The Effects of Clozapine Versus Haloperidol on Measures of Impulsive Aggression and Suicidality in Chronic Schizophrenia Patients: An Open, Nonrandomized, 6-Month Study

Baruch Spivak, M.D.; Evgeny Shabash, M.D.; Brian Sheitman, M.D.; Abraham Weizman, M.D.; and Roberto Mester, M.D.

Background: The risk of suicide for schizophrenia patients is 20 to 50 times higher than that for the general population. Long-term treatment with clozapine, an atypical antipsychotic, has been shown to reduce the rate of suicide by 80% to 85%. The goal of the present study was to examine whether clozapine's effect on the reduction of suicidal behavior in chronic schizophrenic patients could be due to a reduction in impulsive-aggressive behavior.

Method: 44 patients with chronic DSM-IV schizophrenia were treated with clozapine or haloperidol decanoate in an open prospective 6-month trial. Changes in measures of suicidality, impulsiveness, aggression, depressed mood, and positive and negative symptoms were assessed at baseline and at 6 months.

Results: The clozapine-treated group (N = 18) had a significantly greater reduction on all outcome measures compared with the haloperidol decanoate–treated group (N = 26). Only in the clozapine-treated group did the reduction in measures of suicidality correlate significantly with a reduction in impulsiveness and aggression. The reductions in suicidality and impulsive aggression were not significantly correlated with reductions in depressed mood or positive and negative symptom scores in either group.

Conclusion: These data suggest that the reduction in suicidality following long-term clozapine treatment may be related to a reduction in impulsiveness and aggression.

(J Clin Psychiatry 2003;64:755–760)

Received June 17, 2002; accepted Dec. 23, 2002. From the Clinical Research Unit, Ness Ziona Mental Health Center, Ness Ziona, Israel (Drs. Spivak, Shabash, and Mester); Department of Psychiatry, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel (Drs. Spivak, Weizman, and Mester); and the Department of Psychiatry, University of North Carolina at Chapel Hill (Dr. Sheitman).

The authors report no financial or other support of this work.

Corresponding author and reprints: Baruch Spivak, M.D., Clinical Research Unit, Ness Ziona Mental Health Center, P.O. Box 1, Ness Ziona 74100, Israel (e-mail: baruchspivak@int.gov.il).

Suicide is the major cause of premature death among schizophrenia patients. The risk of suicide in patients with schizophrenia is 20 to 50 times higher than that in the general population.[1–4] Over the lifetime course, up to 60% of schizophrenia patients attempt suicide and 9% to 13% successfully commit suicide.[1–4]

Long-term treatment with clozapine, an atypical antipsychotic, has been shown in clinical trials and epidemiologic studies to reduce the rate of suicide by 80% to 85%.[2,4–6] It has been suggested that this decrease in suicide may be related to a unique clozapine-specific effect.[4] Clozapine is effective in improving positive, negative, and depressive symptoms and is associated with minimal extrapyramidal side effects or tardive dyskinesia, which are all considered as risk factors for suicide in schizophrenia patients.[4,5,7–10] In addition, clozapine has been shown to be an effective agent in patients with treatment-resistant schizophrenia in reducing aggression[11–13] and impulsiveness,[14] and its advantage over other antipsychotics as a specific antihostility agent has been reported.[15] Since impulsive-aggressive behavior characterizes individuals at risk for suicide,[16] the anti–impulsive-aggressive properties of clozapine may also be related to the reduction in suicidality among schizophrenia patients.[13]

The goal of the present 6-month open prospective study was to test the hypothesis that the beneficial effect of clozapine on the reduction in suicidality in chronic schizophrenia patients, as compared to the classic antipsychotic haloperidol, is due to a reduction in impulsiveness and aggression.

