

Atypical Antipsychotic Agents in the Treatment of Violent Patients With Schizophrenia and Schizoaffective Disorder

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Context: Violent behavior of patients with schizophrenia prolongs hospital stay and interferes with their integration into the community. Finding appropriate treatment of violent behaviors is of primary importance.

Objective: To compare the efficacy of 2 atypical antipsychotic agents, clozapine and olanzapine, with one another and with haloperidol in the treatment of physical assaults and other aggressive behaviors in physically assaultive patients with schizophrenia and schizoaffective disorder.

Design and Setting: Randomized, double-blind, parallel-group, 12-week trial. Physically assaultive subjects with schizophrenia or schizoaffective disorder who were inpatients in state psychiatric facilities were randomly assigned to treatment with clozapine (n=37), olanzapine (n=37), or haloperidol (n=36).

Main Outcome Measures: Number and severity of physical assaults as measured by the Modified Overt Aggression Scale (MOAS) physical aggression score and the number and severity of all aggressive events as mea-

sured by the MOAS overall score. Psychiatric symptoms were assessed through the Positive and Negative Syndrome Scale (PANSS).

Results: Clozapine was superior to both olanzapine and haloperidol in reducing the number and severity of physical assaults as assessed by the MOAS physical aggression score and in reducing overall aggression as measured by the MOAS total score. Olanzapine was superior to haloperidol in reducing the number and severity of aggressive incidents on these 2 MOAS measures. There were no significant differences among the 3 medication groups in improvement of psychiatric symptoms as measured by the PANSS total score and the 3 PANSS subscales.

Conclusions: Clozapine shows greater efficacy than olanzapine and olanzapine greater efficacy than haloperidol in reducing aggressive behavior. This antiaggressive effect appears to be separate from the antipsychotic and sedative action of these medications.

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VIOLENT BEHAVIOR IN patients with schizophrenia has serious clinical and societal consequences. In addition to the obvious harm to the victims, it also has a profound impact on its perpetrators. Aggressive and violent behavior is a frequent reason for presentation to an emergency department and subsequent admission to a psychiatric inpatient unit.¹ When aggressive behavior persists, it prolongs hospital stays and can constitute an important barrier to appropriate community placement.^{2,3} Although only a small minority of patients with schizophrenia are violent,⁴⁻⁶ this behavior stigmatizes the many nonviolent patients.⁷ Despite the great impact of violent behavior on the lives of patients with schizophrenia, there has been relatively little research on finding appropriate treat-

ments because of difficulties implementing studies involving violent patients.⁸

The new atypical agents differ pharmacologically from previous antipsychotic agents in their lower affinity for dopamine D2 receptors and greater affinities for serotonin (5-hydroxytryptamine_{1A}, 2A, 2C, 3, 6, and 7) and norepinephrine α_1 and α_2 neuroreceptors.^{9,10} Norepinephrine and especially serotonin have been implicated in violent behavior.^{11,12} Deficiency or dysregulation of serotonin has been associated with violence.¹³ Drugs that block the 5-HT_{1A} and 5-HT₂ receptors appear to have selective antiaggressive effects in animals.¹² While atypical agents act as serotonin antagonists, their immediate effect being a decrease in available serotonin, there is evidence that chronic treatment with serotonin antagonists produces changes in the serotonin binding sites that are qualita-

tively and quantitatively similar to those produced by serotonin agonists.¹⁴ Chronic treatment with clozapine has been reported to decrease serotonin turnover in the nucleus accumbens.¹⁵ In animal models, clozapine's antiaggressive effect has been linked to its serotonergic effect.¹⁶

Clozapine was found to have strong antiaggressive effects with minimal motor impairment in mice.¹⁷ It reversed the effect of phencyclidine on threat behaviors in rats¹⁸ and decreased isolation-induced aggression in mice.¹⁶ In psychiatric patients, clozapine is considered to have a "specific" antiaggressive effect; ie, it has an impact on aggression beyond the one it exerts through its antipsychotic or sedative effect. This has been established through various retrospective studies of violent psychiatric inpatients. A significant decrease in the number of violent incidents and episodes of seclusion and restraint was noted in state hospital patients after they began receiving clozapine.^{19,20} Clozapine produced a more dramatic reduction in violence and seclusions/restraints than in psychotic symptoms in 11 violent patients with schizophrenia.²¹ In another retrospective study²² conducted in various state hospitals, clozapine reduced significantly violent incidents; its powerful antiaggressive effect was greater than its global antipsychotic effect. In a study of patients with schizophrenia who were randomly assigned to open-label clozapine or continued receiving conventional antipsychotic medications, the patients treated with clozapine became significantly less disruptive than did patients in the usual care group.²³

