Comparison of Antipsychotics for Metabolic Problems (CAMP): A NIMH Schizophrenia Trials Network Study

T. Scott Stroup,[1] Joseph P. McEvoy,[2] Marvin S. Swartz,[2]
Robert M. Hamer,[1] Diana O. Perkins,[1] Jeffrey A. Lieberman[3]

Abstract

Because of growing concern about the physical health status of persons with schizophrenia and uncertainty regarding optimal strategies to manage metabolic side effects of antipsychotic drugs that increase the risk of cardiovascular disease, we developed a protocol to test the effectiveness of a common strategy—switching to an antipsychotic associated with lower risk of metabolic side effects. In this study we will randomly assign individuals with schizophrenia or schizoaffective disorder who have increased BMI (≥27) and elevated non-HDL cholesterol (≥160 mg/dL) to stay on their current stable dose of olanzapine, quetiapine, or risperidone, or to switch to aripiprazole. All study participants will receive a behavioral treatment that is aimed at modifying cardiovascular risk factors, including weight, activity level, blood sugar, blood pressure, and lipids. Because non-HDL cholesterol is a significant predictor of cardiovascular disease and has some advantages over total cholesterol and LDL cholesterol, the primary outcome will be change in non-HDL cholesterol. Other important metabolic parameters, including fasting blood sugar, glycosylated hemoglobin, triglycerides, and weight will be examined. The study will also examine the effects of switching medications on the status of psychotic illness. Follow-up in the study is six months. The study is underway using the Schizophrenia Trials Network, a research infrastructure established by the National Institute of Mental Health to conduct the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial. ClinicalTrials.gov Identifier: NCT00423878

Rationale

In response to growing concern about the physical health status of persons with schizophrenia (1, 2) and uncertainty regarding optimal strategies to manage metabolic side effects of antipsychotic drugs that increase the risk of cardiovascular disease, we developed a protocol to test the effectiveness of a common strategy—switching to an antipsychotic with lower risk of metabolic side effects.

Among all causes of death, cardiovascular (CV) disease is responsible for as much as 50% of the excess mortality associated with schizophrenia (3). One way to assess cardiovascular risk is by presence of the metabolic syndrome (MS), a diagnostic category intended to help identify individuals at risk of CV disease for the purpose of initiating lifestyle changes that might lower that risk (4). Using baseline data from the National Institute of Mental Health-sponsored Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial, investigators assessed the prevalence of MS prevalence using a standard definition from the National Cholesterol Education Program (NCEP) (5, 6). Only subjects with sufficient data on use of antihypertensives, hypoglycemic medications or insulin, and fasting glucose and lipid values were included in the analysis. Analyses were conducted using a randomly selected sample from the Third National Health and Nutrition Education Survey (NHANES III), matched 1:1 with CATIE subjects on the basis of age, gender, and race/ethnicity. Of 689 CATIE subjects with the requisite data, the crude prevalence of metabolic syndrome was 40.9%, including a prevalence of 36% among men and 51.5% among women (Table 1). The authors concluded that the metabolic syndrome is highly prevalent in this large cohort

[1]Department of Psychiatry, University of North Carolina at Chapel Hill
[2]Department of Psychiatry and Behavioral Sciences, Duke University Medical Center
[3]Department of Psychiatry, College of Physicians and Surgeons of Columbia University

Address for correspondence: T. Scott Stroup, MD, MPH, Department of Psychiatry, University of North Carolina at Chapel Hill, Campus Box 7160, Chapel Hill, NC 27599
Phone: 919-966-6846; E-mail: sstroup@med.unc.edu

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Table 1 Metabolic Syndrome Prevalence Among CATIE Fasting Subjects

Subject Cohort	All	Male	Female	White	Black	Hispanic
Mean Age (yrs.)	40.4±11.2	39.2±11.3	43.7±11.3	40.7±11.2	40.4±11.3	39.2±12.1
Mean BMI (kg/m^2)	29.7±7.0	28.5±6.2	33.0±8.1	29.7±6.9	29.7±7.2	29.5±6.6
MS Prevalence (6)	40.9% (n=686)	36.0% (n=508)	51.6% (n=178)	44.2% (n=434)	29.6% (n=213)	39.5% (n=81)

of schizophrenia patients and represents a substantial source of cardiovascular risk, especially for women with schizophrenia.

The metabolic syndrome, however, is only one way to identify cardiovascular risk, and it has been criticized as arbitrary in its number of criteria and for the cutpoints used for the individual criteria (4). Reaven has stressed that it is the dyslipidemic components of the metabolic syndrome, which are characteristic of insulin-resistant and hyperinsulinemic individuals, that are most highly predictive of CV disease, and that when dyslipidemias are treated successfully this leads to a decreased incidence of CV disease (4). One focus has been on non-HDL cholesterol, which has been shown in large cohort studies to be strongly associated with cardiovascular morbidity and mortality. In the Lipid Research Clinics Program Follow-up Study, for example, within a cohort of 2,462 middle-aged men and women who were followed for an average of nineteen years, non-HDL cholesterol at study entry was a strong predictor of CV disease mortality in both sexes (7). An increase of 30 mg/dL of non-HDL cholesterol was associated with a 19% increase in CV disease mortality in men, and a 15% increase in women.

