The Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC): Design and Baseline Subject Characteristics

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Background: Ziprasidone has been used to treat schizophrenia since 2000. It is unknown whether its modest QTc-prolonging effect increases cardiovascular event risk.

Purpose: To describe the study design of the Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC).

Method: The study was conducted between February 2002 and February 2006. One-year follow-up for the primary endpoint of nonsuicide death ended in April 2007. ZODIAC is an open-label, randomized, postmarketing study enrolling patients with schizophrenia in naturalistic practice in 18 countries. The primary outcome measure was the rate of nonsuicide mortality in the year after initial recommendation for therapy. Subjects were randomly assigned to either ziprasidone or olanzapine, after which follow-up was conducted by investigators aware of the assigned exposure. A physician-administered questionnaire collected baseline information on patients' demographics, medical and psychiatric history, and concomitant medication use. Data were self-reported by patients or reported by enrolling physicians.

Results: ZODIAC enrolled 18,240 patients with schizophrenia. Most (73.0%) were from the United States or Brazil. Patients' baseline mean age was 41.6 years, 55.1% were male, and 60.0% were white. At baseline, approximately 18% had hypertension, 14.8% had hyperlipidemia, 46.5% currently smoked, 28.9% had a body mass index ≥ 30 kg/m^2, and 7.7% had diabetes. Mean time from schizophrenia diagnosis to study enrollment was 10.4 years and mean Clinical Global Impressions scale score was 5.2 (range: 1–8). Nearly one third of patients had ever attempted suicide. Seventy-one percent were using antipsychotics at baseline. Almost 80% were using concomitant medications, with 29.5% using antidepressants, 25.4% using anxiolytics, and 19.0% using mood stabilizers. Less than 3% were using antihypertensives or statins.

Conclusions: ZODIAC is a uniquely designed study with an initial randomization to ziprasidone or olanzapine and follow-up largely consistent with usual practice (i.e., many characteristics of a nonexperimental study). Baseline data suggest this study population has a substantial prevalence of cardiovascular risk factors. Concomitant medications were used frequently, although hyperlipidemia and hypertension may be undertreated.

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Ziprasidone is a novel antipsychotic agent that has demonstrated efficacy in the treatment of schizophrenia in both short-term[1–3] and long-term trials[4,5] as well as in the treatment of bipolar mania,[6,7] along with a low propensity for causing extrapyramidal symptoms[8] and hyperprolactinemia.[9] These same trials have shown ziprasidone to exert a beneficial effect on weight gain and serum lipid levels,[10] 2 well-established cardiovascular risk factors. It has been known since its development that ziprasidone prolongs the QTc interval. In a phase 1 QT

study at high doses, mean QTc prolongation was approximately 9 to 14 milliseconds greater for ziprasidone than for several other antipsychotics tested but approximately 14 milliseconds lower than thioridazine.[11] However, no ziprasidone-treated patient had a QTc ≥ 500 milliseconds, despite coadministration of ketoconazole to patients receiving the maximum recommended daily dose of ziprasidone. In the phase 2/3 development program overall, 2 (0.06%) of the 2988 patients had a QTc interval ≥ 500 milliseconds.[12] The 500 millisecond threshold is important since most reported cases of torsades de pointes occur at this level of prolongation or greater.

However, the precise relationship between QTc prolongation and the risk of serious adverse cardiac events remains unsettled.[13] Significant QTc prolongation is of concern because of its potential to induce torsades de pointes and, rarely, sudden death. Syncope, palpitations, dizziness, or seizures may in some cases also represent a manifestation of torsades de pointes. However, antipsychotic drugs causing much more QTc prolongation than ziprasidone have been shown to increase sudden death only when used at very high doses,[14] although whether this generalizes to ziprasidone is unknown.

The Clinical Antipsychotic Trials of Intervention Effectiveness study[15] included 1460 patients, of whom 185 were randomly assigned to ziprasidone (ziprasidone was added to the study after approximately 40% of subjects had been enrolled). Ziprasidone was comparable in effectiveness to the other medications in the first phase of the trial but was the only study drug associated with improvement in glycosylated hemoglobin, total cholesterol, and triglyceride levels. It was also associated with the lowest proportion of patients (7%) who gained more than 7% of their baseline weight.