There are more limited data on other atypical agents, especially as related to actual physical assaults. In 1 study based on a large multicenter trial that had the primary goal of comparing the general antipsychotic efficacy of risperidone with that of haloperidol, its effect on hostility was superior to haloperidol.²⁴ Two studies analyzed the hostility and aggression data from a double-blind investigation comparing the general antipsychotic efficacy of olanzapine, clozapine, risperidone, and haloperidol in 157 inpatients with schizophrenia or schizoaffective disorder who were not selected for aggressive behavior. In the first study, patients taking clozapine were found to improve more on the hostility item of the Positive and Negative Syndrome Scale (PANSS) than patients taking haloperidol or risperidone.²⁵ This effect on hostility appeared to be independent of the antipsychotic effect of clozapine. In the second study based on these data,²⁶ the comparisons among the 4 drugs were limited to overt incidents of aggression. Once an adequate therapeutic dose of clozapine was reached, it was superior to haloperidol in reducing the number and severity of aggressive incidents.

Some studies on the effect of atypical agents on aggression were conducted in the community. In a prospective study of patients with schizophrenia,²⁷ treatment with atypical antipsychotic medications, including clozapine, risperidone, and olanzapine, significantly reduced violent behavior, whereas treatment with conventional neuroleptics did not significantly reduce violence. In another study by the same group,²⁸ olanzapine was compared with risperidone. Receiving olanzapine for 1 year or longer significantly lowered violence risk, but no significant change in violence risk was found for subjects who received risperidone for 1 year or longer.

Thus, the literature on psychopharmacologic antiaggressive treatments suggests that atypical antipsychotics, particularly clozapine, have superior antiaggressive effects in comparison with typical antipsychotic agents and that they may constitute an important advance in the treatment of violence and aggression. However, most studies that report such effects were uncontrolled while others used data gathered in patients who were not selected on the basis of aggression.

The purpose of the present study is the investigation of the effect of atypical antipsychotic agents on interpersonal violence and aggression. To our knowledge, it is the first randomized, double-blind clinical study specifically designed to assess the efficacy of atypical antipsychotic agents for the treatment of violent behavior among hospitalized patients who were physically assaultive against others.

METHODS

PATIENTS

Written consent was required from each patient according to a protocol approved by the institutional review boards and compliant with the Declaration of Helsinki. Subjects were 110 patients aged 18 to 60 years and diagnosed with schizophrenia or schizoaffective disorder (using diagnostic criteria from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*), randomly assigned to treatment with clozapine, olanzapine, or haloperidol in a 12-week, double-blind study.

INCLUSION AND EXCLUSION CRITERIA

For inclusion in the study, patients were required to have a clearly confirmed episode of physical assault directed at another person during this hospitalization and some persistence of aggression, as evidenced by the presence of some other aggressive event, whether physical or verbal or against property. Research staff monitored subjects and ward documentation (eg, progress notes and treated-as-needed medication records) daily on all hospital wards to detect possible incidents of physical assault. After finding such an assault, research personnel interviewed the nursing staff to confirm the incident and its severity. Information was then obtained retrospectively on all aggressive incidents for the 4 weeks prior to the qualifying assault. This ascertainment relied completely on record review, ward reports, and hospital incident reports.

Patients were excluded from the study if they had been hospitalized for more than a year; if they had a history of nonresponse to clozapine, olanzapine, or haloperidol (defined as a lack of improvement despite a contiguous adequate trial of medication); if they had a history of clozapine, olanzapine, or haloperidol intolerance; or if they had medical conditions that would be adversely affected by any of these 3 medications. Patients who received a depot antipsychotic within 30 days before randomization were also excluded.

