followed for 18 months or until treatment discontinuation. The Framingham risk equation was derived from the Framingham Heart Study. This equation is a validated calculation of 10-year CHD risk and has been tested in various populations. The current study's objective was to assess the effect of specific antipsychotics on estimated 10-year CHD risk over time in patients with schizophrenia.

Study Details

The study population (n=1460) included those who had initially been randomized in the CATIE trial and for whom information was available for at least one follow-up visit. CHD risk was calculated at baseline and at the end of phase I. During the CATIE trial, participants underwent comprehensive medical evaluations, including measurement of vital signs, weight and smoking

status at screening and at 2-3 month intervals up to 18 months. Fasting laboratory measurements were collected at baseline and at 3, 6, 12, and 18 months. The primary outcome variable was change from baseline in 10-year CHD risk using the Framingham Heart Study formula. Secondary outcome measures included changes from baseline by antipsychotic treatment in diabetes status, smoking status, hypertension, total cholesterol and HDL levels. Treatment analyses were adjusted for baseline risk, phase I treatment duration, demographic and other baseline measures associated with CHD risk. Age and gender were also taken into consideration.

Results and Limitations

A significant difference between treatment groups ($p=0.007$) was found in change in the 10-year coronary heart disease risk estimate. Olanzapine was associated with the highest increase, at 0.5% (SE 0.3), followed by quetiapine 0.3% (SE 0.3). Risk estimates decreased for risperidone (-0.6%, SE 0.3), and ziprasidone (-0.6%, SE 0.4), followed by perphenazine (-0.5%, SE 0.3). Individual comparisons between treatment groups showed a significant difference between risperidone and olanzapine ($p=0.004$). Differences between medications were significant for individuals under age 40 ($p=0.016$), and for those aged 50 years and older ($p=0.0008$), but not for those between the ages of 40-49. Change in 10-year cardiac risk was significantly different across treatment arms for patients with a baseline CHD risk of 10% or higher ($n=365$, $p=0.017$). For those with less than 10% baseline CHD risk ($n=760$), change in estimated 10 year CHD risk did not differ across treatment groups. Finally, overall change in 10-year CHD risk was significant for men ($p=0.017$), but not for women.

Regarding individual cardiac risk factors, only total and HDL cholesterol levels differed. High total cholesterol increases CHD risk, while high HDL levels decrease risk. An association between race and effects of antipsychotics on HDL was also found. In whites, perphenazine was associated with a significant elevation in HDL compared to olanzapine ($p<0.001$) and quetiapine ($p=0.002$). However, in nonwhites ziprasidone was associated with increased HDL (4.3 mg/dl, SE=1.4), while perphenazine (-1.3 mg/dl, SE=1.0; $p=0.001$) and olanzapine (-0.9 mg/dl, SE=0.9; $p=0.002$) both decreased HDL. The authors note that the differential association of race with certain antipsychotics and HDL changes has not previously been reported and may warrant further investigation.

Limitations of this study include the fact that the CATIE trial was not initially designed to assess CHD risk, and as such definitions for hypertension, smoking, and diabetes in this study differ from the Framingham definitions. Furthermore, although the Framingham equation has been tested in various populations, it has not yet been validated in a population using antipsychotics.

Clinical Implications

The authors note that this study is distinctive in analyzing overall CHD risk across several antipsychotics in a large randomized, clinical trial. The changes in CHD risk were found in a relatively short period of time (average of 9.5 months, with a maximum treatment exposure of 18 months). Although the authors note that the baseline cardiovascular risk may have accumulated prior to the study, changes from baseline in CHD risk differed significantly across antipsychotic medications. Olanzapine was associated with the highest risk, with quetiapine carrying a similar risk. The lowest overall risk was associated with risperidone, ziprasidone, and perphenazine. The authors conclude, "When initiating or changing therapy, clinicians should consider these changes in likelihood of coronary heart disease, particularly for older patients and those with baseline coronary risk factors."

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