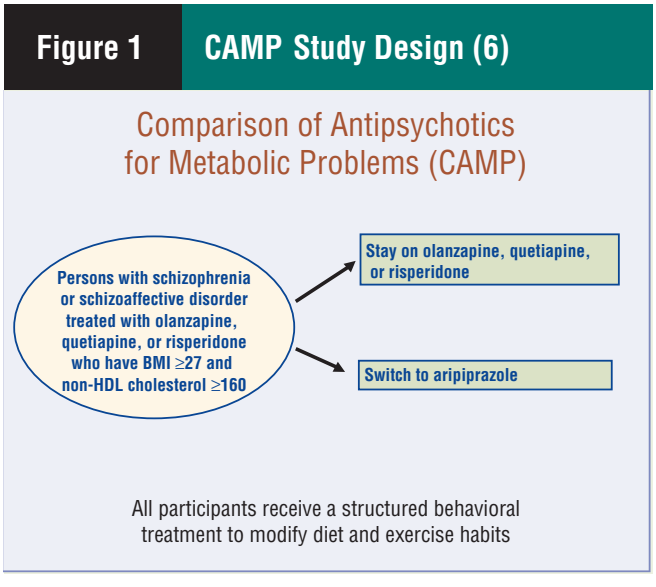
Non-HDL cholesterol has some advantages over other cholesterol measures of cardiovascular risk. Total cholesterol includes both "good" and "bad" cholesterol, while non-HDL cholesterol only contains atherogenic lipid particles (i.e. very low density lipoprotein [VLDL], intermediate density lipoprotein [IDL], low density lipoprotein [LDL], and lipoprotein [a])(8). Non-HDL cholesterol has an advantage over LDL-C because it can be measured directly, while LDL is estimated by the Friedwald equation (Total cholesterol – HDL-C—Triglycerides/5), which is increasingly inaccurate as triglyceride levels rise (8).

Several studies have conducted secondary analyses to examine whether a switch in regimens might be of benefit in patients experiencing weight gain and/or metabolic effects on an atypical antipsychotic regimen. Overall, these short-term studies have suggested that some improvement in weight and lipid profile improvements can be expected when patients switch from olanzapine or risperidone to ziprasidone and from olanzapine to aripiprazole (9-11). Despite these promising data from switch studies, no randomized studies that primarily focus on the effects of switching atypical antipsychotics on metabolic parameters associated with cardiovascular disease have been published.

Comparison of Antipsychotics for Metabolic Problems (CAMP)

The Comparison of Antipsychotics for Metabolic Problems (CAMP) Study is an investigator-initiated clinical trial that will be conducted at thirty research sites that are a part of the NIMH-sponsored Schizophrenia Trials Network (STN). The CAMP study is a multi-site, randomized controlled trial that will enroll 300 patients with schizophrenia or schizoaffective disorder for whom a medication change may be indicated because of an increased risk of cardiovascular disease in spite of a stable antipsychotic treatment regimen. Entering patients will be treated with olanzapine, quetiapine, or risperidone and have a BMI ≥27 and a non-HDL cholesterol ≥160 mg/dL. After baseline assessments have been completed, these patients will be randomly assigned to continue treatment with olanzapine, quetiapine, or risperidone, or to switch to treatment with aripiprazole. The randomization will be stratified according to pre-trial antipsychotic. All treatments will be open label, but raters will be blinded to treatment assignment. Patients will be followed for up to twenty-four weeks. All

Figure 1 CAMP Study Design (6)



patients will receive a behavioral therapy intervention focused on diet and exercise. The study design is summarized in Figure 1.

The aims of the study are to (1) determine the effects of switching to aripiprazole versus continued treatment with olanzapine, quetiapine, or risperidone on metabolic parameters associated with cardiovascular disease, and (2) to determine the effects of switching on clinical status. All individuals in the study will receive a structured program focusing on diet and exercise as a means to reduce the risk of cardiovascular disease. The hypothesis is that switching to aripiprazole will lead to a decreased risk of cardiovascular disease.

Enrollment Criteria

The CAMP study will enroll 300 patients with schizophrenia or schizoaffective disorder for whom a medication change may be indicated because of an increased risk of cardiovascular disease. Specific inclusion and exclusion criteria are in Table 2.