TREATMENTS

Patients who met the study inclusion and exclusion criteria and signed informed consent were transferred to the research ward. The entire study was conducted on the research ward to provide a uniform environment for all patients. This setting allowed also for close monitoring of medication administration because all patients were carefully observed when taking their medications, thus

ensuring high treatment compliance. A detailed description of the clinical setting can be found elsewhere.²⁹

During a baseline screening period of 1 to 2 weeks, patients' prestudy antipsychotic medications were adjusted so that the daily dose at the end of the screening period did not exceed 750 mg per day in chlorpromazine equivalents. After completing baseline assessments, patients were randomly assigned to 1 of the 3 treatment arms: clozapine, olanzapine, or haloperidol. The study used a block randomization scheme with a block size of 3 with no baseline stratification. The medications were administered in a double-blind fashion as were all procedures in the study.

The 12-week trial consisted of a 6-week escalation and fixed-dose period and a 6-week variable-dose period. During the first 6 weeks of the study, the prestudy antipsychotic was gradually discontinued while the doses of olanzapine, clozapine, and haloperidol were escalated to their target levels (20, 500, and 20 mg/d, respectively) at which they remained fixed until the end of the first study period. During the last 6 weeks of the study, antipsychotic dose was allowed to vary within the following ranges: clozapine, 200 to 800 mg per day; olanzapine, 10 to 35 mg per day; and haloperidol, 10 to 30 mg per day. Psychiatrists, blind to treatment group assignment, could change the doses by prescribing various "levels" of medication.

Throughout the study, all patients were receiving (double-blind) either benzotropine or benzotropine placebo or a combination of both. Benzotropine (4 mg/d) was administered prophylactically to all patients receiving haloperidol. Patients assigned to atypical antipsychotics were initially receiving only benzotropine placebo, but if the patient's psychiatrist (who was unaware of the patient's antipsychotic assignment) determined clinically that the patient should be treated for extrapyramidal adverse effects, a prescription could be written for "benzotropine supplements" that would result in real benzotropine gradually replacing benzotropine placebo (up to 6 mg/d). An analogous arrangement for "supplements" was available to raise the dose of benzotropine from 4 to 6 mg per day for emerging extrapyramidal symptoms in patients assigned to haloperidol.

Lorazepam, diphenhydramine hydrochloride, or chloral hydrate were prescribed open-label (by psychiatrists who were blind to antipsychotic treatment assignment) as needed for the treatment of restlessness, agitation, and insomnia. Patients who were receiving mood stabilizers or antidepressants prior to entry into the study continued receiving these medications. Dosage adjustments, if necessary, were done prior to randomization and patients were kept at the same level throughout the study.

ASSESSMENTS

Raters blind to treatment group performed all clinical research assessments. All study procedures, including blood draws, were identical for all 3 groups throughout the study to preserve the blind.

The Modified Overt Aggression Scale (MOAS)³⁰ was used to rate all incidents. The 3 categories of external aggression were used: physical aggression against other people, verbal aggression, and physical aggression against objects. There was a very careful monitoring of all these behaviors occurring on the research ward during the study period. The nursing staff reported all behaviors contemporaneously on a monitoring form that allowed entries to be made for each patient at 30- to 60-minute intervals. Research personnel interviewed the nursing staff after each aggressive event to confirm that an incident of overt aggression had occurred and to obtain detailed information for rating the event and its severity using the 3 categories of aggression. Severity varied for each type of assault from mild to severe. The total score for each type of incident (physical

aggression, verbal aggression, and aggression against property) represents the number of incidents over time as well as their severity. For each subject, the overall total MOAS score was also computed. It was obtained by assigning a different weight for each type of aggressive event, using a psychometrically validated method developed by the MOAS authors.³⁰ Following this method, types of aggressive events were rated on a scale of increasing severity with verbal aggression being assigned the lowest weight and physical aggression the highest. Thus, the overall total score represents the number of incidents over time, their severity, and the type of aggression.

The MOAS total score and the score on the physical aggression subscale were the principal measures of efficacy. The interrater reliability, estimated by intraclass correlation coefficient, for the MOAS was established prior to the study and intermittently throughout the study. It was high throughout with an intraclass correlation coefficient above 0.90.

The PANSS³¹ was used to assess clinical symptoms. It contains 3 subscales, one for positive symptoms, another for negative symptoms, and a general psychopathology subscale. The PANSS was administered at baseline and then weekly during the first month of the study and every other week thereafter. Two independent raters performed assessments at baseline, week 6, and week 12 (or end point); the average of these 2 raters' assessments was included for the analyses of efficacy together with the single-rater ratings from the other points. These paired ratings were also used for the assessment of interrater reliability throughout the study. The interrater reliability, estimated by intraclass correlation coefficient, of the paired ratings for the PANSS total score was above 0.90.

