

No difference in nonsuicide mortality between 2 anti-psychotic drugs

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The potential for harmful side effects associated with anti-psychotic medications for treating schizophrenia is a frustration for mental-health professionals who must balance this with the positive benefits of drugs. For example, the issue of the antipsychotic drug ziprasidone lengthening the QTc interval, a possible indicator of life-threatening heart arrhythmias, has demanded much attention among clinicians since the drug was introduced in 2001.

Ziprasidone (marketed as Geodon and Zeldox by Pfizer Inc.) was the fifth second-generation anti-psychotic to gain [Food and Drug Administration](#) (FDA) approval. These second-generation drugs have been thought to be associated with a lower risk of suicides, better functional capacity, and an improved quality of life for people with schizophrenia. (It is well known that patients with schizophrenia suffer an overall increased risk of death.) But questions remained as to whether the modest QTc prolongation caused by ziprasidone would translate into increased mortality for the patients using it.

A study published online this month in the [American Journal of Psychiatry](#) in advance of print publication in February 2011 showed no difference in nonsuicide mortality between people taking ziprasidone and another second-generation anti-psychotic in real-world use.

Because the number of patients exposed to ziprasidone at the time of marketing authorization was too small to allow for estimation of QTc-related effects on mortality, and because such studies would not reflect

real-world prescribing practices, the Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC) was initiated to provide safety assurance for the use of the drug. ZODIAC was a post-approval commitment by the drug's manufacturer, Pfizer, Inc., to the FDA.

ZODIAC is an international, multimember, randomized trial designed to examine the risks of nonsuicidal mortality and hospitalization associated with ziprasidone and [olanzapine](#), another second-generation antipsychotic approved by the FDA for the treatment of schizophrenia and bipolar disorder. Brian Strom, MD, director of the Center for Clinical Epidemiology and Biostatistics at the University of Pennsylvania School of Medicine, chaired the steering committee that designed and directed the ZODIAC study. Strom is also chair of the Department of Biostatistics and Epidemiology and Vice Dean for Institutional Affairs in the School of Medicine.

Olanzapine (marketed as Zyprexa and other brands names by Eli Lilly and Comp.) was selected for comparison in the study because it was not linked to QTc prolongation in the literature or in a controlled pharmacokinetic study of several agents compared with ziprasidone. The main objective of ZODIAC was to evaluate nonsuicide mortality, which limited the study's ability to provide data on drug efficacy.

ZODIAC, an open-label, randomized trial, enrolled over 18,000 patients with schizophrenia in 18 countries. The primary outcome measure was nonsuicide mortality in the year after initiation of treatment. Patients were randomly assigned to receive treatment with either ziprasidone or olanzapine and followed for one year by unblinded investigators providing usual care. A physician-administered questionnaire was used to collect baseline demographic information, medical and psychiatric history, and concomitant medication use. Follow-up information on hospitalizations and emergency department visits, patients' vital status, and current antipsychotic drug status was also collected.

A total of 205 deaths occurred overall in the study population. Despite the known risk of QTc prolongation with ziprasidone treatment, the findings did not show that ziprasidone is associated with an elevated risk of nonsuicidal mortality relative to olanzapine in real-world use. However the study was not designed to examine the risk of rare cardiac events associated with lengthening of the QTc interval.

"We could not disprove that the drug caused abnormal heart rhythms, but that was not the goal of the study," says Strom. "Our goal was to determine whether there was a difference in risk of nonsuicide death, and there was not."

Provided by University of Pennsylvania School of Medicine

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