ORIGINAL ARTICLE

Clozapine Treatment for Suicidality in Schizophrenia

International Suicide Prevention Trial (InterSePT)

Herbert Y. Meltzer, MD; Larry Alphs, MD, PhD; Alan I. Green, MD; A. Carlo Altamura, MD; Ravi Anand, MD; Alberto Bertoldi, MD; Marc Bourgeois, MD; Guy Chouinard, MD; M. Zahur Islam, PhD; John Kane, MD; Ranga Krishnan, MD; J.-P. Lindenmayer, MD; Steven Potkin, MD; for the InterSePT Study Group

Background: Approximately 50% of patients with schizophrenia or schizoaffective disorder attempt suicide, and approximately 10% die of suicide. Study results suggest that clozapine therapy significantly reduces suicidal behavior in these patients.

Methods: A multicenter, randomized, international, 2-year study comparing the risk for suicidal behavior in patients treated with clozapine vs olanzapine was conducted in 980 patients with schizophrenia or schizoaffective disorder, 26.8% of whom were refractory to previous treatment, who were considered at high risk for suicide because of previous suicide attempts or current suicidal ideation. To equalize clinical contact across treatments, all patients were seen weekly for 6 months and then biweekly for 18 months. Subsequent to randomization, unmasked clinicians at each site could make any interventions necessary to prevent the occurrence of suicide attempts. Suicidal behavior was assessed at each visit. Primary end points included suicide attempts (including those that led to death), hospitalizations to prevent suicide, and a rating of "much worsening of suicidality" from baseline. Masked raters, including an independent suicide monitoring board, determined when end point criteria were achieved.

Results: Suicidal behavior was significantly less in patients treated with clozapine vs olanzapine (hazard ratio, 0.76; 95% confidence interval, 0.58-0.97; $P=.03$). Fewer clozapine-treated patients attempted suicide (34 vs 55; $P=.03$), required hospitalizations (82 vs 107; $P=.05$) or rescue interventions (118 vs 155; $P=.01$) to prevent suicide, or required concomitant treatment with antidepressants (221 vs 258; $P=.01$) or anxiolytics or soporifics (301 vs 331; $P=.03$). Overall, few of these high-risk patients died of suicide during the study (5 clozapine- vs 3 olanzapine-treated patients; $P=.73$).

Conclusions: Clozapine therapy demonstrated superiority to olanzapine therapy in preventing suicide attempts in patients with schizophrenia and schizoaffective disorder at high risk for suicide. Use of clozapine in this population should lead to a significant reduction in suicidal behavior.

Arch Gen Psychiatry. 2003;60:82-91

SUICIDE IS the leading cause of premature death among patients with schizophrenia.[1] Overall, patients with schizophrenia have approximately a 50% lifetime risk for suicide attempts and a 9% to 13% lifetime risk for completed suicide.[2,3] In comparison, the lifetime risk for suicide in the general population of the United States is approximately 1%[4] and in persons with mood disorders, 9% to 15%.[5]

Studies[6-11] examining the effects of typical antipsychotic medications on suicide and suicidal ideation have not identified a change in incidence of suicide with their use. However, several studies suggest that using clozapine, an atypical antipsychotic drug, may reduce suicidal behavior in schizophrenia. Meltzer and Okayli[12] found that among 88 neuroleptic-resistant patients treated with clozapine for 0.5 to 7.0 years and evaluated for changes in suicidal behavior, the percentage with no suicidality of any type increased from 53% to 88%. In another study (which used the Clozaril National Registry to identify 57 000 current, recent, and past clozapine-treated patients, followed by linkage of these data with the National Death Index and Social Security Administration Death Master Files to identify cause of death), Walker and colleagues[13] found that mortality from suicide was markedly decreased in current clozapine users compared with past users. Analyses[14,15] of clozapine registry data from the United States and England support the view that the suicide completion rate in treated patients with schizophrenia is substantially reduced. Similarly, a retrospective study[16] of 295 treatment-resistant outpatients (mainly African Americans) found that

Author affiliations are listed at the end of this article. A complete list of the members of the InterSePT Study Group appears in the box on page 90.

clozapine treatment reduced the expected rate of suicidality during continuous drug administration. In contrast to these findings, a study[17] of the effect of clozapine treatment on completed suicides in the Veterans Administration system did not demonstrate a significant effect of clozapine therapy on the suicide rate. However, despite failure to match the comparison group on variables related to risk of suicide and follow-up that in some cases extended for prolonged periods after patients discontinued clozapine treatment, this study demonstrated a trend toward lowering the suicide rate for clozapine compared with nonclozapine treatment.

Taken together, these studies provide evidence for the ability of clozapine therapy to reduce suicidal behaviors[18]; however, they were retrospective and did not control for possible differences in the risk for suicide between the clozapine and comparison groups, relative differences in the dosage of clozapine vs the comparison antipsychotic drug, differences in the use of concomitant medications, or differences in the frequency of clinical contact (usually increased in patients treated with clozapine because blood monitoring to detect potential emergence of agranulocytosis is required). Furthermore, comparisons of the effects of clozapine therapy on suicidal behavior and the effects produced by using other atypical antipsychotic drugs, for example, quetiapine fumarate, olanzapine, risperidone, or ziprasidone hydrochloride, have not been performed. Because of their potential advantages regarding safety and efficacy relative to typical neuroleptic drugs, these comparators are the most relevant to the issue of drug management of suicidal patients with schizophrenia.

To address these limitations, a randomized, parallel-group study (International Suicide Prevention Trial [InterSePT]) was designed to compare changes in suicidality during treatment with clozapine vs olanzapine in patients with schizophrenia or schizoaffective disorder who are at high risk for suicide. Typical antipsychotic drugs were not included as comparator agents because, as mentioned previously, they have not been demonstrated to reduce the overall rate of suicidal behavior.[6-11] If anything, several studies have suggested that use of typical neuroleptic drugs increases the risk, possibly because of a combination of akathisia and secondary depression, leading to shorter hospitalizations (see Caldwell and Gottesman[9] for a review). Of the newer atypical antipsychotic drugs, olanzapine was selected because results of posthoc analyses suggest that its use may reduce the annual suicide attempt rate compared with haloperidol therapy and, in particular, may produce significantly greater improvement in the "suicidal thoughts" item of the Montgomery Asberg Depression Rating Scale.[19]

METHODS

PATIENTS

Men and women aged 18 to 65 years were included. They had a *DSM-IV* diagnosis of schizophrenia or schizoaffective disorder and were considered to be at high risk for committing suicide. High risk for suicide was defined as any one of the following: (1) a history of previous attempts or hospitalizations to prevent a suicide attempt in the 3 years before enrollment, (2) moderate to severe current suicidal ideation with depressive symptoms, or (3) command hallucinations for self-harm within 1 week of enrollment. Treatment resistance was not a requirement for inclusion in this study. This study was conducted following Good Clinical Practice guidelines to ensure the protection of the participants. Before implementation of this study, institutional review board and ethics committee approvals of the protocol and the consent form were obtained from each of the participating sites.