METHOD

A total of 44 (33 men and 11 women) chronically ill schizophrenia patients (duration of illness at least 2 years), between the ages of 18 and 60 years and with a minimal score of 70 on the Positive and Negative Syndrome Scale (PANSS),[17] were treated with clozapine or depot haloperidol decanoate in an open prospective 6-month trial conducted between December 1997 and January 2000. The management of chronic schizophrenia

Table 1. Demographic Data and Baseline Psychometric Scores Among Chronic Schizophrenic Patients Who Were Assigned to Treatment With Clozapine or Haloperidol Decanoate (N = 44)

	Clozapine-Treated Group (N = 18)[a]		Haloperidol Decanoate–Treated Group (N = 26)[a]		Significance[b]	
Variable	Mean	SD	Mean	SD	t	p
Age, y	35.4	10.4	32.0	8.5	1.2	.2
Duration of illness, y	12.4	9.2	10.6	6.7	0.8	.4
Number of hospitalizations	5.9	4.7	4.0	2.5	1.7	.1
Impulsivity Scale	25.1	5.8	23.0	4.2	1.4	.2
Overt Aggression Scale (OAS)	5.1	2.3	4.3	2.6	1.0	.3
OAS physical aggression against self item	1.9	1.2	1.3	1.1	1.8	.1
Hamilton Rating Scale for Depression (HAM-D)	17.9	8.9	13.7	6.8	1.8	.1
HAM-D suicide item	2.1	1.2	2.0	1.1	0.05	1.0
Positive and Negative Syndrome Scale (PANSS)	117.3	27.8	108.0	27.4	1.1	.3
PANSS positive symptoms	25.7	7.2	25.7	10.6	1.0	1.0
PANSS negative symptoms	30.3	6.7	28.9	6.0	0.8	.5

[a]Clozapine-treated group = 13 men and 5 women; haloperidol decanoate–treated group = 20 men and 6 women; clozapine-treated group versus haloperidol decanoate–treated group, Fisher exact test: p = .1.
[b]Clozapine-treated group versus haloperidol decanoate–treated group, unpaired 2-tailed t test, df = 42 for all.

is dependent on regular administration (very often in depot form) of antipsychotic medication. For that reason, we chose to compare clozapine with the long-acting depot form of haloperidol that is used worldwide.

The diagnosis of schizophrenia was made according to the DSM-IV criteria using the Structured Clinical Interview for Axis I DSM-IV Disorders.[18] Only patients in good physical condition, without chronic or acute physical problems, history of alcohol or drug abuse, or abnormalities on routine laboratory tests, were included. The total number of lifetime suicide attempts and number of current suicide attempts during the month preceding the study were recorded for each patient (categorized as being present or absent). All participants provided written informed consent after receiving comprehensive information about the study. Due to the ethical restrictions of the Israeli Ministry of Health, only patients with documented resistance to treatment with classic antipsychotic agents were approved for treatment with clozapine. Treatment resistance was defined as: (1) persistent symptoms of psychosis over the past 2 years in spite of at least 3 periods of treatment with antipsychotic agents from 3 different chemical classes for at least 6 weeks, with each treatment corresponding to daily dosages ≥ 600 mg of chlorpromazine; (2) a rating of ≥ 4 on at least 3 (of 7) items of positive PANSS or 3 (of 7) items of negative PANSS symptoms; (3) Clinical Global Impressions (CGI) scale score ≥ 4 (moderately ill).

Of 44 chronic schizophrenia patients, 18 met the criteria for treatment resistance and were assigned to treatment with clozapine, while the other 26 patients received haloperidol decanoate. The 2 groups did not differ in demographic and other clinical variables (Table 1). No differences were found between the 2 groups at baseline in respect to the total number of lifetime suicide attempts (7 vs. 7 patients had a total of 11 vs. 11 lifetime suicide attempts; 3 vs. 3 patients once and 4 vs. 4 twice) and in respect to the total number of current suicide attempts (3 vs. 3 patients made 3 vs. 3 suicide attempts during the month preceding the study).

During the first phase of the study (cross-titration phase for 15 days), the clozapine treatment was started at 25 mg/day at baseline and then was increased by 25 mg every 3 days to 150 mg/day at day 15. The haloperidol treatment was started at 2.5 mg/day (orally) at baseline and then was increased by 2.5 mg every 3 days to 15 mg/day at day 15. During this prestudy period, oral antipsychotic, mood stabilizer, and antidepressant and anxiolytic medications were gradually discontinued. During the second phase, which lasted through the total 6 months of the study, the dose of clozapine was increased by 25 mg every 3 days if required on the basis of the patient's clinical status and side effects. The haloperidol decanoate treatment was initiated on day 18 with an intramuscular injection of 150 mg per month and then was increased if clinically required every month. During the second phase, the dose of antipsychotic was allowed to vary up to 500 mg/day for clozapine and up to 300 mg/month for haloperidol decanoate. The final dose of the study medication was chosen by the research team to produce the most likely beneficial effect, according to the clinical response of each particular patient. The administration of concomitant anticholinergic agents and benzodiazepines was permitted during the trial for treatment of agitation, insomnia, and extrapyramidal side effects (EPS). No other adjunctive psychotropic agents were permitted. All patients treated with clozapine were hospitalized for a period of 12 weeks, according to the requirements of the Israeli Ministry of Health, and then were allowed to continue the clozapine therapy in the outpatient clinic. All patients treated with haloperidol decanoate were hospitalized for at least 6 weeks and then were allowed to continue the treatment in the outpatient clinic.

