Patterns of Concomitant Psychotropic Medication Use During a 2-Year Study Comparing Clozapine and Olanzapine for the Prevention of Suicidal Behavior

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Background: Results from the International Suicide Prevention Trial (InterSePT) indicate that clozapine is more effective than olanzapine in reducing suicidal behavior in schizophrenic and schizoaffective patients. However, because InterSePT allowed the uncontrolled use of concomitant psychotropic medications (CPMs), it is possible that the antisuicidal effect of clozapine may have been influenced by greater use of such agents. This article describes the use patterns of CPMs during InterSePT and examines whether CPM use may have affected study outcome.

Method: In this study, 479 patients received clozapine and 477 patients received olanzapine. Concomitant psychotropic medications were grouped into 4 classes: antipsychotics, antidepressants, sedatives/anxiolytics, and mood stabilizers. The doses of each CPM were converted into dosage equivalents of standard reference drugs. An analysis of covariance was performed to compare mean daily doses of CPMs between the 2 groups over the 2-year treatment period. The duration of treatment for each patient was 2 years, with the first patient entering the study in March 1998 and the last patient completing treatment in February 2001.

Results: Approximately 90% of patients in both treatment groups received at least 1 CPM. The mean ± SD number of CPMs per patient was 3.8 ± 2.90 in the clozapine group and 4.2 ± 3.16 in the olanzapine group. For each CPM class, the mean daily dose was statistically significantly lower in the clozapine group (antipsychotics, $p < .001$; antidepressants, $p < .01$; sedatives/anxiolytics, $p < .001$; mood stabilizers, $p < .05$). Analyses of CPM use by study intervals, suicide attempters versus nonattempters, study completers versus noncompleters, and geographic region resulted in similar findings.

Conclusion: The results support the conclusion that the effects of clozapine in reducing the risk of suicidal behavior derive from its intrinsic pharmacology and not from the influence of concomitant psychotropic medications.

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The use of atypical antipsychotics in combination with other psychotropic medications to treat schizophrenia and schizoaffective disorder is common clinical practice.[1,2] In addition to an atypical antipsychotic as the primary medication, treatment may be augmented with a short-acting benzodiazepine (for agitation), an antidepressant (for varying degrees of depressive symptomatology), or a mood stabilizer (for mood swings). Often, 2 antipsychotics are used concurrently in the hope that lower dosages of each agent may reduce the occurrence of adverse effects and/or that the combination may maintain or even enhance efficacy.[1,3]

In contrast to clinical practice, most controlled clinical research studies limit the use of concomitant psychotropic medications (CPMs). Although there are a number of reports in the literature that have characterized antipsychotic and concomitant medication use patterns, drug-drug interactions, and antipsychotic polypharmacy prescribing patterns in schizophrenic patients, most of these studies are retrospective and/or rely on prescription data.[1,2,4,5] To our knowledge, there are no published reports of prospective investigations of unrestricted concomitant medication use in this patient population.

An exception to the exclusion rule for unrestricted use of CPMs in research studies is the International Suicide Prevention Trial (InterSePT), a 2-year study examining the effect of clozapine and olanzapine in reducing the risk of suicidal behavior. The results of InterSePT demonstrate that there is a 26% decrease in the risk for suicidal behav-

ior in patients taking clozapine compared with those taking olanzapine.[6] The design of InterSePT permitted clinicians to use any intervention necessary, including the use of any CPM, to maintain patient safety and control of symptoms. It is therefore possible that any differential effects of study drug may have been influenced by greater use of such agents. In order to describe the patterns of psychotropic medication use during InterSePT and to address the possibility that differential use may have skewed the comparison of the 2 treatments with respect to reduction of risk for suicidal behavior, we devised an approach to evaluate and compare CPM usage over time. In this article, we present the methods and results of this approach. Additionally, because the use of CPMs was consistently documented at all participating sites, the results of our analysis may offer insight into the strategies that clinicians use to treat this challenging population.

METHOD

Patients and Design

InterSePT was a multicenter, randomized study comparing the effects of clozapine and olanzapine on the reduction of risk of suicidal behavior in male and female patients aged 18 to 65 years. The duration of treatment for each patient was 2 years, with the first patient entering the study in March 1998 and the last patient completing treatment in February 2001. Patients were required to have a DSM-IV diagnosis of schizophrenia or schizoaffective disorder and to be at high risk for committing suicide. A total of 980 patients were randomly assigned to treatment with either clozapine or olanzapine, so that there were 490 patients in each treatment group. Patients were recruited from 67 sites in 11 countries (United States, Canada, France, Italy, United Kingdom, the Czech Republic, Hungary, Croatia, South Africa, Argentina, and Chile). The study was carried out in accordance with Good Clinical Practice guidelines, and all patients gave written informed consent.