Nevertheless, the available sample size of patients exposed to ziprasidone before marketing was limited, and the U.S. Food and Drug Administration (FDA) recognized that the premarketing data may not reflect real-world use or real-world drug effects. Further study of a large number of patients was indicated, therefore, in order to provide further safety assurance. This study was a regulatory requirement of both the FDA and the Swedish regulatory authorities.

The Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC), an international, multicenter, randomized, large simple trial, was designed to compare ziprasidone with another agent with respect to mortality and hospitalization outcomes, including the primary outcome nonsuicide mortality. This outcome was chosen as the primary measure since it was the most important. Further, an increase in an uncommon cause of death like torsades de pointes could be counterbalanced by even a small decrease in a more common cause of death, like atherosclerotic events, and given the lack of metabolic effects of ziprasidone, this latter was a possibility. Olanzapine was chosen as the medication for the comparison group since it is a second-generation (atypical) antipsychotic agent without the same effect on QT prolongation.[16] We chose to perform a large simple clinical trial to assure balance between the groups[17] since it was not clear whether patients at higher risk of cardiac outcomes would be more likely to be placed on ziprasidone (because of its lack of metabolic effects) or on olanzapine (because of its lack of QT effects).

METHOD

Study Design

The study design chosen was that of a large simple trial, i.e., a study conducted with minimal modification of normal medical care, other than random allocation among the study arms.[17] Following 1:1 random assignment to treatment with either ziprasidone or olanzapine, patients received the selected medication in an unblinded fashion, and no further study-related interventions were made. Randomization was stratified by country. Patients were prospectively followed as clinically appropriate and outcomes determined. No laboratory testing or clinical monitoring was required by the protocol but was conducted at the discretion of the treating physician as clinically appropriate. Data regarding subjects' vital status, continued use of assigned study drug, and hospitalization status were obtained through follow-up with the treating physician or other designated member of the medical care team. Medical records and other documentation, where applicable, were obtained and analyzed.

Study Sites

Approximately 18,000 patients were to be included in the study, including approximately 9235 patients from 701 centers in the United States, 45 patients from 10 centers in Sweden, 3000 patients from 34 centers in Brazil, 1500 patients from 33 centers in Argentina, 500 patients from 18 centers in Chile, 400 patients from 11 centers in Mexico, 500 patients from 8 centers in Peru, 250 patients from 5 sites in Uruguay, 130 patients from 4 centers in Hong Kong, 300 patients from 8 centers in Malaysia, 90 patients from 3 centers in Singapore, 150 patients from 4 centers in Taiwan, 200 patients from 5 centers in Thailand, 200 patients from 10 centers in South Korea, 500 patients from 15 centers in Hungary, 400 patients from 20 centers in Poland, 200 patients from 15 centers in Slovakia, and 250 patients from 25 sites in Romania.

Study Subjects

Inclusion criteria. The ZODIAC study enrolled patients with schizophrenia, as per physician clinical judgment, from community mental health clinics, private psychiatric practices, residential care facilities, and academic treatment centers in 18 countries between February 2002 and February 2006. One-year follow-up for the primary

endpoint of nonsuicide death ended in April 2007. Patients newly treated for schizophrenia and those receiving continuing treatment were eligible if the treating psychiatrist was ready to initiate a new antipsychotic medication and would consider using either ziprasidone or olanzapine as an appropriate therapy. Male and female patients who met all the following criteria were eligible to be enrolled in this study: aged 18 years or older; treated in an inpatient or outpatient setting; diagnosed with schizophrenia; willing to provide enrolling physician with written, signed, and dated informed consent to participate in study; willing to provide Social Security number (applicable to U.S. participants only); and willing to provide information on at least 1 alternate contact person for study staff to contact regarding patient's whereabouts, should the patient be lost to follow-up over the course of the study.

Exclusion criteria. Patients presenting with any of the following criteria were excluded from the study: pregnant or lactating women; participation in any other studies involving investigational products, concomitantly or within 30 days prior to entry in the study; presence of progressive fatal disease of a life expectancy that prohibits them from participating in a 1-year research study; or previously randomly assigned to study medication and enrolled in this study.