STUDY SITES AND DESIGN

Patients were recruited from 67 medical centers in 11 countries (the United States, Canada, France, Italy, the United Kingdom, the Czech Republic, Hungary, Croatia, South Africa, Argentina, and Chile). Selection of sites was based on demonstrated expertise in managing large numbers of schizophrenic patients at risk for suicide, expertise in conducting clinical trials, and the presence of adequate staff to manage these patients for 2 years.

The methods of the InterSePT study were developed collaboratively with academic experts. The design and data analysis were approved by the US Food and Drug Administration (FDA).

A 2-year study duration was chosen to provide time to obtain sufficient end points to differentiate between the 2 treatments. Because managing patients at high risk for suicide in a 2-year, double-blind study was not considered clinically feasible or acceptable and because treatment with clozapine is often associated with a variety of unique, clinically obvious adverse effects, the InterSePT was conducted as a randomized, open-label trial with masked ratings. After discussing the protocol and other treatment options in detail with the patient, written informed consent was obtained. Screened patients meeting inclusion criteria were assigned to treatment with either clozapine or olanzapine. For randomization, patients were blocked by country and medical center. The 2 treatment groups were allocated randomly in a 1:1 ratio within blocks of 4 patients in each medical center.

Recognizing the inherent problems associated with an open-label trial, extensive efforts were made to ensure masking of the raters. All aspects of the primary end points were limited to ratings from 1 of 2 groups of masked raters. A 3-member suicide monitoring board (SMB) determined whether potential end points met the criteria for a suicide attempt or a hospitalization to prevent suicide. The SMB was nominated by the study sponsor, Novartis Pharmaceuticals Corp, East Hanover, NJ, and approved by an academic steering committee. The SMB was chaired by one of us (R.K.) and included Hannale Heila, MD, from the National Public Health Institute in Helsinki, Finland, and Isaac Sakinsofsky, PhD, from the University of Toronto, Toronto, Ontario. Each member had extensive experience working with suicidal patients. This team remained constant throughout the study.

Every type 1 end point (see the "Outcome Definitions" subsection) was reviewed by all of the members of the SMB, and consensus was obtained. At the onset of the study, the SMB developed the specific procedures for which data and how data would be reviewed and guidelines for how case evaluations would occur. Potential end point packages were reviewed and edited if necessary to eliminate any indication of the antipsychotic drug used, for example, adverse effects and blood monitoring. Masking of the SMB was monitored by Kevin Cox from Ingenix Pharmaceutical Services, San Diego, Calif, who ensured that all of the data received by the SMB was masked before delivery to the SMB. The institutions for which members of the SMB worked were not included as participant sites in the study.

Table 1. Clinical Global Impression for Severity of Suicidality

Considering all of the information available to you, what was the most severe level of suicidality experienced by this patient in the past 7 days?	1 Not at all suicidal 2 Mildly suicidal 3 Moderately suicidal 4 Severely suicidal 5 Attempted suicide
Considering all of the information available to you, how much has the patient's suicidality changed compared with his or her condition at baseline?	1 Very much improved 2 Much improved 3 Minimally improved 4 No change 5 Minimally worsened 6 Much worse 7 Very much worse

For purposes of end point assessment, suicide attempts were defined as actions committed by a patient, either with willful intent or as a response to internal compulsions or disordered thinking, that put him or her at high risk for death. Potential end points were identified by investigators and by study monitors who reviewed medical records and adverse event data for potential end points. The SMB determined whether these potential end points met predefined criteria of intent and seriousness to qualify as a study end point.

In addition to these ratings by the SMB, masked psychiatrists at each participating site rated the global assessment of suicidality for type 2 events (see the "Outcome Definitions" subsection). Because these were ratings of an individual patient's suicidality compared with baseline, they could not be assessed by the independent SMB. These site raters' interactions with patients in this study were limited to these ratings, and they had no other clinical contact with them. Raters were required to verify their masking at the time of each rating, and they were regularly monitored by Ingenix Pharmaceutical Services to ensure that they had remained masked to the patient's treatment.

The weekly or biweekly clinical contact required to monitor for clozapine-associated agranulocytosis was matched with a similar visit schedule for olanzapine-treated patients, during which vital signs were obtained. To ensure the safety of patients during this trial, clinicians were allowed to make any interventions necessary to prevent the occurrence of suicide attempts, including changing dosages, adding other medications, switching medications, and increasing surveillance. In addition, patients were queried at each visit about suicidality, and they were referred to their treating physician if a full evaluation was indicated. Rescue interventions required to prevent suicide-related events were analyzed as secondary end points.

The first patient was enrolled in the InterSePT on March 19, 1998, and the last patient was enrolled on February 14, 1999. The last patient completed his last visit on February 14, 2001.

OUTCOME DEFINITIONS

It was recognized at the outset that use of suicide deaths alone as an end point would require approximately 20 000 patients if the study were powered to detect a decreased relative risk with clozapine therapy by 20%. Furthermore, because failure to intervene to prevent suicide during the follow-up care of patients in this study was considered ethically unacceptable, every effort was made to prevent this outcome. Thus, suicide deaths alone were not regarded as the primary end point but were included as a subset of a much larger group of suicidal behaviors that might occur during the study.

After consultation with external clinical experts in psychiatry, statistical experts, and the Neuropharmacology Division of the US FDA, 2 types of primary end points were prespecified for this trial. A type 1 event was defined as the occurrence of a significant suicide attempt (which included completed suicides as a subset) or hospitalization because of imminent suicide risk (which included increased levels of surveillance) that was confirmed by an external masked group (the SMB). A type 2 event was defined as ratings from a masked psychiatrist on the Clinical Global Impression of Suicide Severity (CGI-SS) of "much worse" or "very much worse" from baseline (**Table 1**). Because patients with potential type 2 events were not always observed by a masked psychiatrist, criteria for a significant level of worsening from baseline were also defined to have been met whenever a type 1 event occurred.

Other objective measures of suicidality included the individual components of the main outcome variable—the specific time to an SMB-determined suicide attempt (including death by suicide) or hospitalization to prevent suicide or the number of suicide attempts, the number of hospitalizations to prevent suicide, and the number of interventions to prevent suicide, irrespective of SMB validation.

Patients were enrolled for 2 years of follow-up. Attempts were made to continue to collect basic end point information even if the patient discontinued study participation early. This information was included in the intent-to-treat analysis.

In addition to these measures, the change in suicide risk was assessed clinically using the CGI-SS as an additional element of the combined end point. Information for rating this scale was collected during a semistructured interview designed to elicit the necessary information for ratings. Validation of this standardized clinical assessment demonstrates that this instrument is reliable and valid for assessing current suicidal thinking in patients with schizophrenia and schizoaffective disorder by clinicians and researchers. Additional information about the the validation of this instrument is available elsewhere.[20] This 2-item scale measured severity of suicidality and change in suicidality from baseline (Table 1). Individuals were assessed on the CGI-SS by masked raters at each site at baseline and at study weeks 8, 16, 24, 32, 40, 48, 52, 60, 68, 80, 92, and 104.