Patients were seen weekly by site staff for the first 6 months of the study and biweekly thereafter. Monitoring of white blood cell counts in clozapine-treated patients was matched by general medical-management visits for olanzapine-treated patients. Because of the at-risk population involved, clinicians were allowed to make any intervention necessary to prevent the occurrence of a suicide attempt, including adjusting the dosage of study medication, adding other psychotropic medications, and switching medications. The reader is referred to the article by Meltzer et al.[6] for details of the study design and the baseline characteristics of the participating patients.

Data Analysis

All concomitant medications used during the study were recorded in case report forms and included as part of the clinical trial database. The concomitant psychotropic medications used after randomization to study drug were identified and grouped into the following 4 classes: antipsychotics, antidepressants, sedatives/anxiolytics, and mood stabilizers. Stimulants, antidementia drugs, and analgesics were not considered for this analysis, as these medications were used either for nonpsychiatric indications (e.g., pain) or for indications outside the scope of InterSePT (e.g., attention-deficit/hyperactivity disorder). With the exception of propranolol, β-blockers were excluded from the analysis. Once a concomitant medication was assigned to a psychotropic class, all cases of use for that medication were included in the analysis.

To compare medications with different potencies, the daily dose of each concomitant psychotropic medication was converted into dosage equivalents within each drug class based on conversion data and average dosages as reported in the literature.[7,8] The use of equivalents is considered a valid approach for comparing dosages of medications with different potencies.[9,10] Antidepressants were converted to fluoxetine equivalents, sedatives/anxiolytics to diazepam equivalents, antipsychotics to haloperidol equivalents, and mood stabilizers to carbamazepine equivalents. A list of the conversion factors used for the most commonly prescribed CPMs is presented in Appendix 1. Psychotropic medications that were listed on the case report form as being taken on an as-needed basis (p.r.n. medication) were excluded from the main analysis because the calculation of dosage over time for these medications was not possible. Data concerning antidepressants or mood stabilizers that were used for less than 14 days were also excluded from the analysis, as it was felt that 2 weeks is the minimum treatment period necessary to achieve a clinically relevant degree of efficacy.

Statistical Analysis

To describe the pattern of use for each class of CPM during the course of the study, we computed the total daily dose of each CPM class for each patient and day of administration; the total daily dose of each class of CPM was then averaged across all patients receiving that CPM class. This calculation allowed plots of the mean daily dose of each class of CPM during the study. In order to calculate the mean daily CPM dose during successive 6-month intervals, the total dose of each CPM class for each patient was calculated by first multiplying the equivalent daily dose of each medication by duration of use (in days) and dividing by the total number of days that the patients stayed in the study during that 6-month interval.

An analysis of covariance was performed to compare the mean daily dose between the 2 treatment groups for each CPM class over the entire 2-year treatment period and for successive 6-month treatment intervals. The factors in the analysis of variance model included treatment, concomitant medication dosage at baseline, and geo-

Table 1. Number of Patients Receiving Concomitant Psychotropic Medication and Least Squares Mean Daily Dose by Medication Class and Treatment Group[a]

	Clozapine		Olanzapine		
Medication Class	N	Daily Dose, mg, Mean (SD)	N	Daily Dose, mg, Mean (SD)	p Value[b]
Antipsychotics	410	2.1 (0.33)	390	3.8 (0.34)	< .001
Antidepressants	241	16.7 (1.05)	270	20.7 (0.97)	< .01
Sedatives/anxiolytics	284	6.3 (0.64)	315	10.1 (0.61)	< .001
Mood stabilizers	120	487.3 (43.2)	144	620.6 (39.9)	< .05

[a]Mean daily dose is the mean equivalent daily dose for all patients receiving a class of concomitant psychotropic medication calculated over the 2-year study duration. Mean daily doses are expressed as equivalents for each concomitant psychotropic medication class: antipsychotics = haloperidol equivalents, antidepressants = fluoxetine equivalents, sedatives/anxiolytics = diazepam equivalents, mood stabilizers = carbamazepine equivalents.
[b]The p values were calculated from an analysis of covariance model that included factors for treatment, country region, and concomitant medication dosage at baseline.

graphic region. For the geographic region factor, data from countries and investigative sites within countries were pooled with other countries based on geographic location and prevailing medical practice patterns. Statistical significance was defined as $p < .05$.