The patients were evaluated at baseline and after 6 months of treatment with the study medications by the

Table 2. Scores at Baseline and Endpoint on Psychometric Scales Among Patients Who Completed the 6-Month Protocol

	Clozapine-Treated Group (N = 15)						Haloperidol Decanoate–Treated Group (N = 22)					
	Baseline		6 Month		Δ (reduction in scores = 6 month – baseline)		Baseline		6 Month		Δ (reduction in scores = 6 month – baseline)	
Assessment	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Impulsivity Scale	25.3	4.5	11.2	2.6	–14.1**	5.3	23.0	3.1	14.4	4.6	–8.5	3.5
Overt Aggression Scale (OAS)	5.2	2.5	0	0	–5.2*	2.5	4.4	2.4	2.1	1.9	–2.2	1.2
OAS physical aggression against self item	2.1	1.2	0	0	–2.1*	1.2	1.3	1.2	0.9	0.8	–0.4	0.7
HAM-D	18.4	9.6	6.8	3.3	–11.6****	8.2	15.0	5.3	9.2	3.7	–5.8	3.8
HAM-D suicide item	2.2	1.1	0	0	–2.2***	1.1	2.4	1.1	1.1	0.9	–1.0	1.0
PANSS	117.3	29.8	65.7	15.0	–51.6****	19.8	105.5	28.1	81.8	16.3	–23.8	20.6
PANSS positive symptoms	25.6	7.3	14.9	5.2	–10.7	5.1	25.6	11.3	15.3	6.8	–10.3	10.3
PANSS negative symptoms	30.3	7.3	17.4	2.9	–12.9*	6.3	28.5	6.1	23.5	4.7	–5.1	4.5

Significance (clozapine-treated group versus haloperidol decanoate–treated group, unpaired 2-tailed t test with Bonferroni correction): *p < .001; **p < .005; ***p < .01; ****p < .05.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, PANSS = Positive and Negative Syndrome Scale.

PANSS,[17] the Hamilton Rating Scale for Depression (HAM-D),[19] the Overt Aggression Scale (OAS),[20] and the Impulsivity Scale (IS).[21] One trained rater (E.S.) performed all the clinical assessments.

The change in rating score (Δ = 6-month score – baseline score) on the "physical aggression against self" item of the OAS and on the suicide item of the HAM-D were the principal outcome measures of suicidality. The change in rating scores (Δs) on the OAS and on the IS were the principal outcome measures of impulsiveness and aggression. The correlations between the Δs of the OAS "physical aggression against self" item and the HAM-D suicide item and the Δs of the IS and the OAS scores for both groups were the additional principal measures of the study. Other outcome measures of the study were the changes (Δs) on the HAM-D and the PANSS scores during the 6 months of treatment.

The baseline psychometric data and the changes (Δs) in psychometric evaluation during the study between the 2 groups were analyzed using unpaired 2-tailed Student t test with Bonferroni correction for multiple tests. Fisher exact test was used to compare the categorical data between the groups. Pearson correlation test with Bonferroni correction for multiple tests was performed to assess the correlation between the Δs of the OAS "physical aggression against self" item and the HAM-D suicide item and the Δs of the PANSS, the HAM-D, the IS, and the OAS scores. All results are expressed as mean ± SD.

RESULTS

Noncompliance with study medication and follow-up resulted in 3 patients (2 men and 1 women) in the clozapine-treated group and 1 male patient in the haloperidol decanoate–treated group dropping out. Haloperidol decanoate treatment was discontinued because of clinical deterioration and emergence of EPS in the case of 3 patients (1 man and 2 women).