Staff at the investigational sites were trained on InterSePT procedures and scales and were certified by study monitors as qualified raters before being permitted to participate. All new raters in the study were trained to meet prespecified criteria. Additional training was provided during the study to ensure that reliability was maintained over time.

STATISTICAL ANALYSIS

After the primary data were locked and verified, statistical analyses were conducted by Ingenix Pharmaceutical Services and supplied to us for examination, checking, and reporting. There were no interim analyses of data other than a masked review of safety data. Every effort was made to follow all patients to completion of the 2-year evaluation. All data obtained were used in the intent-to-treat analysis.

The null hypothesis for this study stated that the relative hazard for type 1 and type 2 events during treatment with clozapine compared with olanzapine treatment would not differ from 1. After consultation with the FDA, the predefined main analysis to test this null hypothesis used the method of Wei et al[21] for analysis of multiple events. In this analysis, the factor country was used as strata and randomized treatment group was used as the only covariate.

Supplementary supportive analyses of the SMB-determined end points were completed using the Cox proportional hazards regression model.[22,23] Putative explanatory variables, that

Table 2. Demographic Characteristics of the Treatment Groups at Baseline

Characteristic	Clozapine Group (n = 490)	Olanzapine Group (n = 490)	Total (N = 980)	*P* Value* (Clozapine vs Olanzapine)
Age, mean ± SD, y	37.1 ± 10.3	37.0 ± 10.3	37.1 ± 10.3	.74
Male sex, No. (%)	301 (61.4)	301 (61.4)	**602** (61.4)	.98
Race, No. (%)				.49
White	356 (72.7)	337 (68.8)	**693** (70.7)	
Black	65 (13.3)	86 (17.6)	**151** (15.4)	
Oriental	6 (1.2)	7 (1.4)	**13** (1.3)	
Other	63 (12.9)	60 (12.2)	**123** (12.6)	
Diagnosis, No. (%)				.50
Schizophrenic	300 (61.2)	309 (63.1)	**609** (62.1)	
Schizoaffective	190 (38.8)	181 (36.9)	**371** (37.9)	
Lifetime suicide attempts†				
No. (%)‡	413 (84.3)	403 (82.2)	**816** (83.3)	.58
No., mean ± SD	3.6 ± 7.5	3.2 ± 4.5	3.4 ± 6.2	.80
Suicide attempts in the past 36 mo, No. (%)	307 (62.7)	311 (63.5)	**618** (63.1)	.76

*Continuous variables were analyzed using an analysis of variance model (eg, model age = treatment + pooled country). Categorical variables were analyzed using the Cochran-Mantel-Haenszel method stratified by pooled country.

†Results were analyzed using the Wilcoxon test.

‡Number of patients who made ≥1 suicide attempt before baseline.

is, factors that may have contributed to the primary end point in this model, included treatment, number of previous suicide attempts, active substance or alcohol abuse, country, medical center, sex, and age group (18-32, 33-44, and ≥45 years) at baseline. The hazard ratio, a measure of the relative risk between groups, and its 95% confidence interval (CI), were computed on the basis of the fitted model. In addition, Kaplan-Meier estimates of survival probabilities were calculated. The average number of patients needed to treat to show a benefit of clozapine use over olanzapine use regarding the primary end point was computed using the method of Altman.[24] Annualized rates of suicide attempts were calculated as the number of total suicide attempts (including suicide) among the randomized patients divided by the total number of patient-years in the study. For this calculation, the total number of patient-years included the time during follow-up after dropout from the study. Compliance was estimated by dividing the number of study drug pills returned by the number of study drug pills dispensed, subtracting from 1 and multiplying by 100.

Because the CGI-SS was assessed relatively infrequently during the study, based on an agreement with the FDA, an inferred rating of "much worsening from baseline" was assumed on this scale if a patient attempted suicide or was hospitalized to prevent suicide. The number of patients with "much worsening from baseline CGI-SS" was analyzed using the Fisher exact test. Time to the "much worsening of CGI-SS" was analyzed with the methods used for the primary efficacy variable.

Event rates were computed for other efficacy and safety assessments, and the tests of significance were performed using the Fisher exact test. All *P* values were based on 2-sided alternative hypotheses.

RESULTS

PATIENTS

Of 1065 patients screened for participation in this study, 980 (92%; 490 per group) met the inclusion criteria and gave written informed consent. They were then randomly assigned to treatment with either clozapine or olanzapine. Of the total sample, 609 patients (62%) were diagnosed as having schizophrenia and 371 (38%) as having schizoaffective disorder. At the time of enrollment, 263 patients (27%) were rated as treatment resistant. Of the total population studied, 477 patients received olanzapine, 479 received clozapine, and 24 were never treated for various administrative reasons. Eighty-three percent of patients had attempted suicide at least once during their lifetime, and 84% had been hospitalized to prevent a suicide attempt. Sixty-three percent of patients had attempted suicide in the previous 36 months. Patients treated with olanzapine or clozapine did not significantly differ in age, sex, race, diagnosis, treatment resistance, number of previous suicide attempts, or baseline concomitant medications (**Table 2**).

TREATMENT AND EVENTS

The mean±SD prescribed dosages of study drugs were 16.6±6.4 mg daily for olanzapine and 274.2±155.0 mg daily for clozapine. Compliance was 94.4% for the clozapine-treated group and 95.8% for the olanzapine-treated group. Overall dropout rates for patients treated with clozapine vs olanzapine were not different. Reasons for dropout are summarized in **Table 3**. A total of 380 patients (39%) discontinued taking the study drug early: 99 (10%) withdrew consent, 74 (8%) for adverse events, and 72 (7%) were lost to follow-up. The rates of discontinuation for other reasons were infrequent and did not differ between treatment groups, except for discontinuations for unsatisfactory antisuicidal effect (6 olanzapine-treated patients [1%] and 0 clozapine-treated patients; $P = .03$). Every effort was made to follow patients for study end points for the full 2 years of evaluation, even after they formally discontinued using the study drug. Such information from "retrieved dropouts" was included in the intent-to-treat analyses. More discontinuations occurred early in the course of clozapine treatment (usually for adverse events), whereas there tended to be more olanzapine dropouts later in the study.