Subject Enrollment

After a physician determined that a patient was eligible for inclusion in the study and willing to participate, the patient signed a written and dated informed consent document acknowledging his or her understanding of the risks and benefits of participating in the study and providing access to future medical and hospital records. In Argentina, Chile, Mexico, Peru, Uruguay, Hong Kong, Malaysia, Singapore, Thailand, Taiwan, South Korea, Hungary, and Poland, a urine pregnancy test was performed prior to enrollment among women of childbearing potential, per local country regulations. Minimal information, including demographics, a measure of the severity of the underlying schizophrenia, cardiac risk factors, and prior antipsychotic medication use, was collected on the baseline questionnaire.

The patients were assigned to ziprasidone or olanzapine in a strictly random fashion within each country. The enrolling physician ascertained the treatment group using a central telephone randomization system. Following random allocation in the United States, Sweden, Hong Kong, and Singapore, the enrolling physician wrote a prescription for the study medication to be filled at a local pharmacy and either gave the patient a pharmacy card (United States and Sweden) or a prescription form (Hong Kong, South Korea, and Singapore) for study drug reimbursement. In Brazil, Argentina, Chile, Peru, Mexico, Uruguay, Malaysia, Taiwan, Thailand, Hungary, Poland, Romania, and Slovakia, following randomization to treatment, the enrolling physician dispensed the randomized drug to the patient on site. Neither the physician nor the patient was blinded to the treatment allocation, consistent with normal medical care. Physicians and patients were free to change regimens and dosing based on patients' responses to the assigned medication.

Physicians were provided with the labeling for ziprasidone and olanzapine approved by their national regulatory agency and asked to use this information, coupled with their clinical judgment, to determine whether patients were eligible to be randomly assigned into the study.

Study Outcomes

Each patient was to be followed for 1 year, regardless of how long she or he continued treatment, to determine the outcomes of the study. In the event that the patient was unable to be contacted, information from his or her alternative contact person was used. Follow-up information on the occurrence of possible serious cardiovascular events and the patient's vital status was collected at regular intervals by the treating physician or other designated member of the medical care team.

The primary outcome of interest was nonsuicide mortality; secondary endpoints included sudden death, suicide, all-cause and cardiovascular mortality, as well as all-cause hospitalization and hospitalization for arrhythmia, diabetic ketoacidosis, and myocardial infarction. Discontinuation of randomized treatment was also ascertained.

Data Collection

Data collection forms were brief. The baseline and follow-up questionnaires were translated and back translated into the relevant local languages when required.

Baseline data. The baseline questionnaire was completed by the treating clinician at the time of patient recruitment. Data elements included the patient's study identification number, birth date, height, weight, age at onset and severity of schizophrenia (assessed using the Clinical Global Impressions scale),[18] number of previous psychiatric hospitalizations, history of cardiovascular disease, prior antipsychotic use, history of diabetes diagnoses and prior use of insulin or oral hypoglycemics, and smoking status. The questionnaire was completed immediately after the patient signed the consent form and forwarded to the national coordinating center by physicians or collected by study monitors during monitoring visits and subsequently mailed to the national coordinating center, where the questionnaire was checked to be sure that no personal identifiers were present. If a personal identifier was found, the national coordinating center made this personal identifier unreadable. Only the national coordinating center was able to identify and track

the data as outlined in the patient consent form. Questionnaires without personal identifiers were forwarded to the data management center for inclusion in the study database.

The patient was also asked to identify his or her primary care physician and next of kin or other contacts to be contacted if the patient was lost to follow-up. The patient was also asked to provide his or her Social Security number/national identification number or health insurance number (such as the Assistência Médica Internacional Ltda. [AMIL], Bradesco, Sul America, and others in Brazil; Social Security or national health insurance identification in Argentina, Chile, Uruguay, Peru, and Hungary; Clave Unica de Registro de Población [CURP] [unique population register code] in Mexico; identification card numbers in Hong Kong, Malaysia, Singapore, Taiwan, Thailand, and South Korea; *controllo nei documenti rumeni* [CNP] number in Romania; and the Polish Powszechny Elektroniczny System Ewidencji Ludności [PESEL] number in Poland), which was recorded on a separate form and stored separately from the questionnaire data.