Several safety measures were performed throughout the study. Weekly white blood cell counts were done throughout the study in all patients. This was necessary for clozapine treatment, and it was also done for patients receiving olanzapine and haloperidol to maintain blind conditions. An electrocardiogram and physical examination were done prior to entry in study and at regular intervals during the study. Adverse effects were measured weekly by the Extrapyramidal Symptom Rating Scale³² and a checklist of adverse reactions. Vital signs were done twice a day for all patients during the period of clozapine dose escalation (or corresponding period) and once a week thereafter.

We hypothesized that the 3 study medications differ in their effects on overt aggression as measured by the overall MOAS score and the MOAS physical aggression score with clozapine showing the lowest overt aggression score and haloperidol the highest.

STATISTICAL ANALYSES

The principal analysis of efficacy was based on the intent-to-treat principle; thus, all randomized patients were included in the analyses. Difference among the treatment groups in terms of categorical efficacy measures was investigated by generalized linear model analysis. This method, unlike the traditional linear models, makes allowance for nonnormally distributed observations such as ordered categorical data and counts of events occurring during a given period of time. The total physical aggression score on the MOAS scale and, separately, the overall total MOAS score were used as the dependent variables. Treatment assignment was applied as independent variable in the generalized linear model analysis. Because a preliminary inspection of the data indicated that increasingly higher scores on the MOAS scale occurred with a decreasing frequency (ie, the distribution of the dependent variable displayed an inverted J curve), similarly to data from other studies, the generalized linear model analysis in our study was based on the

Poisson distribution. If the analysis indicated a significant overall difference among the treatments, post hoc analyses were conducted to investigate pairwise treatment differences.

In addition to the physical aggression subscale and the overall total MOAS score, which were the principle measures in our study, separate analyses were conducted for the other 2 MOAS subscale scores, verbal aggression and aggression against objects. Differences among groups in improvement of symptom severity (as measured by the PANSS score and the 3 individual subscale scores) were investigated by analysis of covariance. Change in symptom severity over time (from pretreatment baseline to end point) was used as the dependent variable. Treatment group served as the independent variable and baseline severity was used as a covariate. A separate analysis of covariance was performed for each of the measures.

RESULTS

SAMPLE CHARACTERISTICS AND BASELINE INFORMATION

The study was conducted between June 1999 and November 2004. The recruitment and follow-up of study patients is shown in the **Figure**. There were 134 eligible patients who met all inclusion and exclusion criteria; 24 refused to participate in the study and 110 were randomized. Out of these 110 patients, 102 patients were enrolled in 1 site. A second site was recruited for the trial while the study was already ongoing and contributed only 8 patients. Because the overwhelming majority of the patients were coming from 1 site, we pooled patients from the second site with patients from the first for the purpose of statistical analyses.

Thirty-seven patients were assigned to clozapine, 37 to olanzapine, and 36 to haloperidol. Forty patients did not complete the full 12 weeks. Nonparametric survival analysis (Kaplan-Meier method) of participation in the double-blind treatment showed no significant difference among the 3 treatment groups in the median time of survival (attrition) in the study ($\chi^2=2.4$, $P=.29$ by log-rank test). The mean (SE) survival time in the study was 9.2 (0.50), 7.8 (0.45), and 8.3 (0.61) weeks for the clozapine, olanzapine, and haloperidol groups, respectively.

There were no significant differences among the 3 groups in length of hospitalization upon entry in the study with a median length of hospitalization of 48 days at that point. There were no differences among the 3 groups in the proportion of subjects who were receiving typical or atypical antipsychotic agents prior to randomization and no differences in the proportion of subjects receiving other psychotropic medications, including mood stabilizers or antidepressants.