Further statistical analyses were conducted to compare the treatment groups with respect to the number of CPMs per patient and the daily dose of CPM in those patients who manifested suicidal behavior and in those who completed the 2-year treatment period. Finally, CPM dose as a function of geographic region grouping was also analyzed.

RESULTS

Of the 980 patients randomly assigned to study medication, 479 patients in the clozapine group and 477 patients in the olanzapine group took at least 1 dose of the assigned study drug. Of these patients, 92.4% of the clozapine group and 91.8% of the olanzapine group received at least 1 CPM during InterSePT. The mean ± SD number of CPMs per patient was 3.8 ± 2.90 in the clozapine group and 4.2 ± 3.16 in the olanzapine group. The specific psychiatric medications taken by 5% or more of the patients are listed in Appendix 1. As stated previously, the use of CPM taken p.r.n. could not be quantitated. However, a review of the concomitant medication records showed that use of p.r.n. medication was equally distributed between the 2 treatment groups, with 210 patients in the clozapine group and 216 patients in the olanzapine group having at least 1 p.r.n. medication.

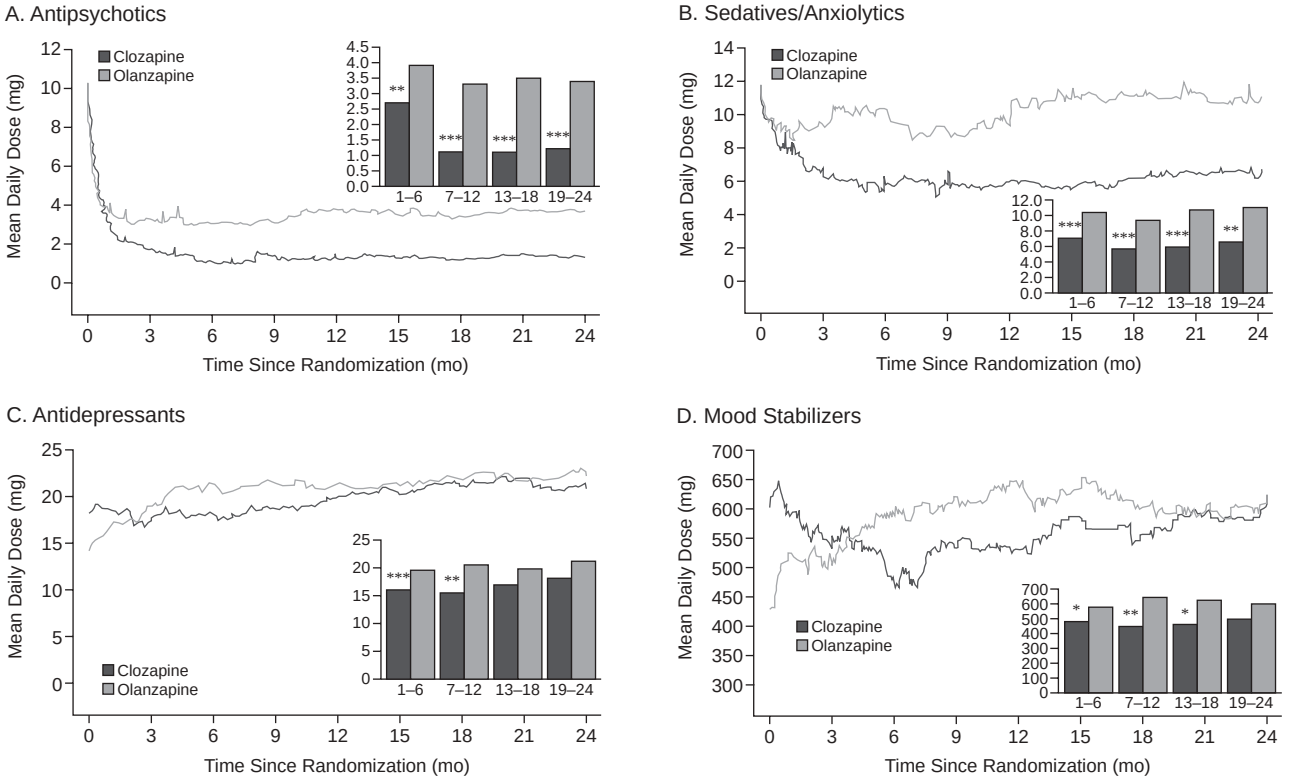
For the 2 treatment groups, the overall mean daily doses during the 2-year course of InterSePT for each class of concomitant psychotropic medication are summarized in Table 1. For all medication classes, the adjusted mean daily dose was statistically significantly greater in the olanzapine group compared with the clozapine group. The use patterns of the 4 CPM classes over the 2-year duration of InterSePT are illustrated for each treatment group in Figure 1A–D. For concomitant antipsychotics, there was a sharp drop in the mean daily dose over the first 2 months of the study to approximately 1.5 mg in the clozapine group and 3.5 mg in the olanzapine group, which probably reflects patients' switching from their prior antipsychotic to the assigned study medication (Figure 1A).