Follow-up data. Two methods were used to identify endpoints: (1) physician or other treatment team member reporting death, hospitalization, or discontinuation of assigned study drug by telephone or, in some cases, on the follow-up questionnaire and (2) standard follow-up methods used in cohort studies to track subjects in addition to querying national or regional death certificate data for patients lost to follow-up.

The follow-up questionnaires, administered by telephone or in person, often when the patient returned to receive study medication or a refill prescription per usual medical practice, collected data on the patient's continuation of the study drug, current medication use, and hospitalizations or emergency room visits.

Physicians treating patients who did not return to receive their medication or follow-up pharmacy cards and were lost to follow-up were contacted by the national coordinating center and reminded to conduct patient follow-up, either in person or by telephone, and utilize information on alternate contacts as necessary.

In some cases, the endpoints of all-cause hospitalization or hospitalization for arrhythmia, myocardial infarction, or diabetic ketoacidosis may not be known by the enrolling physician or other treatment team members. In the United States, to quantify the potential impact of unknown hospitalizations on the secondary analyses, the hospitalization records for patients enrolled in state Medicaid programs will be obtained. This subset will include newly enrolled U.S. study patients previously enrolled in the Medicaid program. Using the patient's Social Security number, the national coordinating center will match this subset of patients with their Medicaid hospitalization records.

Oversight Committees

Scientific Steering Committee. The study Scientific Steering Committee (SSC) served 3 roles: to provide clarification of open reports and study conduct at open meetings, to safeguard the interests of the participating patients, and, together with the sponsor study team, to monitor study conduct. The SSC also reviewed any data safety monitoring board (DSMB) or sponsor recommendations to change the study design and determined by consensus whether to accept the recommendation; the final decision remained with the SSC. The SSC comprised experts with extensive knowledge in the areas of psychiatry, pharmacoepidemiology, statistics, and cardiology, specifically cardiac electrophysiology.

Data Safety Monitoring Board. The DSMB evaluated the conduct of the study, including the recruitment, management, and retention of the study patients; evaluated the interim ad hoc analyses of study endpoints; and, based on these analyses, decided whether to continue the study. The DSMB was composed of an independent group of clinicians and statisticians experienced in the treatment of patients with psychiatric disorders, epidemiology, cardiology, and the conduct of large-scale simplified trials.

A formal biostatistical stopping rule was not used in this study since both study drugs were marketed products and this study was not a study of drug efficacy. Instead, the DSMB was to use clinical judgment about the severity and frequency of any observed adverse event combined with biological understanding of the plausibility of a causal link, knowledge about the premarketing experience with the drug, and epidemiologic and biostatistical expertise. The DSMB could make recommendations to the SSC about additional analyses to use for monitoring the study, additional data collection, cessation of the study, label changes to either of the 2 agents, or drug withdrawal.

The DSMB was biannually provided with both open and closed study reports. Open reports informed the committee about the distribution of patient demographics, the conduct and progress of the study, and the data tables for the interim ad hoc study analyses. Closed reports consisted of the intent-to-treat analysis and similar summaries and statistics as presented in the open report. A pre-study meeting of the DSMB was convened to define the DSMB's purpose, establish its charter, and define its procedure. The DSMB met every 6 months, following receipt of the open and closed study reports, in open session with the SSC chair and the sponsor to review study progress and data provided in the open report, as well as in closed session with the unblinded contract research organization statistician to review the closed report. In addition, the DSMB chair and the SSC chair could choose to convene the DSMB to evaluate any emergent safety or study conduct issues; no such ad hoc meetings were held over the course of the study.

Endpoint Committee. The ZODIAC Endpoint Committee adjudicated the endpoints based on a review of copies of medical and hospital records. The committee, composed of an independent group of psychiatrists, cardiologists, epidemiologists, and endocrinologists, received on a monthly basis anonymized data gathered on any subject who experienced a potential study outcome. Two committee members reviewed each set of records individually and classified them using standard criteria for observational studies.[19–23] Endpoint committee members were blind to treatment status when adjudicating outcomes. If there was no consensus, the forms could be adjudicated within the committee, or the chair could evaluate the endpoint.