There were no differences among the 3 medication groups in the total number of physical assaults ($F_{2,109}=1.76$, $P=.19$) during the 4-week period preceding the qualifying physical assault as determined by the retrospective review of records on the various wards (clozapine: mean \pm SD, 0.92 ± 0.68 [median, 1.0]; olanzapine: mean \pm SD, 0.97 ± 0.73 [median, 1.0]; haloperidol: mean \pm SD, 1.22 ± 0.80 [median, 1.0]). Furthermore, there were no differences ($F_{2,109}=2.17$, $P=.12$) among the 3 groups in the total number of aggressive incidents, including physical and verbal aggression as well as aggres-

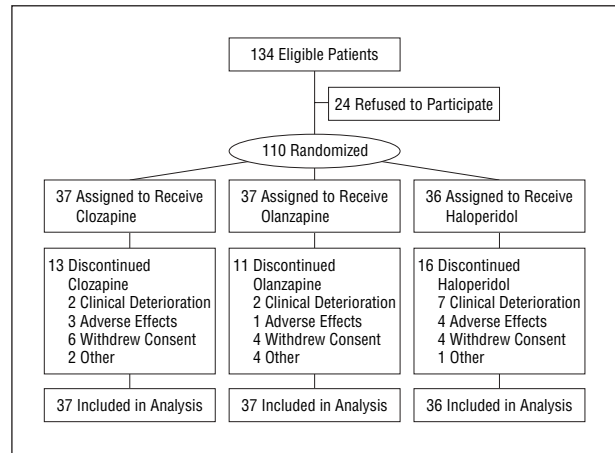


Figure. Patient flowchart.

sion against property, during this 4-week period (clozapine: mean \pm SD, 2.14 ± 1.27 [median, 2.0]; olanzapine: mean \pm SD, 2.16 ± 1.44 [median, 2.0]; haloperidol: mean \pm SD, 2.80 ± 1.88 [median, 2.5]).

Table 1 displays the demographic and psychiatric characteristics by treatment group. Patients randomized to clozapine, olanzapine, and haloperidol did not differ on any of these baseline characteristics (Table 1).

At the end point of the first 6 weeks, the escalation and fixed-dose period, the average dose was 457.1 mg per day for clozapine (SD, 128.2 mg/d; median dose, 500.0 mg/d), 19.8 mg per day for olanzapine (SD, 3.1 mg/d; median, 20.0 mg/d), and 19.6 mg per day for haloperidol (SD, 3.9 mg/d; median, 20.0 mg/d). At the end of the last 6 weeks of the study, the variable-dose period, the average dose was 565.5 mg per day for clozapine (SD, 112.7 mg/d; median dose, 550.0 mg/d), 24.7 mg per day for olanzapine (SD, 6.1 mg/d; median, 25.0 mg/d), and 23.3 mg per day for haloperidol (SD, 7.1 mg/d; median, 25.0 mg/d).

There were no significant differences among the 3 groups in the use of treated-as-needed medication, including lorazepam, diphenhydramine hydrochloride, or chloral hydrate. There were no differences in sedation or extrapyramidal symptoms among the 3 medication groups. Lack of differences in extrapyramidal symptoms was probably due to the prophylactic use of anticholinergic medication in the haloperidol group.

AGGRESSIVE BEHAVIORS

The primary variables of interest for this study were the total MOAS score and the MOAS physical aggression score for each patient during participation in the study. The 3 medication groups differed in MOAS total score (clozapine: mean, 25.1; median, 18; interquartile range, 6-34; olanzapine: mean, 32.7; median, 29; interquartile range, 6-51; haloperidol: mean, 40.9; median, 24; interquartile range, 3-48). Generalized linear model analysis indicated that this difference in total MOAS score among the 3 groups was significant ($\chi^2=159.2$, $P<.001$). Post hoc comparisons showed that clozapine was superior to both haloperidol ($\chi^2=154.7$, $P<.001$) and olanzapine ($\chi^2=36.2$, $P<.001$) and that olanzapine was superior to haloperidol ($\chi^2=44.9$, $P<.001$) (**Table 2**).