Of the 577 cases sent to the SMB for review (representing 443 unique patients), 483 were determined to

Table 3. Patient Study Discontinuations*

Reason†	Clozapine Group (n = 490)	Olanzapine Group (n = 490)	Total (N = 980)	*P* Value‡
Adverse event(s)	41 (8.4)	33 (6.7)	**74** (7.6)	.40
Abnormal laboratory value(s)	2 (0.4)	0	**2** (0.2)	.50
Abnormal test procedure result(s)	1 (0.2)	0	**1** (0.1)	>.99
Unsatisfactory therapeutic effect on psychosis	5 (1.0)	9 (1.8)	**14** (1.4)	.42
Unsatisfactory therapeutic effect for lowering suicide risk	0	6 (1.2)	**6** (0.6)	.03§
Deaths	8 (1.6)	5 (1.0)	13 (1.3)	.42
Protocol violation	29 (5.9)	20 (4.1)	**49** (5.0)	.24
Consent withdrawal	50 (10.2)	49 (10.0)	**99** (10.1)	>.99
Lost to follow-up	33 (6.7)	39 (8.0)	**72** (7.3)	.54
Administrative problems	23 (4.7)	26 (5.3)	**49** (5.0)	.77
Total	**192** (39.2)	**187** (38.2)	**379** (38.7)	.79

*Values are given as number (percentage) of patients.
†Rated by treating physician.
‡Fisher exact test.
§Statistically significant difference.

Table 4. SMB-Certified and Other Measures of Suicidality*

	Clozapine Group (n = 490)	Olanzapine Group (n = 490)	*P* Value† (95% CI of the Difference) (Olanzapine – Clozapine)
SMB-determined end points			
Patients with end points, total‡	102 (20.8)	141 (28.8)	.005 (.03 to .13)
Patients with significant suicide attempts‡	34 (6.9)	55 (11.2)	.03 (.01 to .08)
Patients with hospitalizations to prevent suicide‡	82 (16.7)	107 (21.8)	.05 (.00 to .10)
All SMB-determined end points, total No.	217	266	. . .
Patients showing "much worsening from baseline" on the CGI-SS‡§	120 (24.5)	161 (32.9)	.005 (.03 to .14)
Discontinuations for unsatisfactory antisuicidal effect‡	0	6 (1.2)	.03
Concomitant medications			
Antidepressants‖	235 (49.1)	263 (55.1)	.01 (.02 to .14)
Anxiolytics/soporifics‖	297 (60.2)	331 (69.4)	.05 (.01 to .13)
Adverse events			
Patients experiencing "suicide attempt"‖	37 (7.7)	66 (13.8)	.002 (.02 to .10)
Patients experiencing "suicidal ideation"‖	125 (26.1)	153 (32.1)	.05 (.00 to .12)
Suicide deaths‡¶	5 (1.0)	3 (0.6)	.73 (–.02 to .01)
All rescue interventions to prevent suicide‡	118 (24.1)	155 (31.6)	.01 (.02 to .13)

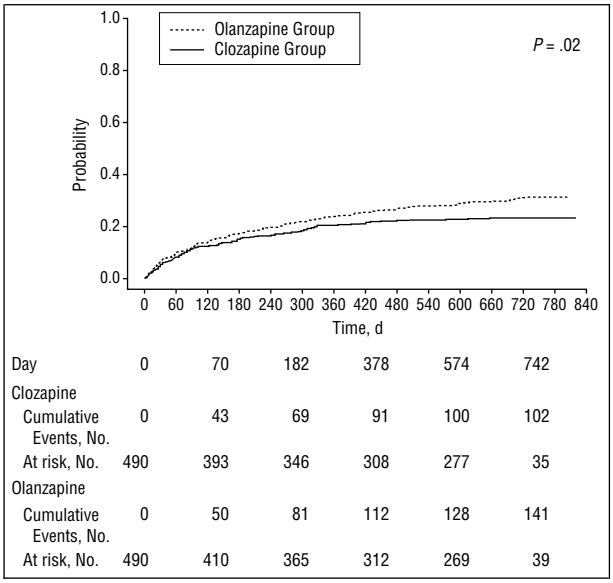
Abbreviations: CGI-SS, Clinical Global Impression of Suicide Severity; CI, confidence interval; SMB, Suicide Monitoring Board.
*Values are given as number (percentage) of patients, unless otherwise indicated. Ellipses indicate not applicable.
†Fisher exact test.
‡Intention-to-treat population (all randomized patients): clozapine, n = 490; olanzapine, n = 490.
§Ratings by a masked psychiatrist. Includes implied worsening if a patient was hospitalized to prevent a suicide attempt or attempted suicide.
‖Safety population (all randomized patients who took the study drug); clozapine, n = 479; olanzapine, n = 477.
¶Includes all suicide deaths *and* all events leading to death by suicide.

meet end point criteria; of these, 111 (clozapine, 43; olanzapine, 68) were considered suicide attempts and 372 (clozapine, 174; olanzapine, 198) were hospitalizations to prevent suicide.

MAIN OUTCOME VARIABLES

Primary Analysis

The results of the main analysis for primary efficacy, based on the method of Wei et al,[21] demonstrate a significant difference ($P=.03$) between the clozapine group and the olanzapine group in reducing suicidality as measured by SMB-determined suicide attempts or hospitalizations to prevent suicide and much or very much worsening in the CGI-SS from baseline as assessed by the masked psychiatrist. Results from the individual components of this end point indicate that compared with olanzapine therapy, clozapine use had hazard ratios of 0.76 (95% CI, 0.58-0.97) for type 1 events (suicide attempts or hospitalizations to prevent suicide) ($P=.03$) and 0.78 (95% CI, 0.61-0.99) for type 2 events (worsening on the CGI-SS or implicit worsening of suicidality severity as demonstrated by occurrence of a type 1 event) ($P=.04$), indicating a 24% and a 22% advantage, respectively, for clozapine therapy. Other efficacy results are summarized in Table 3 and **Table 4**. Because patients may have experienced more than 1 end point that met SMB criteria during the 2 years of observation, the absolute number of end points in each treatment group was also determined. There were more SMB-determined end points in the olanzapine-treated group than in the clozapine-



Day	0	70	182	378	574	742
Clozapine						
Cumulative Events, No.	0	43	69	91	100	102
At risk, No.	490	393	346	308	277	35
Olanzapine						
Cumulative Events, No.	0	50	81	112	128	141
At risk, No.	490	410	365	312	269	39

Kaplan-Meier estimates of the probability of a suicide attempt or hospitalization to prevent suicide.

treated group (266 vs 217 events). Of the prognostic factors examined using the Cox proportional hazards regression model as potential predictors of suicide events, only the number of lifetime suicide attempts at baseline (hazard ratio, 1.03; 95% CI, 1.01-1.04; $P<.001$) and current or previous history of alcohol or other drug abuse at baseline (hazard ratio, 1.48; 95% CI, 1.11-1.99; $P=.008$) predicted the SMB-determined suicide events. The results were largely consistent across countries, regions, and diagnoses. Treatment resistance did not predict differential response to clozapine or olanzapine regarding suicidality (data not shown).

Secondary Analysis for Primary End Points

During the InterSePT, the percentage of patients experiencing at least 1 significant suicide attempt or hospitalization to prevent suicide that met criteria established by the masked SMB was greater in the olanzapine-treated group than in the clozapine-treated group (28.8% vs 20.8%; $P=.005$) (Table 4). The olanzapine-treated group experienced significantly more SMB-determined suicide attempts (11.2% vs 6.9%; $P=.03$) and SMB-determined hospitalizations to prevent suicide (21.8% vs 16.7%; $P=.05$). In the analyses of the changes from baseline in CGI-SS scores, there was a significant difference in the percentage of patients who experienced "much worsening from baseline" (olanzapine, 32.9% vs clozapine, 24.5%; $P=.005$).