After 2 months, the mean daily dose of concomitant antipsychotics in both groups remained relatively stable, with the olanzapine group having a consistently greater mean dosage until the end of the study (month 24). A similar pattern was seen for sedatives/anxiolytics, where the mean daily dose over the first 2 months decreased to approximately 7.5 mg and 8.5 mg in the clozapine and olanzapine treatment groups, respectively (Figure 1B). For the remainder of the study period, the mean daily dose of sedative/anxiolytic in the clozapine group was fairly constant, ending at approximately 6.5 mg, while the mean daily dose in the olanzapine group increased to approximately 11 mg after 12 months and remained constant thereafter.

For antidepressants and mood stabilizers, the greatest differences in mean daily dose between the 2 groups occurred during the second quarter of the study. At the end of the study (month 24), the mean daily dose of antidepressants was slightly lower in the clozapine group than in the olanzapine group (20 and 22 mg fluoxetine equivalents, respectively, Figure 1C). For mood stabilizers, a relatively large difference in mean daily dose between the treatment groups was observed from month 4 through month 20 (Figure 1D). During this time, the patients in the clozapine group on average required less concomitant mood stabilizer. After month 20, the mean dosage of mood stabilizers in the clozapine group increased to approximately equal that of the olanzapine group.

In order to allow for a statistical comparison of CPM use in the 2 treatment groups at discrete points during InterSePT, the mean daily dose of each CPM class was calculated for successive 6-month intervals. This information is shown in the insets in each of the parts of Figure 1A–D. For each medication class, the mean daily CPM dose in every 6-month interval was higher for the olanzapine group than for the clozapine group. For antipsy-

Figure 1. Patterns of Concomitant Psychotropic Medication Use by Medication Class and Treatment Group[a]



[a]The insets in Figures 1A–D represent the least square mean daily dose of concomitant psychotropic medication by 6-month intervals, medication class, and treatment group.
*p < .05.
**p < .01.
***p < .001.

chotics and sedatives/anxiolytics, the difference in mean daily dose was statistically significant for all intervals postbaseline; for antidepressants and mood stabilizers, the difference between the treatment groups was statistically significant during the first 12 and 18 months of treatment, respectively.

CPM use among suicide attempters and nonattempters is summarized in Table 2. Attempters were defined as patients who met the primary outcome endpoint of the study (suicide attempt or hospitalization to prevent a suicide attempt), while nonattempters were patients who did not manifest suicidal behavior. The attempters in both treatment groups required a greater mean number and a higher mean daily dose of CPMs than did nonattempters. Among the attempters, patients in the olanzapine group had a statistically significantly higher mean daily dose of sedatives/anxiolytics than did the clozapine patients. Among the nonattempters, the olanzapine treatment group required significantly greater mean daily doses of all CPM classes than did the clozapine group.

Sixty percent of patients in InterSePT completed the 2-year study, so that any inequality in the relative proportions of patients in the 2 treatment groups with regard to extended use of CPMs may have affected the outcome of the study.[6] To examine this possibility, we conducted an analysis of patients with regular CPM use, whereby regular use was defined as continuous use of a CPM for at least 4 contiguous weeks and for greater than 75% of the time that a patient was enrolled in the study. The results of this analysis show that there was little difference between the treatment groups with regard to the proportion of patients with regular CPM use (antipsychotics: clozapine, 30.2%, olanzapine, 41.3%; antidepressants: clozapine, 61.8%, olanzapine, 62.5%; sedatives/anxiolytics: clozapine, 51.7%, olanzapine, 58.0%; mood stabilizers: clozapine, 69.8%, olanzapine, 67.6%).

