Comparison of Longer-Term Safety and Effectiveness of 4 Atypical Antipsychotics in Patients Over Age 40: A Trial Using Equipoise-Stratified Randomization

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Objective: To compare longer-term safety and effectiveness of the 4 most commonly used atypical antipsychotics (aripiprazole, olanzapine, quetiapine, and risperidone) in 332 patients, aged > 40 years, having psychosis associated with schizophrenia, mood disorders, posttraumatic stress disorder, or dementia, diagnosed using DSM-IV-TR criteria.

Method: We used equipoise-stratified randomization (a hybrid of complete randomization and clinician’s choice methods) that allowed patients or their treating psychiatrists to exclude 1 or 2 of the study atypical antipsychotics due to past experience or anticipated risk. Patients were followed for up to 2 years, with assessments at baseline, 6 weeks, 12 weeks, and every 12 weeks thereafter. Medications were administered employing open-label design and flexible dosages, but with blind raters. The study was conducted from October 2005 to October 2010.

Outcome Measures: Primary metabolic markers (body mass index, blood pressure, fasting blood glucose, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides), percentage of patients who stay on the randomly assigned atypical antipsychotic for at least 6 months, psychopathology, percentage of patients who develop metabolic syndrome, and percentage of patients who develop serious and nonserious adverse events.

Results: Because of a high incidence of serious adverse events, quetiapine was discontinued midway through the trial. There were significant differences among patients willing to be randomized to different atypical antipsychotics (P < .01), suggesting that treating clinicians tended to exclude olanzapine and prefer aripiprazole as one of the possible choices in patients with metabolic problems. Yet, the atypical antipsychotic groups did not differ in longitudinal changes in metabolic parameters or on most other outcome measures. Overall results suggested a high discontinuation rate (median duration 26 weeks prior to discontinuation), lack of significant improvement in psychopathology, and high cumulative incidence of metabolic syndrome (36.5% in 1 year) and of serious (23.7%) and nonserious (50.8%) adverse events for all atypical antipsychotics in the study.

Conclusions: Employing a study design that closely mimicked clinical practice, we found a lack of effectiveness and a high incidence of side effects with 4 commonly prescribed atypical antipsychotics across diagnostic groups in patients over age 40, with relatively few differences among the drugs. Caution in the use of these drugs is warranted in middle-aged and older patients.

Trial Registration: ClinicalTrials.gov identifier: NCT00245206

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