Overall, there were fewer deaths from suicide than expected, particularly considering that only individuals at high risk for suicide were included in this study. Three suicide attempts in the olanzapine-treated group (0.6%) and 5 in the clozapine-treated group (1.0%) resulted in death (95% CI, 0.40%-7.04%; $P=.73$). On the other hand, when suicide attempts were rated for probability of success by the SMB, a "high probability for success" of a completed suicide was found for 8 events in the clozapine group and 14 events in the olanzapine group. The latter group included

Table 5. Summary Statistics for Individuals Who Received Rescue Interventions*

Rescue Intervention	Clozapine Group (n = 490)	Olanzapine Group (n = 490)	*P* Value†
Hospitalization for imminent risk of suicide	100 (20.4)	128 (26.1)	.04
Increase in level of surveillance	41 (8.4)	57 (11.6)	.11
Addition of an antidepressant agent	15 (3.1)	33 (6.7)	.01
Addition of or change in an antipsychotic agent	15 (3.1)	29 (5.9)	.04
Increase in dose of study medication	37 (7.6)	34 (6.9)	.81
Addition of a mood stabilizer	6 (1.2)	14 (2.9)	.11
Addition of other medications	29 (5.9)	42 (8.6)	.14
Admission to a partial hospital program	2 (0.4)	3 (0.6)	>.99
Increase in medication monitoring visits	5 (1.0)	9 (1.8)	.42
Institution of psychotherapy	6 (1.2)	4 (0.8)	.75
Increase in frequency of psychotherapy visits	1 (0.2)	7 (1.4)	.07
Emergency department visits	34 (6.9)	43 (8.8)	.34
Crisis team visit	7 (1.4)	4 (0.8)	.55
Electroconvulsive therapy	5 (1.0)	0	.06
Increase in frequency of clinic visits	4 (0.8)	10 (2.0)	.18
Other	19 (3.9)	26 (5.3)	.36
Total	118 (24.1)	155 (31.6)	.01

*Values are given as number (percentage) of patients.
†Fisher exact test.

the 6 patients discontinued from olanzapine therapy for unsatisfactory control of suicidality. None of the clozapine-treated patients were discontinued for this reason.

The supportive analysis using the Cox proportional hazards regression model with treatment, number of previous suicide attempts, active substance or alcohol abuse, country, sex, and age group at baseline in the model demonstrated a 26% reduced risk for suicide attempt or hospitalization to prevent suicide (type 1 event) for patients randomized to clozapine treatment compared with olanzapine treatment ($P = .02$; hazards ratio, 0.74; 95% CI, 0.57-0.96). Kaplan-Meier estimates for probability of an event were estimated for the 2 treatment groups (**Figure**). The time in days to observe the first 70 type 1 events was 185 days for the clozapine-treated patients and 126 days for the olanzapine-treated patients. A significant reduction in the 2-year event rate at the end of the study (olanzapine, 32.2% vs clozapine, 24.0%; 95% CI of the difference, 0.02-0.14; number needed to treat, 12) and a delay in time to event were demonstrated for clozapine-treated patients. The number needed to treat of 13 indicates that under similar treatment conditions, on average, for every 13 high-risk patients treated, suicidal events, as defined herein, would be observed in 1 less patient if they were treated with clozapine rather than olanzapine. The overall annualized rate for attempted suicides (including suicide deaths) was 7.1%, with a rate of 8.5% for olanzapine-treated patients and 5.6% for clozapine-treated patients.

Table 6. Adverse Events of Interest in the Safety Population*

Adverse Event	Clozapine Group (n = 479)	Olanzapine Group (n = 477)	*P* Value†
Suicidal ideation	125 (26.1)	153 (32.1)	.05
Suicide attempt	37 (7.7)	66 (13.8)	.002
Laceration	2 (0.4)	19 (4.0)	<.001
Depression NEC	137 (28.6)	173 (36.3)	.01
Mood alteration	5 (1.0)	13 (2.7)	.06
Mood disorder	0	8 (1.7)	.004
Insomnia NEC	96 (20.0)	155 (32.5)	<.001
Somnolence	220 (45.9)	118 (24.7)	<.001
Convulsions	12 (2.5)	2 (0.4)	.01
Diabetes mellitus NOS	16 (3.3)	21 (4.4)	.41
Weight gain	150 (31.3)	265 (55.6)	<.001
Cardiomyopathy	0	1 (0.2)	.50
Postural hypotension	21 (4.4)	1 (0.2)	<.001
Dizziness (excluding vertigo)	129 (26.9)	59 (12.4)	<.001
Syncope	15 (3.1)	5 (1.0)	.03
Akathisia	21 (4.4)	39 (8.2)	.02
Muscle rigidity	1 (0.2)	6 (1.3)	.02
Dysarthria	23 (4.8)	2 (0.4)	<.001
Constipation	120 (25.1)	46 (9.6)	<.001
Dry mouth	26 (5.4)	43 (9.0)	.03
Salivary hypersecretion	229 (47.8)	28 (5.9)	<.001
Dyspepsia	66 (13.8)	40 (8.4)	.01
Nausea	79 (16.5)	47 (9.9)	.003
Vomiting NOS	79 (16.5)	42 (8.8)	<.001
Urinary incontinence	31 (6.5)	6 (1.3)	<.001
Weakness	36 (7.5)	11 (2.3)	<.001
Drug abuse	4 (0.8)	14 (2.9)	.02
Alcoholism	13 (2.7)	21 (4.4)	.17
WBC count decreased	28 (5.8)	4 (0.8)	<.001

Abbreviations: NEC, not elsewhere classified; NOS, not otherwise specified; WBC, white blood cell.
*Values are given as number (percentage) of patients.
†Fisher exact test.

Secondary Outcome Analysis

To maintain the safety of individuals participating in this study, clinicians were permitted to make any interventions they believed necessary to prevent an impending suicide attempt. Rescue interventions to prevent suicide were significantly greater in the olanzapine-treated group vs the clozapine-treated group (31.6% vs 24.1%; *P*=.01) (**Table 5**).

Comparison of the overall use of concomitant medications for any reason, not only suicidality, shows that antidepressants were used more frequently in patients treated with olanzapine (55.1%) than in those treated with clozapine (49.1%) (*P*=.01) (Table 4). Anxiolytics and soporifics were also used more frequently in patients treated with olanzapine (69.4%) than in those treated with clozapine (60.2%) (*P*=.05). Significant differences in the use of other concomitant medications (antipsychotics and mood stabilizers) between treatment groups were not seen. There were more discontinuations because of an unsatisfactory antisuicidal therapeutic effect as determined by the treating physician in the olanzapine-treated group (n=6; 1.2%) vs the clozapine-treated group (n=0) (*P*=.03) (Table 4). More suicide attempts met the criteria for an adverse event (but not necessarily the more rigorous criteria of the SMB) in the olanzapine-treated group vs the clozapine-treated group (13.8% vs 7.7%; *P*=.002) (Table 4). Similarly, there were more adverse events of "suicidal ideation" in the olanzapine-treated group vs the clozapine-treated group (32.1% vs 26.1%; *P*=.05).