Another potential confounding factor in the interpretation of any study outcome is the difference in the concomitant medication profiles of patients who discontinue versus those who remain in the study. To pursue this point, an analysis was conducted to examine the mean daily dose of CPMs for patients who completed and those who did not complete the 2-year study. It was found that patients who completed the study received lower

Table 2. Number and Daily Dose of Concomitant Psychotropic Medications in Suicide Attempters and Nonattempters[a,b]

	Attempters			Nonattempters		
Medication Class	Clozapine (N = 102)	Olanzapine (N = 141)	p Value	Clozapine (N = 388)	Olanzapine (N = 349)	p Value
Antipsychotics						
Patients, N	93	123		317	267	
No. drugs, mean (SD)	1.9 (1.3)	1.9 (1.3)		1.3 (1.0)	1.3 (1.1)	
Daily dose, mean (SD)	2.7 (0.9)	4.1 (0.8)	.15	2.1 (0.4)	3.8 (0.4)	.001
Antidepressants						
Patients, N	69	105		172	165	
No. drugs, mean (SD)	1.3 (1.1)	1.4 (1.2)		0.7 (1.0)	0.8 (1.1)	
Daily dose, mean (SD)	20.7 (2.5)	23.8 (2.0)	.20	15.6 (1.1)	19.3 (1.1)	< .01
Sedatives/anxiolytics						
Patients, N	75	112		220	213	
No. drugs, mean (SD)	1.9 (2.0)	2.1 (1.8)		1.0 (1.3)	1.2 (1.4)	
Daily dose, mean (SD)	8.9 (1.4)	12.1 (1.1)	< .05	5.7 (0.7)	9.6 (0.7)	< .001
Mood stabilizers						
Patients, N	39	62		81	82	
No. drugs, mean (SD)	0.5 (0.7)	0.6 (0.7)		0.3 (0.6)	0.3 (0.6)	
Daily dose, mean (SD)	535.7 (115.3)	656.2 (92.0)	.26	503.9 (44.4)	624.9 (42.9)	< .05

[a]Suicide attempters are patients who met the primary endpoint of the International Suicide Prevention Trial,[6] which was defined as a suicide attempt or hospitalization to prevent suicide.
[b]Mean daily dose is the mean equivalent daily dose for all patients receiving a class of concomitant psychotropic medication during the study.

Table 3. Daily Dose of Concomitant Psychotropic Medication (mg) by Patients Who Completed or Did Not Complete InterSePT[a]

	Completers			Noncompleters		
Medication Class	Clozapine Mean (SD)	Olanzapine Mean (SD)	p Value	Clozapine Mean (SD)	Olanzapine Mean (SD)	p Value
Antipsychotics	1.2 (0.36)	3.5 (0.37)	< .001	4.5 (0.72)	4.8 (0.73)	.71
Antidepressants	16.6 (1.25)	19.8 (1.15)	< .05	17.0 (2.29)	22.7 (2.15)	< .01
Sedatives/anxiolytics	6.3 (0.74)	9.6 (0.73)	< .01	6.9 (1.29)	11.6 (1.16)	< .01
Mood stabilizers	475.7 (48.98)	574.9 (47.11)	.12	544.1 (107.8)	824.9 (95.08)	< .01

[a]Mean daily dose is the mean equivalent daily dose for all patients receiving a class of concomitant psychotropic medication during the study.
Abbreviation: InterSePT = International Suicide Prevention Trial.[6]

mean daily doses of antipsychotics and mood stabilizers than did those patients who did not complete the study (Table 3). Regardless of whether or not they completed the study, patients in the clozapine group had significantly lower mean daily doses of concomitant antidepressant and sedative/anxiolytic medications than did patients treated with olanzapine. In addition, clozapine patients who completed the study had a significantly lower mean daily dose of concomitant antipsychotic than did the olanzapine patients.

As InterSePT was conducted in 11 countries on different continents, an analysis of CPM use by geographic region was conducted. In all 3 geographic regions (North America, South America, Europe), the mean daily dose of all CPM classes was greater in the olanzapine group than in the clozapine group (Table 4). The between-group difference was statistically significant for concomitant sedatives/anxiolytics in all 3 regions: for antipsychotics in North and South America, for antidepressants in North America alone, and for mood stabilizers in Europe alone.