Table 1. Baseline Characteristics of Patients Assigned to Receive Clozapine, Olanzapine, and Haloperidol

Characteristics	Clozapine (n = 37)	Olanzapine (n = 37)	Haloperidol (n = 36)	Test Statistic (P Value)*
Male, No. (%)	31 (83.8)	29 (78.4)	30 (83.3)	0.5 (.80)*
Race/ethnicity, No. (%)				
White	7 (18.9)	5 (13.5)	7 (19.4)	7.6 (.47)*
Black	20 (54.1)	28 (75.7)	21 (58.3)	
Hispanic	8 (21.6)	4 (10.8)	8 (22.2)	
Other	2 (5.4)	0	0	
Diagnosis, No. (%)				
Schizophrenia	27 (73.0)	23 (62.2)	21 (58.3)	1.9 (.40)*
Schizoaffective disorder	10 (27.0)	14 (37.8)	15 (41.7)	
Age at randomization, mean ± SD, y	35.1 ± 12.3	35.6 ± 9.4	32.7 ± 10.6	0.8 (.48)
Duration of illness, mean ± SD, y	15.7 ± 9.5	16.8 ± 11.2	13.9 ± 11.2	0.6 (.56)
Prior psychiatric hospitalizations, mean ± SD, No.	12.3 ± 9.8	11.4 ± 9.6	8.9 ± 4.7	1.8 (.18)
Positive and Negative Syndrome Scale scores, mean ± SD				
Positive subscale	22.9 ± 5.4	22.9 ± 5.7	23.0 ± 6.4	0.0 (.99)
Negative subscale	20.3 ± 4.5	18.9 ± 3.4	19.8 ± 4.7	1.1 (.34)
General subscale	43.2 ± 7.2	41.9 ± 7.4	42.6 ± 6.6	0.3 (.73)
Total	86.4 ± 14.4	83.7 ± 14.1	85.5 ± 13.2	0.4 (.70)

* χ^2 Was computed for the categorical variables and analysis of variance for the continuous variables.

Table 2. Differences in the Various Forms of Overt Aggression Among Patients Treated With Clozapine, Olanzapine, and Haloperidol*

MOAS	Comparison	OR (95% CI) for Less Severe Violence†	χ^2 (P Value)
Total score	Clozapine vs haloperidol	1.69 (1.6-1.8)	154.7 (<.001)‡
	Clozapine vs olanzapine	1.30 (1.2-1.4)	36.2 (<.001)†
	Olanzapine vs haloperidol	1.30 (1.2-1.4)	44.9 (<.001)‡
Physical aggression	Clozapine vs haloperidol	2.04 (1.8-2.3)	134.0 (<.001)‡
	Clozapine vs olanzapine	1.33 (1.2-1.5)	21.3 (<.001)‡
	Olanzapine vs haloperidol	1.54 (1.4-1.7)	54.0 (<.001)‡
Aggression against property	Clozapine vs haloperidol	1.85 (1.4-2.4)	18.6 (<.001)‡
	Clozapine vs olanzapine	1.10 (0.8-1.5)	0.1 (.78)
	Olanzapine vs haloperidol	1.67 (1.3-2.2)	16.4 (<.001)‡
Verbal aggression	Clozapine vs haloperidol	1.35 (1.2-1.5)	21.7 (<.001)‡
	Clozapine vs olanzapine	1.32 (1.1-1.5)	17.6 (<.001)‡
	Olanzapine vs haloperidol	1.03 (0.9-1.2)	0.3 (.57)

Abbreviations: CI, confidence interval; MOAS, Modified Overt Aggression Scale; OR, odds ratio.

*Generalized linear model analyses were used. An overall difference among the groups was found on each of the 4 measures of violence (see the "Aggressive Behaviors" subsection of the "Results" section). Pairwise differences are provided in the table.

†The odds ratio represents the odds of a lower MOAS score (one point) during the study period for the first as compared with the second medication in the pair for each type of aggressive behavior.

‡Results remain significant after correcting for multiple testing (Bonferroni correction).

The 3 medication groups differed in the MOAS physical aggression score (clozapine: mean, 10.3; median, 4; interquartile range, 0-16; olanzapine: mean, 14.1; median, 12; interquartile range, 0-20; haloperidol: mean, 20.7; median, 6; interquartile range, 0-20). This difference among the 3 groups was significant ($\chi^2=145.4$, $P<.001$). Post hoc comparisons indicated that clozapine was superior to haloperidol ($\chi^2=134.0$, $P<.001$) and to olanzapine ($\chi^2=21.3$, $P<.001$). Olanzapine was superior to haloperidol ($\chi^2=54.0$, $P<.001$) (Table 2).