SAFETY AND TOLERABILITY

The overall number of adverse events and clinically serious adverse events did not differ between treatment groups in this 2-year, prospective comparative study of 2 widely used antipsychotic drugs. However, several differences in the specific adverse event profile for clozapine use and olanzapine use were noted (**Table 6**). The most frequently observed adverse events attributed to clozapine treatment were salivary hypersecretion, somnolence, weight gain, and dizziness (excluding vertigo). The most frequently observed adverse events attributed to olanzapine treatment were weight gain, somnolence, dry mouth, and dizziness (excluding vertigo). These results will be presented in more detail elsewhere (John Kane, MD, unpublished observations, 2002; Tom Fahy, MD, unpublished observations, 2002). Decreased white blood cell counts were reported as an adverse event in 0.8% of olanzapine-treated patients and 5.8% of clozapine-treated patients (*P*<.001). However, no agranulocytosis or deaths related to granulocytopenia were reported for either treatment group.

There were 8 deaths (1.7%) for any reason in the olanzapine group and 12 (2.5%) in the clozapine group (*P*=.50). Causes of death for olanzapine-treated patients were suicide (n=3, 0.6%), cardiorespiratory arrest (n=2, 0.4%), and carcinoma, cardiac arrhythmia, and myocardial infarction (after randomization but before treatment) (n=1 each, 0.2%). Causes of death for clozapine-treated patients were suicide (n=5, 1.0%), cardiac arrhythmia (n=2, 0.4%), and lymphoma, coronary artery disease, pulmonary embolism, car accident, and stroke (n=1 each, 0.2%).

COMMENT

The major finding of this randomized study is that clozapine therapy is superior to olanzapine therapy in reducing key measures of suicidality in patients with schizophrenia or schizoaffective disorder who are at high risk for suicide. In particular, the treatment effect on the most objective measures of suicidality (time to suicide attempts [including deaths by suicide] and time to hospitalizations to prevent suicide) significantly favored clozapine treatment over olanzapine use when analyzed by multiple approaches (including various analyses of time to event, survival analysis methods, and evaluation of the total number of events). The hazard ratios identified in this study suggest that serious suicide attempts and hospitalizations to prevent suicide can be reduced by about one fourth with clozapine treatment vs olanzapine treatment.

Although the total number of suicide-related deaths was greater in the olanzapine-treated group, this was not significant and, as indicated already, the study was not powered to evaluate this as an end point. To have made this the sole primary end point, the observed suicide rate

in this study indicates that approximately 20 000 patients would have been needed to find a 20% reduction in relative risk between the 2 drugs. Many factors contribute to whether a serious suicide attempt will lead to death. In addition, when the overall use of various interventions to prevent suicide attempts was compared between treatments, the results consistently supported the superiority of clozapine therapy over olanzapine therapy to reduce the risk of suicide. In particular, antidepressant and anxiolytic drugs were most likely given to alleviate depression, hopelessness, or anxiety or agitation—conditions that are frequently associated with increased risk for suicide.[4] Although use of these agents may have served to diminish the rate of suicidal behavior observed in both treatment groups, the more frequent prescription of these agents in olanzapine-treated patients did not succeed in equalizing the effects of olanzapine therapy and clozapine therapy on suicidality.

Khan et al[11] recently used an FDA database to access data from 10 118 patients participating in pivotal clinical trials of treatment with olanzapine, risperidone, and quetiapine fumarate and compared the rates of suicide and suicide attempts with those of patients randomized to receive placebo or established ("typical") antipsychotic drugs. Annualized rates of attempted suicide (including completed suicides) were 3.3% during placebo treatment, 5.7% during treatment with an established antipsychotic agent, and 5.0% during atypical antipsychotic drug treatment (not including clozapine). Despite the statistical power provided by the large sample size, the rates for suicide attempts (including completed suicides) among these 3 schizophrenic treatment groups (not preselected for suicidality) were not significantly different from each other. In addition, these data affirm the high risk for suicide in patients with schizophrenia.

The annualized rate for attempted suicide (including completed suicide) in the InterSePT, which selected schizophrenic patients at high risk for suicide, was 7.1%, a rate not appreciably different from that for use of atypical antipsychotic drugs in the study by Khan et al.[11] Given that the selection criteria for the InterSePT study population required evidence for a high risk of suicide, a higher rate of treatment-emergent suicidal behaviors was expected than was described in the FDA sample. The fact that the rate is similar to that reported by Khan et al[11] suggests that the InterSePT itself (through the psychosocial interventions, the drugs used, or both) seemed to decrease the expected suicide rate. The advantages of using clozapine over olanzapine for reducing suicidality might be even more evident in clinical practice than reported herein because the increased clinical contact required for clozapine treatment to manage the risk of agranulocytosis might further reduce suicide risk relative to other antipsychotic drug treatments. It is unlikely that the extra contact available to the olanzapine-treated patients would be available in usual clinical practice.

Because risk of suicide is now one of the chief indicators for hospitalization of patients with schizophrenia or schizoaffective disorder, these results suggest that wider use of clozapine in suicidal patients with schizophrenia could reduce costs of their treatment. In addition, the decrease in suicidal behaviors observed with clozapine treatment has important potential quality-of-life benefits for individual patients, their families, and society. Together with the reduced risk of suicide when receiving clozapine therapy, these considerations suggest a more favorable risk-benefit analysis for the use of clozapine, especially in patients at risk for suicide.

Some limitations of this study should be noted. Although treatment assignment was randomized and the key ratings were masked, the study was not completely double-blinded. The decision not to use a double-blind design was based on concerns that a true blinding could not be maintained during a 2-year study given the well-known, recognizable, and common differentiating adverse effects of the 2 treatments. Another concern was that masked drug treatment might have hampered the flexibility of clinical care necessary to reduce the possibility of death by suicide in patients during a 2-year study. With full awareness of potential problems in a masked rater study, care was taken to ensure that the SMB and the masked raters did not have access to any source of data that might unblind them. Second, although clozapine treatment requires additional clinical contact related to white blood cell count monitoring, this study was not designed to determine whether any beneficial effects of clozapine treatment on suicidality are related to this additional contact. However, the equivalent clinical contact in the olanzapine-treated group demonstrates that increased contact alone cannot account for the clozapine effect on suicidality relative to olanzapine observed in this and other studies. Third, this study did not include a typical neuroleptic drug as a comparator. However, given the evidence that these drugs do not reduce the risk of suicide and[6-9] that the adverse effects of these drugs may be associated with increased risk for suicide[2] and independent evidence indicating that clozapine treatment reduces the suicide attempt and completion rate by approximately 80% compared with typical neuroleptic-treated patients,[9,15] there is no reason to expect that use of a typical antipsychotic agent would have had an effect on suicidal behavior comparable to clozapine therapy.