DISCUSSION

The design of InterSePT allowed the investigators to undertake any therapeutic measures necessary, including the administration of multiple concomitant psychotropic medications, to avert suicidal behavior in a population that was at high risk for suicide. The results described here show that concomitant medications were prescribed extensively but not equally in the clozapine or olanzapine treatment groups during the 2-year treatment period of InterSePT. The vast majority of patients in both treatment groups received, at some point during the study, concomitant antipsychotics, antidepressants, and sedatives/anxiolytics, while mood stabilizers were used less commonly. Although patients in both treatment groups received approximately 4 medications each and similar proportions of patients in both treatment groups were regular users of CPMs, the mean dosage of all 4 classes of concomitant psychotropic medications was statistically significantly greater in the olanzapine group

Table 4. Daily Dose of Concomitant Psychotropic Medication (mg) by Geographic Region[a]

	North America (N = 415)[b]		South America (N = 93)[c]		Europe (N = 472)[d]	
Medication Class	Clozapine Mean (SD)	Olanzapine Mean (SD)	Clozapine Mean (SD)	Olanzapine Mean (SD)	Clozapine Mean (SD)	Olanzapine Mean (SD)
Antipsychotics	2.7 (0.44)	4.1 (0.46)*	0.6 (1.12)	5.7 (1.20)*	2.4 (0.46)	3.6 (0.46)
Antidepressants	20.5 (1.26)	25.4 (1.21)**	11.5 (5.26)	13.0 (3.03)	18.2 (1.21)	19.1 (1.16)
Sedatives/anxiolytics	4.4 (0.66)	6.8 (0.63)**	2.0 (1.27)	7.2 (1.16)*	7.9 (0.99)	12.4 (0.95)*
Mood stabilizers	675.2 (62.8)	762.1 (58.3)	305.8 (136.9)	637.6 (122.6)	380.3 (40.19)	552.3 (34.7)*

[a]Mean daily dose is the mean equivalent daily dose for all patients receiving a class of concomitant psychotropic medication during the study.
[b]North America: United States, Canada.
[c]South America: Argentina, Chile.
[d]Europe: United Kingdom, Croatia, Czech Republic, Hungary, Italy, South Africa, France.
*$p < .05$.
**$p < .01$.

(Table 1). This was also generally the case for the subgroups of patients who completed or dropped out of the study (Table 3).

Examination of CPM use patterns during the 2-year study period reveals specific differences between the 2 treatment groups for the CPM classes: for antipsychotics and sedatives/anxiolytics, the mean daily dose was consistently and significantly greater in the olanzapine group than in the clozapine group throughout the study (Figures 1A and 1B), while for antidepressants the greatest differences in mean daily dose were seen in the first 12 months of the study (Figure 1C) and for mood stabilizers in the middle 12 months (Figure 1D). Interestingly, the mean daily doses of antipsychotics and sedatives/anxiolytics in both treatment groups remained constant from approximately month 4, while the mean daily doses of antidepressants and mood stabilizers tended to increase over longer segments of the study duration. This finding indicates that, at least in the context of InterSePT, physicians tend to establish maintenance doses of antipsychotics and anxiolytics but address the manifest or anticipated affective symptoms that are often associated with suicidal behavior in a more flexible manner. This approach appears to apply, in particular, to use of the mood stabilizers, the mean daily dose of which clearly undulated in both treatment groups during the course of this 2-year study (Figure 1D).

Although the study protocol did not require that treating physicians document reasons for prescribing concomitant medications, the results of this study are consistent with certain speculations about the comparative therapeutic profiles of the 2 study drugs. Given the nature of this study population—high risk for suicidal behavior—the results suggest that patients at particular risk for suicidal behavior who were treated with olanzapine may have experienced greater agitation, anxiety, and depressive symptoms than did patients taking clozapine. These potential early warning signals may have encouraged the investigators to take preemptive therapeutic action to avert decompensation and thus lower risk of self-harm. This interpretation is supported by the fact that the mean daily doses of all CPM classes among the suicide nonattempters (i.e., those patients who through pharmacologic and other interventions were prevented from suicidal behavior) were significantly higher in the olanzapine than in the clozapine group (Table 2). The data in Table 2 also show that, with the exception of sedatives/anxiolytics, the mean daily doses of the CPM classes were not substantially higher in the attempter than in the nonattempter subgroups. This finding suggests that clinicians resort most readily to sedatives/anxiolytics and not to antipsychotics or antidepressants in patients who are most likely to manifest suicidal behavior.