In addition to the total MOAS score and the MOAS physical aggression score, we investigated also aggression against property and verbal aggression in secondary analyses. The 3 medication groups differed on the MOAS aggression against property (clozapine: mean, 2.6;

median, 0; interquartile range, 0-2; olanzapine: mean, 2.7; median, 0; interquartile range, 0-4; haloperidol: mean, 4.7; median, 0; interquartile range, 0-6). This overall difference among the groups was significant ($\chi^2=24.8$, $P<.001$). In post hoc tests, clozapine was superior to haloperidol ($\chi^2=18.6$, $P<.001$) as was olanzapine ($\chi^2=16.4$, $P<.001$), but there was no significant difference between clozapine and olanzapine for this type of aggression (Table 2).

The 3 medication groups differed in MOAS verbal aggression score (clozapine: mean, 12.2; median, 9; interquartile range, 2-15; olanzapine: mean, 16.0; median, 11; interquartile range, 4-23; haloperidol: mean, 15.6; median, 7.5; interquartile range, 2-25). This overall difference among the groups was significant ($\chi^2=26.4$, $P<.001$).

Clozapine was superior to both haloperidol ($\chi^2=21.7$, $P<.001$) and olanzapine ($\chi^2=17.6$, $P<.001$), but there was no significant difference between olanzapine and haloperidol (Table 2). The effect sizes for the primary variables, the physical aggression and total MOAS score, as well as for aggression against property and verbal aggression are presented in Table 2.

We repeated all of these analyses for each type of assault using as covariates the corresponding MOAS scores derived retrospectively from hospital records for the 4-week period prior to study entry. The results remained unchanged; the same significant differences among the 3 medication groups were found in these analyses. Similarly, the results remained unchanged when we repeated the analyses for each type of assault using every patient's duration in the study as a covariate in the analyses.

PSYCHOTIC SYMPTOMS

We investigated the differences among the 3 groups in improvement of symptom severity as measured by the PANSS total score and the individual subscale scores (including the subscale for positive symptoms, negative symptoms, and general psychopathology). Change in symptom severity over time (from pretreatment baseline to end point) was used as the dependent variable. Patients receiving olanzapine showed the most improvement and those receiving haloperidol the least, but these differences were not statistically significant on any of these measures (Table 3). We repeated the analyses, removing the hostility item from the PANSS, because its rating is influenced by aggression. The results were essentially unchanged.

COMMENT

The 3 medications showed significant differences in their effects on the likelihood and severity of aggressive incidents over the 12-week study period. Clozapine was superior to both olanzapine and haloperidol while olanzapine was superior to haloperidol in its effect on the 2 primary measures of aggression in this study, the MOAS physical aggression score and the overall MOAS score.

In addition to these, there were also significant differences between clozapine and haloperidol on the 2 secondary measures of aggression, the MOAS aggression against property and MOAS verbal aggression scores. Furthermore, clozapine was superior to olanzapine in reducing verbal aggression and olanzapine was superior to haloperidol in reducing aggression against property. There was no significant difference between clozapine and olanzapine in MOAS aggression against property and no difference between olanzapine and haloperidol in MOAS verbal aggression.

There were no significant differences in psychiatric symptoms as measured by the PANSS among the 3 medication groups. The discrepancy between the antipsychotic and antiaggressive effects of the atypical antipsychotic agents is consistent with the studies mentioned earlier in the article^{21,22,25} that showed decreases in aggression with clozapine that were far greater than what could be attributed to the reduction in psychotic symp-

Table 3. Change in the Positive and Negative Syndrome Scale Total Score and in the 3 PANSS Subscale Scores (With Baseline Values as Covariates)*

PANSS Variable	Medication Group	Analysis	
		Mean \pm SD	F (P Value)
Total score	Clozapine	2.39 \pm 14.2	1.23 (.30)
	Olanzapine	4.83 \pm 9.7	
	Haloperidol	0.58 \pm 15.2	
Positive symptoms	Clozapine	1.54 \pm 5.0	2.30 (.11)
	Olanzapine	1.41 \pm 3.6	
	Haloperidol	-0.50 \pm 5.3	
Negative symptoms	Clozapine	-0.56 \pm 4.9	1.65 (.20)
	Olanzapine	0.72 \pm 3.0	
	Haloperidol	0.44 \pm 4.6	
General psychopathology	Clozapine	1.43 \pm 7.0	1.21 (.30)
	Olanzapine	2.69 \pm 5.5	
	Haloperidol	0.64 \pm 8.2	

Abbreviation: PANSS, Positive and Negative Syndrome Scale.