Fifteen clozapine- (11 men and 4 women) and 22 (18 men and 4 women) haloperidol decanoate–treated patients completed the 6-month study. Among the completers, the mean ± SD age of the clozapine group of patients was 34.7 ± 11.1 years, duration of illness was 11.5 ± 9.6 years, and number of hospitalizations was 5.8 ± 5.2. The mean ± SD age of the haloperidol decanoate group of patients was 31.3 ± 8.8 years, duration of illness was 9.9 ± 6.6 years, and number of hospitalizations was 3.7 ± 2.4 (nonsignificant differences between groups). Among the completers, the differences between treatment groups in baseline scores on the PANSS, IS, HAM-D, HAM-D suicide item, OAS, and OAS "physical aggression against self" item were not significant (Table 1). The mean ± SD doses that were achieved during the study were 246.7 ± 90.0 mg/day for clozapine and 200.0 ± 62.8 mg/month for haloperidol decanoate (no significant differences between the groups [2-tail t = 1.5, df with correction for unequal variances = 31, p = .2], as calculated according to Shiloh et al.[22] in chlorpromazine equivalents [mg/day] with adjustment of the monthly doses of haloperidol decanoate to the daily doses). All patients, except 1, in the haloperidol decanoate–treatment group were treated for EPS with concomitant anticholinergic medication, 14 with trihexyphenidyl up to 10 mg/day, and 7 with biperiden up to 6 mg/day; 7 of these anticholinergic-treated patients were also treated with diazepam up to 10 mg/day. None of the patients in the clozapine-treated group were treated with any concomitant medications during the trial.

A reduction in all psychometric scale scores was noted for both groups during the 6 months of the study (Table 2). However, the magnitude of the reductions (Δs) in the OAS, the OAS "physical aggression against self" item, the HAM-D, the HAM-D suicide item, and the IS score was significantly higher in the clozapine-treated group compared with the haloperidol decanoate–treated group (Table 2). In addition, there were significantly greater reductions in the clozapine-treated group in the PANSS

Table 3. Scores at Baseline and Endpoint on Psychometric Scales in Clozapine Responders[a] Versus Nonresponders in Completers of a 6-Month Study

	Clozapine Responders (N = 9)						Clozapine Nonresponders (N = 6)					
	Baseline		6 Month		Δ (reduction in scores = 6 month – baseline)		Baseline		6 Month		Δ (reduction in scores = 6 month – baseline)	
Assessment	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Impulsivity Scale	24.3	3.7	11.1	1.5	–13.2	3.4	26.6	5.6	11.3	3.9	–15.3	7.5
Overt Agression Scale (OAS)	5.2	2.3	0	0	–5.2	2.3	5.2	3.0	0	0	–5.2	3.0
OAS physical aggression against self item	2.1	1.1	0	0	–2.1	1.1	2.0	1.5	0	0	–2.0	1.5
HAM-D	21.6	10.7	6.4	3.5	–15.2	8.7	13.7	5.4	7.5	3.1	–6.2	3.1
HAM-D suicide item	2.1	0.9	0	0	–2.1	0.9	2.3	1.4	0	0	–2.3	1.4
PANSS	126.3	30.4	64.4	13.8	–61.9*	18.3	103.8	25.5	67.7	18.0	–36.2	9.0
PANSS positive symptoms	25.6	7.6	13.9	4.5	–11.7	6.3	25.7	7.6	16.5	6.3	–9.2	2.4
PANSS negative symptoms	33.0	6.2	16.7	2.1	–16.3*	4.6	26.2	7.3	18.5	3.8	–7.7	4.8

[a]Responders ≥ 40% reduction in PANSS scores in completers of a 6-month study.
Significance (clozapine responders versus nonresponders, unpaired 2-tailed t test with Bonferroni correction): *p < .05.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, PANSS = Positive and Negative Syndrome Scale.

total and negative symptom scores (no statistical difference in positive symptom scores) (Table 2). During the 6 months of the study, none of the patients from either group attempted suicide.