Table 2 Enrollment Criteria

Key Inclusion Criteria
-Outpatients 18-65 years of age with a diagnosis of schizophrenia or schizoaffective disorder
-Currently treated with olanzapine, quetiapine, or risperidone and on that drug for the three months prior to study entry with no dose adjustments of this drug and no use of other antipsychotics in the most recent month.
-BMI ≥27
-Non-HDL cholesterol ≥160 mg/dL
Key Exclusion Criteria
-Diabetes or treatment with oral hypoglycemic drug or insulin
-History of cerebrovascular or cardiovascular disease (i.e. stroke, transient ischemic attacks (TIAs), coronary artery disease, angina, heart attack/myocardial infarction, peripheral vascular disease, abdominal aortic aneurysm, or congestive heart failure)
-Non-HDL cholesterol >300 mg/dL
-Serum triglycerides >500 mg/dL
-Patients who first began antipsychotic drug treatment for psychosis within the previous 6 months
-Women who are pregnant or breastfeeding
-High risk of suicide in the judgment of the investigator
-History of HIV infection or AIDS
-Other serious and unstable medical condition
-Known hypersensitivity to aripiprazole
-Weight-loss medications are not permitted
-Patients on valproate, lithium, topiramate are allowed if there have been no dose adjustments in the month prior to study entry
-Patients on lipid-lowering medications (e.g. statins or fibrates) are allowed if there have been no dose adjustments in the month prior to study entry

Treatments

Medications

The dosage ranges for the study drugs are as follows:

Aripiprazole (Abilify) 5-30 mg/day
Quetiapine (Seroquel) 200-800 mg/day
Risperidone (Risperdal) 1-16 mg/day
Olanzapine (Zyprexa) 5-20 mg/day

Cross-titration for those assigned to switch to aripiprazole:

- Day 0: maintain full dose previous drug and start 5 mg aripiprazole
- Day 7: decrease 25-50% of current dose previous drug and increase aripiprazole to 10 mg
- Day 14: decrease 50-75% of original dose previous drug and stay at aripiprazole 10 mg or increase to 15 mg
- Day 21: stop previous drug and adjust dose aripiprazole as needed between 5-20 mg/day
- Day 28: adjust dose aripiprazole as needed between 5-30 mg/day

All subjects will have weekly visits during the cross-titration for medication management.

Behavioral Treatment

All study participants will receive individual behavioral treatment, adapted from the "Behavioral Group-Based Treatment for Weight Reduction in Schizophrenia and Other Severe Mental Illnesses" developed by Rohan Ganguli, MD, and colleagues at the University of Pittsburgh (12). The program is aimed at modifying cardiovascular risk factors, including weight, activity level, blood sugar, blood pressure, and lipids, and will be provided to all study participants (Table 3). Study participants will keep food and exercise diaries, and will track physical activities and weight. Behavioral treatment sessions

Table 3 Behavioral Treatment Topics

Self-monitoring: awareness of body weight and what one eats
Burning calories by exercise
Controlling urges to overeat and snack
Burning calories by using energy
Decreasing cues to overeat and snack
Developing good eating habits
Self-control of overeating
Changing snack habits

are scheduled weekly during the initial month of study treatment (during cross-titration) and then at each monthly visit.

Outcomes

The primary outcome measure is the mean difference in non-HDL cholesterol level changes between patients assigned to stay on their current antipsychotic compared to patients assigned to switch to aripiprazole at the last observation. Only patients who have at least one post-baseline measurement of non-HDL cholesterol will be evaluable for this primary outcome. In addition, the study will examine changes in weight and other metabolic outcomes, including triglycerides, LDL cholesterol, insulin levels, C-reactive protein, glycosylated hemoglobin, and 2-hour oral glucose tolerance test.

The key secondary outcome measure is illness exacerbation, defined as psychiatric hospitalization, a 25% increase from baseline on the Positive and Negative Syndrome Scale (PANSS) (or a 10-point increase for individuals with a baseline total score of 40 or less), or substantial clinical deterioration on the Clinical Global Impressions-Change (CGI-C) Scale (i.e. "much worse" or "very much worse").

Anticipated Results

The CAMP study will provide empirical evidence regarding the effectiveness of switching antipsychotic medications to address the metabolic problems that are common in individuals with schizophrenia or schizoaffective disorder. We anticipate that both groups of enrollees will have some improvement in weight and metabolic parameters but that the patients assigned to switch to aripiprazole will have greater improvements than those who stay on olanzapine, quetiapine, or risperidone. Although we anticipate that some patients will have difficulties switching medications, the study protocol is designed to minimize these problems by using a careful cross-titration schedule, weekly clinical visits during the switch, and the use of concomitant medications as needed. Although we expect that illness exacerbations will be minimized using these techniques, a substantial rate of exacerbations among the switchers will be interpreted as cause for caution in using the strategy of switching to aripiprazole, especially if the metabolic improvements are modest.

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