The differences between the treatment groups in the use of CPMs described previously for the complete dataset also apply to the geographic regions in which InterSePT was conducted. However, there were several noteworthy regional differences with regard to the dosing of the 4 CPM classes. Concomitant antipsychotics and antidepressants were dosed much lower in the South American countries than in the United States and Europe, while mood stabilizers were dosed considerably higher in the United States than in the other geographic regions. Most evident is the finding that sedatives/anxiolytics were administered at much higher doses in the European countries than in either North or South America. The clinical significance of these differences is unknown, however, since geographic region as a factor did not influence the results of InterSePT.[6]

In conclusion, the data presented here indicate that the use of concomitant psychotropic medications did not bias the outcome of InterSePT, namely, that the risk of suicidal behavior was significantly reduced in patients taking clozapine. If anything, in light of the greater use of CPMs in the olanzapine group, the results of the present analysis strengthen the conclusion of Meltzer et al.[6] that the differential effects of clozapine on suicidal behavior may derive from its intrinsic pharmacologic properties and not from the circumstances of the study design or conduct. However, the "optimal" use of CPMs in patients taking antipsychotics is still unclear and remains an issue that needs to be more systematically addressed. Clinical trial designs similar to InterSePT, which include patients in real world clinical settings (e.g., CATIE [Clinical Antipsychotic Trials

of Intervention Effectiveness][11]), may help to provide additional data and a better understanding of the role adjunctive treatments have in clinical outcome.

Drug names: alprazolam (Xanax and others), amitriptyline (Limbitrol and others), buspirone (BuSpar), carbamazepine (Tegretol, Epitol, and others), citalopram (Celexa), clomipramine (Anafranil), clonazepam (Klonopin and others), clonidine (Catapres and others), clozapine (Clozaril and others), desipramine (Norpramin and others), diazepam (Valium and others), fluoxetine (Prozac and others), fluphenazine (Permitil, Prolixin, and others), gabapentin (Neurontin), haloperidol (Haldol and others), imipramine (Tofranil, Surmontil), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), midazolam (Versed and others), olanzapine (Zyprexa), oxazepam (Serax), paroxetine (Paxil and others), propranolol (Inderide, Innopran, and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), temazepam (Restoril), topiramate (Topamax), trazodone (Desyrel and others), valproic acid (Depakene and others), venlafaxine (Effexor), ziprasidone (Geodon), zolpidem (Ambien).

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Appendix 1. Conversions of Frequently Used Psychotropic Medications[a]

Concomitant Medicines	Equivalents (mg/d)	Conversion Factors
Antipsychotics	Haloperidol	
Haloperidol* (reference)	8	1
Olanzapine*	10	0.8
Clozapine*	300	0.0267
Risperidone*	5	1.6
Fluphenazine*	10	0.8
Thioridazine*	300	0.0267
Amisulpride	800	0.01
Quetiapine	400	0.02
Ziprasidone	80	0.1
Zotepine	200	0.04
Thioridazine	300	0.0267
Antidepressants	Fluoxetine	
Fluoxetine* (reference)	20	1
Venlafaxine*	100	0.2
Trazodone*	300	0.0667
Paroxetine*	20	1
Sertraline*	50	0.4
Amitriptyline	75	0.2667
Citalopram	20	1
Clomipramine	100	0.2
Desipramine	100	0.2
Imipramine	100	0.2
Sedatives/Anxiolytics	Diazepam	
Diazepam* (reference)	10	1
Alprazolam*	1	10
Clonazepam*	8	1.25
Lorazepam*	2.5	4
Temazepam*	20	0.5
Zolpidem*	10	1
Zopiclone*	7.5	1.333
Buspirone	30	0.3333
Midazolam	15	0.6667
Oxazepam	50	0.2
Propranolol	160	0.0625
Mood Stabilizers	Carbamazepine	
Carbamazepine* (reference)	1000	1
Lithium*	1200	0.8333
Clonidine	0.24	4166.6667
Gabapentin	1800	0.5556
Lamotrigine	300	3.3333
Topiramate	300	3.3333
Valproic Acid	1500	0.6667

[a]Data from Bezchlibnyk-Butler et al.[7] and the WHO Collaborating Centre for Drug Statistics Methodology.[8]
*Medication used by at least 25% of study patients.