Statistical Analysis

The data were collected and entered into a database as the study proceeded so that periodic ad hoc analyses could be performed for the purpose of quality assurance and safety assessment.

Main analyses will begin with a comparison of the baseline characteristics of the 2 study groups to evaluate whether randomization was successful and then a calculation of the incidence rates of each of the events of interest in each study group. For any given analysis, follow-up will be censored upon the first occurrence of the outcome event of interest. Thus, for analyses of myocardial infarction, follow-up will be censored after a first myocardial infarction. In analyses of death, follow-up for that same patient would continue past the myocardial infarction until the end of the study or death.

Relative risks and 95% confidence intervals will be calculated for each of the key events of interest, comparing their rate in the ziprasidone versus the olanzapine group. All subjects randomly assigned to treatment will be evaluated in the analyses. The primary analysis will be intent to treat. All patients were followed for 1 year, regardless of actual drug use, and outcomes were assessed at the end of the year of observation. Outcomes will be compared based on the study medication the patient was assigned. For a secondary analysis on the intent-to-treat population, a Cox analysis will be performed, censoring at time of nonsuicide mortality or withdrawal. In addition, a person-time on treatment analysis (an analysis of events during the time when patients were using the study medication) will be conducted as a secondary analysis.

Given that the study is randomized, it should not be necessary to perform multivariate analysis. In the unlikely event that this appears necessary, multivariate analyses for calculations of relative risks and survival analysis using logistic and Cox proportional hazards regression methods will be completed.

The sensitivity of each hospitalization endpoint will be estimated by using hospitalizations identified in the Medicaid inpatient records as the complete comparison group (i.e., the "gold standard"). The sensitivity of each hospitalization endpoint, as reported directly by the enrolling physicians, will be calculated as a proportion of the comparable hospitalizations identified in the Medicaid hospitalization records. In addition, a sensitivity analysis will be performed to quantify the potential impact of missing hospitalization information for the entire study population, in which the proportion of missing reports for the study population can be varied around that found for the Medicaid subset.

To estimate the sample size required for the study, the study originally assumed that the rate of nonsuicide mortality is 2% per patient year (based on the ziprasidone clinical trial database), that a relative risk of 1.0 should be rejected if the relative risk was actually 1.5, and that patients are enrolled in the study for only 6 months; 9000 patients were needed in each treatment arm, giving the study 85% power assuming a 2-sided type I error rate of 0.05. The assumptions used for this calculation were thought to be conservative. The real life mortality rate could have been significantly higher than 2% per patient-year, as suggested by a recent risperidone study in which the rate was 4% per patient-year.[24] Additionally, the study actually enrolled patients for 1 year of follow-up, not 6 months as was assumed in the calculation above. If the mortality rate were 4% per patient-year and patients were followed up for 1 year, the study would actually be powered to detect a relative risk of 1.2.

The study was approved by the St. Davids Human Research Review Board, the University of Pennsylvania Institutional Review Board, and 125 local institutional review boards, including those at a few of the U.S. sites, and institutional review boards in each of the participating countries.

RESULTS

The ZODIAC study enrolled 18,240 patients with schizophrenia. Frequencies for selected baseline characteristics of 18,094 patients randomly assigned in ZODIAC are presented.

Demographics

The breakdown by country of the 18,094 patients randomly assigned in ZODIAC is given in Table 1. The majority (73.0%) of patients are from the United States and Brazil, followed by other countries in Latin America (16.2%), Central and Eastern Europe (5.4%), and East Asia (5.1%). The mean age of patients was 41.6 (± SD 13.0) years, 55.1% were male, and 60.0% were white.