Strengths of this study include (1) the large sample size; (2) the use of a masked SMB, which utilized a uniform set of criteria for classifying potential suicide events; (3) clinician freedom to use adjunctive treatments as needed to minimize suicidality; (4) the inclusion of a broad range of nonrefractory patients at risk for suicide, including schizoaffective patients, whose risk for suicide tends to be greater than that of schizophrenic patients[25]; and (5) a dropout rate well within the range found in clinical trials of schizophrenia (despite the length of the study and the demanding nature of the protocol). Moreover, clinicians were free to use any dose of clozapine or olanzapine that they believed was merited by their patients' clinical conditions. The mean dose of clozapine was much lower than that usually used to treat refractory patients, reflecting the fact that only one quarter of the patients were refractory. Plasma levels of clozapine were not determined during the study. On the other hand, the olanzapine dose was similar to the mean daily dose cur-

InterSePT Study Group

In addition to the authors of this article, the InterSePT Study Group included the following principal investigators, Steering Committee members, Suicide Monitoring Board members, and Novartis Pharmaceuticals Corp employees: Saide Altinsan, MD; Siemion Altman, MD; Likiana Avigo, MD; Richard Balon, MD; Vanda Benešová, MD; Luis Bengochea, MD; Istvan Bitter, MD; Elisabeth Bokowska, MD; Bernardo Carpiniello, MD; Daniel Casey, MD; Giovanni Cassano, MD; James Chou, MD; Guy Chouinard, MD; Libor Chvila, MD; Jean Dalery, MD; Pedro Delgado, MD; Liliana Dell'Osso, MD; Carl Eisdorfer, MD, PhD; Robin A. Emsley, MD; Dawn Eng, MD; Tom A. Fahy, MD; Vera Folnegovic, MD; Sophie Frangou, MD; Pedro Gargoloff, MD; Alberto Giannelli, MD; Ira Glick, MD; Richard Greenberg, MD; George T. Grossberg, MD; Doris Gundersen, MD; Hannale Heila, MD; George Hsu, MD; Naveed Iqbal, MD; M. Miro Jakovljevic, MD; Richard C. Josiassen, PhD; Akos Kassaifarkas, MD; Rob Kerwin, MD; Frederic Khidichian, MD; Mary Ann Knesevich, MD; Jack Krasuski, MD; Vinod Kumar, MD; Veronica Walters Larach, MD; Michael Lesem, MD; Shon Lewis, MD; Pierre-Michel Llorca, MD; H. Edward Logue, MD; Stephen Martin, MD; Muriel Maurel-Raymondet, MD; Laszlo Mod, MD; Eva Morik, MD; Carlos Morra, MD; Ann Mortimer, MD; Mojtaba Noursalehi, PhD; Gyorgy Ostorharics-Horvath, MD; Ivo Paclt, MD; Jorg J. Pahl, MD; Linda Pestreich, Jeffrey Lee Peters, MD; Rosario Pioli, MD; Michael G. Plopper, MD; Thomas Posever, MD; Mark Rapaport, MD; Delbert Robinson, MD; Carlo Andrea Robotti, MD; Harry Rohme, PhD; Frederic Rouillon, MD; David Sack, MD; Isaac Sakinsofsky, PhD; Phillip Seibel, MD; George Simpson, MD; Nancy Temkin, PhD; Oladapo Tomori, MD; Santha Vaidain, MD; Zdeòka Vyhnándová, MD; Frederick Young, PhD; Daniel Zimbroff, MD; Marie-Agathe Zimmerman, MD.

rently used in the United States to treat patients with schizophrenia.

The results reported herein are consistent with a large body of data from the United States, the United Kingdom, and elsewhere indicating that clozapine treatment can reduce the suicide rate in these patients.[12-16] Some studies suggest that treatment response to clozapine administration is particularly evident in patients who have increased suicidality, and that this response may extend to patients with bipolar disorders.[25-28] Although these data provide compelling evidence for an effect of clozapine use in reducing suicidality, the mechanism for this effect requires further study. Data from this study suggest that the effect of clozapine therapy may not relate to its superior efficacy for treatment-resistant psychotic symptoms. Alternative mechanisms that have been suggested for the effect of clozapine use include an intrinsic antidepressant activity,[12] as also suggested by effects on mood symptoms and the differential antidepressant drug use in this study. Other data[20] suggest that suicidality may represent a separate symptom domain that is related to, but independent of, depression or psychosis.[20] The failure of treatment with typical antipsychotic agents to reduce suicidal behavior indicates that these symptoms are distinct from the major positive symptoms—delusions and hallucinations—for which these drugs are effective in approximately 70% of patients. Similarly, some studies indicate that classifying patients with schizophrenia as treatment responders and nonresponders to the antipsychotic effects of neuroleptic therapy does not differentiate them with regard to suicidality[12] or, as shown here, with regard to the ability of clozapine therapy to reduce suicidality. Together, these data indicate that the effect of clozapine use on suicidal behavior, although perhaps related to some of its other clinical advantages, could represent a separate outcome of clozapine treatment.

Suicidal behavior in persons with schizophrenia and schizoaffective disorder is recognized as a pressing public health problem.[29,30] To our knowledge, except for clozapine therapy, no pharmacologic treatment has been demonstrated to be useful in reducing suicidal behavior in patients with schizophrenia. The InterSePT indicates that, on average, treatment of only 12 patients with clozapine rather than olanzapine will show benefit for clozapine to reduce suicidal behavior. As discussed herin, these results suggest an advantage of clozapine therapy over olanzapine therapy to reduce the risk of suicide in patients with schizophrenia and schizoaffective disorder. Additional study is needed to determine whether the advantage of clozapine therapy for reducing suicidal behavior also holds for patients with other conditions in which antipsychotic drug use is widespread and suicide occurs at high rates, particularly bipolar disorder, major depression with psychotic features, and borderline personality disorder.

Submitted for publication February 14, 2002; final revision received June 14, 2002; accepted June 14, 2002.

From the Department of Psychiatry, Vanderbilt University, Nashville, Tenn (Dr Meltzer); Pfizer Inc, Ann Arbor, Mich (Dr Alphs); the Departments of Psychiatry, Dartmouth Medical School, Hanover, Mass (Dr Green), and University of Milan, Milan, Italy (Dr Altamura); Organon, Oss, the Netherlands (Dr Anand); the Departments of Psychiatry, La Plata University, La Plata, Argentina (Dr Bertoldi), University of Bordeaux, Bordeaux, France (Dr Bourgeois), McGill University, Montreal, Quebec (Dr Chouinard), and University of Montreal, Montreal (Dr Chouinard); Novartis Pharmaceuticals Corp, East Hanover, NJ (Dr Islam); and the Departments of Psychiatry, Hillside Hospital, Glen Oaks, NY (Dr Kane), Albert Einstein University, Bronx, NY (Dr Kane), Duke University, Durham, NC (Dr Krishnan), Manhattan Psychiatric Center–Nathan Kline Institute for Psychiatric Research, Wards Island, NY (Dr Lindenmayer), and University of California, Irvine (Dr Potkin). Drs Meltzer, Green, Chouinard, Kane, Lindenmayer, and Potkin have received grants from or are consultants to Novartis Pharmaceuticals Corp. Dr Chouinard has also received research support from Merck Frosst Canada, Inc, Dorval, Quebec; Janssen-Ortho Inc, Toronto, Ontario; and Pfizer Canada Inc, Dorval; and is a consultant to Janssen-Ortho Inc and Organon.