*Differences among groups in improvement of symptom severity were investigated by analysis of covariance with baseline severity as covariate. A separate analysis of covariance was performed for each of the measures ($df = 2$). Positive values indicate improvement.

toms per se. The differences in aggression could not be attributed to differences in the sedative properties of the medications because there were no significant differences in sedation among the 3 medication groups.

The reason for the specific antiaggressive effect of clozapine and, to a lesser extent, olanzapine is not clear. It may be attributable to the differences in serotonergic or adrenergic receptor activities of these agents as compared with conventional antipsychotic agents. It is possible that their antiaggressive effect reflects normalization of serotonergic function. The greater limbic selectivity of clozapine,³³ shared also by olanzapine,³⁴ may also play a role in this antiaggressive effect.³⁵

The 2 atypical agents in our study showed better antipsychotic efficacy than haloperidol, but the effect size was modest and the difference did not reach statistical significance. Our results contrast with several studies that report significantly greater antipsychotic efficacy for atypical agents.^{36,37} They are similar in this respect to other findings, such as the study by Rosenheck et al,³⁸ who found no significant difference in psychiatric symptoms between olanzapine and haloperidol in a double-blind, randomized, controlled trial comparing these 2 medication groups. It should be noted, however, that our study uses a different population (ie, patients selected on the basis of violent behavior) and was not designed to evaluate differences in antipsychotic effects in regular schizophrenic populations. These results, therefore, cannot be used to guide clinical practice in such populations.

The patients in this study were not treatment resistant, as a history of treatment resistance to any of the 3 study drugs was an exclusion criterion, but the length of the present hospitalization is longer than the duration in nonstate facilities. Although the presence of physical assaults prolongs hospitalization in all facilities,³ this difference in length of stay should be taken into consideration because it may limit the generalizability of the findings.

The study was conducted entirely on a research ward in an inpatient setting. This allowed for a uniform environment, careful monitoring of violent incidents, and close supervision of the administration of medication, ensuring high treatment compliance. The setting, however, limits the generalizability of the findings with regard to treatment of violence in the community. There are additional factors that are associated with community violence, such as treatment compliance, substance abuse,³⁹ homelessness, and adverse social environments. Thus, antipsychotic agents may exert their influence on violent behavior indirectly through their impact on these factors. In the studies conducted in the community,^{27,28} the advantage of the atypical agents over conventional antipsychotic medications²⁷ and of olanzapine over risperidone²⁸ was due, in part, to greater treatment compliance with these medications. Clozapine has also been associated with decreased substance abuse,^{40,41} and this may mediate, to some extent, its reduction of violence in the community.

The present study was not designed to examine these factors. As we gain better understanding of the complex and varied etiology of violence in patients with schizophrenia, we will be able to design treatments that will target diverse factors that contribute to the behavior, such as drug addiction, trauma sequelae, or treatment compliance.

This article deals with long-term management of inpatients with persistent aggressive behavior. It is unique in being the first double-blind study of atypical agents that was specifically designed for the investigation of aggression with subjects who were selected on the basis of physical assaults. The study confirms findings reported in the literature in open studies and in populations that were not selected on the basis of violent behavior. The findings of the study point to the value of clozapine and to a lesser degree olanzapine in the treatment of violence. Treatment with these medications should be considered as an important component of violence risk management, especially in patients with a history of persistent violence. It has important implications in facilitating discharge planning and reintegration of the patient back into the community. A trial of clozapine should be offered to patients with schizophrenia or schizoaffective disorder whose violent behavior does not respond well to adequate trial of other antipsychotic medications.

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Announcement

Clinical Trials Registration Required. In concert with the International Committee of Medical Journal Editors, *Archives of General Psychiatry* will require, as a condition of consideration for publication, registration of clinical trials in a public trials registry (such as <http://ClinicalTrials.gov> or <http://controlled-trials.com>). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after March 1, 2006. For trials that began enrollment before this date, registration will be required by June 1, 2006. The trial registration number should be supplied at the time of submission.

For details about this new policy see the editorials by DeAngelis et al in the September 8, 2004 (2004;292:1363-1364) and June 15, 2005 (2005;293:2927-2929) issues of *JAMA*.