History of Cardiovascular Conditions and Risk Factors

Almost 18% of the study population reported a history of hypertension, 14.8% of patients reported hyperlipidemia, and 46.5% of patients currently smoked at the

Table 1. Enrollment by Country in the ZODIAC Study

Country/Region	N (%)
United States	9696 (53.6)
Brazil	3510 (19.4)
Sweden	47 (0.3)
Latin America (Argentina, Chile, Peru, Uruguay, Mexico)	2924 (16.2)
East Asia (Hong Kong, South Korea, Malaysia, Singapore, Taiwan, Thailand)	918 (5.1)
Central and Eastern Europe (Hungary, Poland, Romania, Slovakia)	999 (5.4)

Abbreviation: ZODIAC = Ziprasidone Observational Study of Cardiac Outcomes.

baseline visit. Less than 3% of patients had previously suffered from coronary artery disease or angina, and 1.6% had previously experienced a myocardial infarction at baseline. Diabetes was present at baseline in almost 8% of patients. Almost one third were overweight, per the Centers for Disease Control and Prevention (CDC) definition[25] of body mass index (BMI) of 25.0 to 29.9 kg/m^2, and over one quarter of patients (28.9%) were obese, per the CDC definition of BMI ≥ 30 kg/m^2.

Psychiatric History

A mean ± SD of 10.4 ± 10.8 years had elapsed since randomly assigned patients in ZODIAC were diagnosed with schizophrenia (Table 2). The mean ± SD clinician-rated Clinical Global Impressions scale score, which can range from 1 to 8, with higher scores indicating increasing severity of schizophrenia, was 5.2 ± 1.1. The majority (74.0%) of patients had been hospitalized in an inpatient psychiatric unit, and almost one third (30.0%) of patients reported at baseline that they had attempted to commit suicide in the past.

Medication Use at Baseline

The ZODIAC population was characterized by a high (78.0%) prevalence of medication use at baseline. Antipsychotics were used at baseline by over two thirds (70.7%) of patients. More than 29% of patients reported using antidepressants. Anxiolytics such as clonazepam, diazepam, lorazepam, alprazolam, and buspirone were used by one quarter of patients. One fifth of patients reported use of mood stabilizers, including valproic acid, lithium, carbamazepine, gabapentin, topiramate, lamotrigine, and oxcarbazepine. Despite the fact that nearly 18% of patients had a history of hypertension at baseline, only 1.3% of patients reported using antihypertensives. Statins were used by less than 3% of the study population, even though high cholesterol or triglyceride levels were indicated by 14.8% on the baseline questionnaire. Among the 1396 patients with diabetes at baseline, the majority (60.2%) was using oral hypoglycemic agents; 22.8% of diabetic patients reported using injected insulin.

Table 2. Psychiatric History at Baseline of Patients Randomly Assigned in the ZODIAC Study

Psychiatric Characteristic	Value
Years since schizophrenia diagnosis, mean ± SD[a]	10.4 ± 10.8
Clinician-rated Clinical Global Impressions Scale score, N (%)	
1 (Not assessed)	119 (0.7)
2 (Normal, not ill at all)	180 (1.0)
3 (Borderline mentally ill)	648 (3.5)
4 (Mildly ill)	3,012 (16.7)
5 (Moderately ill)	7,840 (43.5)
6 (Markedly ill)	4,398 (24.4)
7 (Severely ill)	1,602 (8.9)
8 (Among the most extremely ill)	239 (1.3)
Missing, N	56
Ever hospitalized in an inpatient psychiatric unit, N (%)	13,384 (74.0)
Ever attempted to commit suicide, N (%)	5,438 (30.0)

[a]Years since schizophrenia diagnosis was missing for 37.3% (N = 6,753) of patients.
Abbreviation: ZODIAC = Ziprasidone Observational Study of Cardiac Outcomes.

DISCUSSION

ZODIAC is, to our knowledge, the largest prospective, randomized study conducted among schizophrenia patients to date. It promises to yield clinically relevant information on the safety of 2 widely used atypical antipsychotics and should also provide a valuable global perspective on the routine medical care of patients with schizophrenia. Previous data indicated that use of ziprasidone was associated with a modest prolongation of mean QTc, although with no evidence of marked outliers. Thus, the goal of this study is to determine whether the modest increases in the QTc interval observed with ziprasidone are associated with an increased risk of serious cardiovascular morbidity and mortality in a large at-risk population. In contrast, similar studies of olanzapine suggest that it has a minimal effect on the QTc interval.[26] This study was therefore designed to compare ziprasidone to olanzapine in the treatment of schizophrenia in clinical practice settings.