This study was supported by Novartis Pharmaceuticals Corp and by additional grants from the William K. Warren Research Foundation, Tulsa, Okla, and the Donald Test Foundation Trust and Lydia Bryant Test, Dallas, Tex (Dr Meltzer).

We thank Ingenix Pharmaceutical Services for monitoring this study, ensuring that it was conducted according to protocol, and maintaining the study masking by coordinating communication and data transfers among the sponsor, the sites, and the SMB. We also thank the InterSePT Study Group for work on this project.

Corresponding author and reprints: Herbert Y. Meltzer, MD, Psychiatric Hospital at Vanderbilt, 160123rd Ave S, Suite 306, Nashville, TN 37212 (e-mail: herbert.meltzer @mcmail.vanderbilt.edu).

REFERENCES

1. Cohen LJ, Test MA, Brown RL. Suicide and schizophrenia: data from a prospective community treatment study. *Am J Psychiatry*. 1990;147:602-607.
2. Meltzer HY, Fatemi H. Suicide in schizophrenia: the effect of clozapine. *Clin Neuropharmacol*. 1995;18(suppl):S18-S24.
3. Nyman A, Jonsson H. Patterns of self-destructive behaviour in schizophrenia. *Acta Psychiatr Scand*. 1986;73:252-262.
4. Caldwell CB, Gottesman II. Schizophrenia: a high-risk factor for suicide: clues to risk reduction. *Suicide Life Threat Behav*. 1992;22:479-493.
5. Harris EC, Barraclough B. Suicide as an outcome for mental disorders: a meta-analysis. *Br J Psychiatry*. 1997;170:205-228.
6. Axelsson R, Lagerkvist-Briggs M. Factors predicting suicide in psychotic patients. *Eur Arch Psychiatr Clin Neurosci*. 1992;241:259-266.
7. Winokur G, Tsuang M. The Iowa 500: suicide in mania, depression and schizophrenia. *Am J Psychiatry*. 1975;132:650-651.
8. Johns CA, Stanley M, Stanley R. Suicide in schizophrenia. *Ann N Y Acad Sci*. 1986;487:294-300.
9. Caldwell CB, Gottesman II. Schizophrenics kill themselves too: a review of risk factors for suicide. *Schizophr Bull*. 1990;16:571-589.
10. Siris SG. Suicide and schizophrenia. *J Psychopharmacol*. 2001;15:127-135.
11. Khan A, Khan SR, Leventhal RM, Brown WA. Symptom reduction and suicide risk among patients treated with placebo in antipsychotic clinical trials: an analysis of the Food and Drug Administration database. *Am J Psychiatry*. 2001;158:1449-1454.
12. Meltzer HY, Okayli G. Reduction of suicidality during clozapine treatment of neuroleptic-resistant schizophrenia: impact on risk-benefit assessment. *Am J Psychiatry*. 1995;152:183-190.
13. Walker AM, Lanza LL, Arellano F, Rothman KJ. Mortality in current and former users of clozapine. *Epidemiology*. 1997;8:671-677.
14. Reid WH, Mason M, Hogan T. Suicide prevention effects associated with clozapine therapy in schizophrenia and schizoaffective disorder. *Psychiatr Serv*. 1998;40:1029-1033.
15. Munro J, O'Sullivan D, Andrews C, Arana A, Mortimer A, Kerwin R. Active monitoring of 12,760 clozapine recipients in the UK and Ireland: beyond pharmacovigilance. *Br J Psychiatry*. 1999;175:576-580.
16. Reinstein MJ, Chasonov MA, Colombo KD, Jones LE, Sonnenberg JG. Reduction in suicide inpatients with schizophrenia receiving clozapine. *Clin Drug Invest*. 2002;22:341-346.
17. Sernyak MJ, Desai R, Stolar M, Rosenheck R. Impact of clozapine on completed suicide. *Am J Psychiatry*. 2001;158:931-937.
18. Meltzer HY. Treatment of suicidality in schizophrenia. *Ann N Y Acad Sci*. 2001;932:44-60.
19. Tran PV, Hamilton SH, Kuntz AJ, Potvin JH, Andersen SW, Beasley C Jr, Tollefson GD. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. *J Clin Psychopharmacol*. 1997;17:407-418.
20. Lindenmayer JP, Czobor P, Alphs L, et al, for the InterSePT Study Group. The InterSePT Scale for Suicidal Thinking (ISST) reliability and validity. *Schizophr Res*. In press.
21. Wei LJ, Lin DY, Weissfeld L. Regression analysis of multivariate incomplete failure time data by modeling marginal distributions. *JAMA*. 1989;84:1065-1073.
22. Allison PD. *Survival Analysis Using the SAS® System: A Practical Guide*. Cary, NC: SAS Institute Inc; 1995.
23. Collett D. *Modeling Survival Data in Medical Research*. London, England: Chapman & Hall; 1994.
24. Altman DG. Confidence intervals for the number needed to treat. *BMJ*. 1998;317:1309-1312.
25. Radomsky ED, Haas GL, Mann JJ, Sweeney JA. Suicidal behavior in patients with schizophrenia and other psychotic disorders. *Am J Psychiatry*. 1999;156:1590-1595.
26. Suppes T, Webb A, Paul B, Carmody T, Kraemer H, Rush AJ. Clinical outcome in a randomized 1-year trial of clozapine versus treatment as usual for patients with treatment-resistant illness and a history of mania. *Am J Psychiatry*. 1999;156:1164-1169.
27. Ciapparelli A, Dell'Osso L, Pini S, Chiavacci MC, Fenzi M, Cassano GB. Clozapine for treatment-refractory schizophrenia, schizoaffective disorder, and psychotic bipolar disorder: a 24-month naturalistic study. *J Clin Psychiatry*. 2000;61:329-334.
28. Sajatovic M, Bingham CR, Garver D, Ramirez LF, Ripper G, Blow F, Lehmann LS. An assessment of clinical practice of clozapine therapy for veterans. *Psychiatr Serv*. 2000;51:669-671.
29. Levin A. Conference focuses on mental health stigma. *Psychiatric News*. 2001;36(9):8.
30. Singh BS. Suicide: the public health crisis of our time. *Aust N Z J Med*. 1998;28:295-300.