The reductions (Δs) in the HAM-D suicide item and in the OAS "physical aggression against self" item were correlated significantly with the reduction (Δ) in the IS score (correlation analysis with Bonferroni correction: N = 15, r = 0.75, p < .03 and r = 0.8, p < .03, respectively), as well as with reduction (Δ) in the OAS score (r = 0.8, p < .03, and r = 0.9, p < .03, respectively) in the clozapine-treated group only. The reduction (Δ) in the IS score correlated significantly with the reduction (Δ) in the OAS score in the clozapine-treated group only (r = 0.8, p < .03). No significant correlations between the reductions in measures of suicidal and impulsive-aggressive behavior and the reductions in the HAM-D, the PANSS total, and positive and negative symptoms scores were detected in either group.

In spite of the small sample size of clozapine-treated patients, an additional analysis was performed, using 40% or higher reduction in PANSS scores as a cutoff among the completers, in order to examine if antisuicidal and anti–impulsive-aggressive benefits of clozapine treatment were present in clozapine responders (N = 9) versus nonresponders (N = 6) (Table 3). No significant differences between clozapine responders and nonresponders with respect to measures of impulsiveness, aggression, and suicidality were detected (Table 3).

DISCUSSION

The main finding of the present study is the strong correlation between the reduction of suicidality and the reduction of impulsive-aggressive behavior in the clozapine-treated patients as opposed to the lack of such a correlation in the classic antipsychotic haloperidol decanoate–treated subjects. In spite of the lack of significant differences between the groups on positive symptoms, there was a significant effect of clozapine on impulsiveness, aggression, and suicidality. Moreover, the reductions in the scores of impulsiveness, aggression, and suicidality did not differ significantly between clozapine responders and nonresponders. This may indicate that the anti–impulsive/aggressive/suicidal effect of clozapine may be potentially independent of its effect on the positive symptoms.

It has been suggested that greater impulsivity may underline a generalized propensity to suicidal and aggressive acts regardless of psychiatric diagnosis. The greater impulsivity may interfere with a decision-making process and eventually may be manifested in externally and self-directed aggression.[16]

Preclinical data suggest that clozapine and haloperidol evoke different patterns of neuronal activity and their different clinical profiles may be related to the regionally different effects in the brain.[23] Cognitive and neuroimaging studies of violent offenders and neurologic patients indicate that prefrontal dysfunction significantly contributes to the development of impulsive-aggressive behavior.[24–26] Unlike haloperidol, clozapine increases the neuronal activity in the prefrontal cortex,[23] a phenomenon that may explain its superiority to haloperidol in reduction of impulsiveness, aggression, and ultimately suicidality.

A reduction in serotonin (5-HT) function appears to be associated with both impulsive-aggressive and suicidal behaviors.[27–30] Clozapine, in contrast to the classic antipsychotic haloperidol, has an ability to block a variety of 5-HT receptors[31] and to enhance 5-HT release in rat prefrontal cortex.[32] Neurologic patients with bilateral lesions of the prefrontal cortex demonstrate a specific abnormality in decision-making process, as reflected in neuropsychological tests by repeated impulsive engagement in decisions that lead to negative consequences.[25] It was suggested that long-term clozapine administration is associated with normalization of 5-HT activity due to down-regulation of central 5-HT_{2A} receptors[4] and increased

availability of central 5-HT.[2,33] This normalization of central 5-HT activity, especially in the prefrontal cortex, may be the biological basis of the anti–impulsive-aggressive effect of clozapine that leads to the reduction of suicidality in chronic schizophrenia patients. Furthermore, in animal models, long-term clozapine administration increases the release of norepinephrine and dopamine in the prefrontal cortex.[32] In chronic schizophrenia patients, increased central availability of norepinephrine and dopamine, along with normalization of central 5-HT function, may further contribute to clozapine's antidepressive effect and to reduction in suicidality.[3,33]

Significant reduction in HAM-D scores in clozapine-treated patients (versus haloperidol-treated group) in our sample is consistent with the results of a larger study by Meltzer and Okayli,[5] which demonstrated that marked decrease in suicidality in treatment-resistant schizophrenia patients was associated with improvement in depression and hopelessness. In regard to Meltzer and Okayli's findings,[5] it is possible that a correlation between the reduction in impulsiveness and aggression as measured by rating scales and the HAM-D suicide item may reflect a general improvement in psychopathology in the clozapine-treated patients. It should be mentioned that one large VA study failed to support the hypothesis that clozapine treatment is associated with significantly fewer deaths due to suicide.[34] The authors noted that veterans who were exposed to clozapine while inpatients were significantly less likely to die during 3 years of follow-up than those in the control group, but that was not due to a lower rate of suicide in clozapine-treated patients.[34] Future prospective studies in larger samples of patients may enable the use of a multiple regression analysis, in order to discriminate between a potentially specific anti–aggressive/impulsive/suicidal effect of clozapine and its general beneficial effect on psychopathology.