ZODIAC has a number of design features of note. First, its large sample size provides power needed to evaluate small absolute and relative risks. Of course, any study has its limits in sample size, and ZODIAC will be unable, for example, to evaluate differences in the incidence of uncommon but important outcomes, like the occurrence of torsades de pointes. Instead, in designing the study, we chose to focus on nonsuicide mortality, since even a larger increase in an uncommon cause of death like torsades de pointes could be counterbalanced by a small decrease in a more common cause of death, like atherosclerotic events, and, given the lack of metabolic effects of ziprasidone, this was a possibility. An aggregate measure like all-cause nonsuicide death was deemed to be the more important and appropriate outcome.

Second, simple study procedures permit approximation of real-world clinical practice and allow for observation periods that are much longer than in typical clinical trials. Broad inclusion criteria were utilized, and the only intervention is being randomly assigned to treatment. There were no additional study-mandated tests, monitoring, or visits for patients after they were randomly assigned. Rather, follow-up took place during routine medical care. Thus, in many ways, this is similar to the normal observational study methods, and indeed the outcomes of interest—hospitalization or death—are readily identified while a patient is receiving usual care. Of course, once again, torsades de pointes would not be reliably detected as part of normal medical care. Further, as a large simple trial, ZODIAC is not well designed to characterize patients in detail at baseline in terms of the cardiac and metabolic risk factors. Of course, randomization should assure that these factors are balanced. Further, outcomes other than death will be less completely recorded, since we rely on reports from psychiatrists or other treatment team members for these outcomes.

Third, in contrast to the normal observational study, ZODIAC is a randomized trial. This feature minimizes selection bias, which is the major limitation of nonexperimental studies. In other words, the study avoided the problem that can occur without randomization, which is that patients who receive different drugs may be inherently at a different risk of the outcome of interest. Randomization of exposure must give increased credibility to the study's comparative results when they become available. In typical practice, patients treated with ziprasidone may be systematically different from those treated with other antipsychotic drugs due to physicians' possibly prescribing the drug for patients with worse schizophrenia. This possibility exists because ziprasidone was the newest of the available antipsychotics at the time of study initiation and was most likely to be used in patients who had failed prior therapies. In addition, patients treated with ziprasidone may be systematically different from those treated with other antipsychotic drugs due to prescribers' channeling of the drug to patients with underlying cardiovascular disease. This possibility exists given the weight gain or adverse effects on lipids associated with olanzapine. Conversely, prescribing physicians concerned about QT prolongation in patients with underlying heart disease may selectively avoid ziprasidone. Given these likely selection phenomena, random allocation of patients would be the only approach affording the certainty of a fair comparison between groups.

In conclusion, we present the design and the baseline characteristics of participants in an international, multicenter, randomized, large simple trial involving over 18,000 patients with schizophrenia. The ZODIAC study has a number of unique design features, chosen specifically to optimize its likelihood of providing valid answers to the key question it was designed to address, i.e., the comparative rate of nonsuicide mortality in users of ziprasidone versus olanzapine. As a large simple trial, the study is very large and naturalistic and yet uses randomization. Examining the baseline data now available, one can see that cardiovascular risk factors, most notably hypertension, hyperlipidemia, and obesity, are highly prevalent in this population. In addition, diabetes is more commonly reported and may be more severe in this population than in the general population, with over 20% of diabetic subjects reporting the use of injected insulin. Concomitant psychotropic medications were used frequently by study participants. The majority of patients were not antipsychotic-naive, and many also reported using antidepressants, anxiolytics, or mood stabilizers. Finally, use of antihypertensives or statins was reported by a very low proportion of subjects, suggesting that hypertension and hyperlipidemia may be undertreated.

Drug names: alprazolam (Xanax, Niravam, and others), buspirone (BuSpar and others), carbamazepine (Carbatrol, Equetro, and others), clonazepam (Klonopin and others), diazepam (Diastat, Valium, and others), gabapentin (Neurontin and others), ketoconazole (Nizoral, and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal and others), topiramate (Topamax), valproic acid (Depakene and others), ziprasidone (Geodon).

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