Important limitations are that the design of the present study is open-label and that subjects were not selected specifically due to a history of impulsive-aggressive and suicidal behavior. Thus, our sample of schizophrenia patients was not one at high risk for either suicide or aggression. This bias in the selection of patients limits the potential generalizability[35] of our results. However, our results are consistent with other studies of psychotic patients that have shown a significant reduction in impulsivity-related behavior such as reductions in suicidality[5,6] and in arrest rates[36] following clozapine treatment. Another limitation, resulting from an ethical consideration, is that clozapine administration was limited only to treatment-resistant patients. However, the baseline psychometric characteristics of impulsiveness, aggression, and suicidal behavior were not significantly different between the 2 groups. Furthermore, previous studies demonstrated that the risk of suicide is not significantly different in antipsychotic-resistant or antipsychotic-responsive schizophrenia patients.[4]

The length of hospitalization of the haloperidol group was shorter than that of the clozapine group, so the haloperidol group could potentially have faced more stressors and more access to substance/alcohol abuse. Even though the rate of substance abuse and alcoholism is relatively low in Israel,[37] such confounding factors could affect the outcome measures in favor of clozapine-treated patients.

This study used clinical reports to assess impulsivity. However, impulsivity can also be assessed by neuropsychological tests and behavioral laboratory measures.[25,30,38] The advantages of these latter measures include their suitability for repeated use that is especially relevant for long-term treatment studies.[38] Employment of specific and sensitive neuropsychological tests and laboratory paradigms for the measurement of impulsivity that results in impaired decision-making may be a more sensitive approach than clinical history alone[16,25,30,38] and should be considered in the design of future studies.

Drug names: biperiden (Akineton), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), diazepam (Valium and others), haloperidol (Haldol and others), trihexyphenidyl (Artane and others).

REFERENCES

1. Caldwell CB, Gottesman II. Schizophrenia: a high-risk factor for suicide: clues to risk reduction. Suicide Life Threat Behav 1992;22:479–493
2. Meltzer HY, Fatemi H. Suicide in schizophrenia: the effect of clozapine. Clin Neuropharmacol 1995;18(suppl l3):S18–S24
3. Meltzer HY. Suicide in schizophrenia: risk factors and clozapine treatment. J Clin Psychiatry 1998;59(suppl 3):15–20
4. Meltzer HY. Suicide and schizophrenia: clozapine and the InterSePT study. J Clin Psychiatry 1999;60(suppl 12):47–50
5. 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
6. Walker AM, Lanza LL, Arellano F, et al. Mortality in current and former users of clozapine. Epidemiology 1997;8:671–677
7. Hogan TP, Awad AG. Pharmacotherapy and suicide risk in schizophrenia. Can J Psychiatry 1983;28:277–281
8. Dassori AM, Mezzich JE, Keshavan M. Suicidal indicators in schizophrenia. Acta Psychiatr Scand 1990;81:409–413
9. Roy A. Suicide in chronic schizophrenia. Br J Psychiatry 1992;141: 171–177
10. Naber D, Hippius H. The European experience with use of clozapine. Hosp Community Psychiatry 1990;41:886–890
11. Volavka J, Zito JM, Vitai J, et al. Clozapine effects on hostility and aggression in schizophrenia. J Clin Psychopharmacol 1993;13:287–289
12. Buckley P, Bartell J, Donenwirth K, et al. Violence and schizophrenia: clozapine as a specific antiaggressive agent. Bull Am Acad Psychiatry Law 1995;23:607–611
13. Spivak B, Roitman S, Vered Y, et al. Diminished suicidal and aggressive behavior, high plasma norepinephrine levels, and serum triglyceride levels in chronic neuroleptic-resistant schizophrenic patients maintained on clozapine. Clin Neuropharmacol 1998;21:245–250
14. Spivak B, Mester R, Wittenberg N, et al. Reduction of aggressiveness and impulsiveness during clozapine treatment in chronic neuroleptic-resistant schizophrenic patients. Clin Neuropharmacol 1997;20:442–446
15. Citrome L, Volavka J, Czobar P, et al. Effects of clozapine, olanzapine, risperidone, and haloperidol on hostility among patients with schizophrenia. Psychiatr Serv 2001;52:1510–1514
16. Mann JJ, Waternaux C, Haas GL, et al. Toward a clinical model of suicide behavior in psychiatric patients. Am J Psychiatry 1999;156:181–189
17. Kay SR, Fiszbein A, Opler LA. Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276

18. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for Axis I DSM-IV Disorders, Patient Version (SCID-P, Hebrew Version). Tel Aviv, Israel: Jakobsohn; 1994
19. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
20. Yudofsky SC, Silver JM, Jackson W, et al. The Overt Aggression Scale for the objective rating of verbal and physical aggression. Am J Psychiatry 1986;143:35–39
21. Plutchik R, van Praag HM. The measurement of suicidality, aggressivity and impulsivity. Prog Neuropsychopharmacol Biol Psychiatry 1989; 13:23–34
22. Shiloh R, Nutt D, Weizman A. Antipsychotic drugs: doses and $T_{1/2}$. In: Shiloh R, Nutt D, Weizman A, eds. Essentials in Clinical Psychiatric Pharmacotherapy. London, England: Martin Dunitz; 2001:62
23. Ananth J, Burgoyne KS, Gadasalli R, et al. How do the atypical antipsychotics work? J Psychiatry Neurosci 2001;26:385–394
24. Raine A, Meloy JR, Bihrle S, et al. Reduced prefrontal and increased subcortical brain functioning assessed using positron emission tomography in predatory and affective murderers. Behav Sci Law 1998; 16:319–332
25. Becbara A. Neurobiology of decision-making: risk and reward. Semin Clin Neuropsychiatry 2001;6:205–216
26. Bergvall AH, Wessely H, Forsman A, et al. A deficit in attentional set-shifting of violent offenders. Psychol Med 2001;31:1095–1105
27. New AS, Gelernter J, Goodman M, et al. Suicide, impulsive aggression, and HTR1B genotype. Biol Psychiatry 2001;50:62–65
28. Weiss D, Coccaro EF. Neuroendocrine challenge studies of suicidal behavior. Psychiatr Clin North Am 1997;20:563–579
29. Coccaro EF, Berman ME, Kavoussi RJ, et al. Relationship of prolactin response to d-fenfluramine to behavioral and questionnaire assessments of aggression in personality disordered men. Biol Psychiatry 1996;40: 157–164
30. Evenden J. Impulsivity: a discussion of clinical and experimental findings. J Psychopharmacol 1999;13:180–192
31. Kahn RS, Davidson M, Siever L, et al. Serotonin function and treatment response to clozapine in schizophrenic patients. Am J Psychiatry 1993; 150:1337–1342
32. Yamamoto BK, Pehek EA, Meltzer HY. Brain region effect of clozapine on amino acid and monoamine transmission. J Clin Psychiatry 1994; 55(suppl B):8–14
33. Verkes RJ, Kerkhof GA, Beld E, et al. Suicidality, circadian activity rhythms and platelet serotonergic measures in patients with recurrent suicidal behavior. Acta Psychiatr Scand 1996;93:27–34
34. Sernyak MJ, Desai R, Stolar M, et al. Impact of clozapine on completed suicide. Am J Psychiatry 2001;158:931–937
35. Volavka J, Citrome L. Atypical antipsychotics in the treatment of persistently aggressive psychotic patients: methodological concerns. Schizophr Res 1999;35:S23–S33
36. Frenkle WG, Shera D, Berger-Hershkowitz H, et al. Clozapine-associated reduction in arrest rates of psychotic patients with criminal histories. Am J Psychiatry 2001;158:270–274
37. Spivak B, Segal M, Laufer N, et al. Lifetime psychiatric comorbidity rate in Israeli non-help-seeking patients with combat-related post-traumatic stress disorder. J Affect Disord 2000;57:185–188
38. Moeller FG, Barratt ES, Dougherty DM, et al. Psychiatric aspects of impulsivity. Am J Psychiatry 2001;158:1783–1793

