

The Effects of Clozapine on Aggression and Substance Abuse in Schizophrenic Patients

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Aggressive behavior in schizophrenic patients, although infrequent, is a serious problem. It is, however, a relatively common reason for psychiatric admission and poses an increasing threat as more patients are cared for in the community. There is a strong association between substance abuse and violent behavior, and comorbid substance abuse in schizophrenia is also a major problem. The recent introduction of the atypical antipsychotics has brought hope for the pharmacologic management of this group of patients. These newer agents are thought to have antiaggressive effects and perhaps decrease cravings for illicit substances and alcohol. Data from a number of studies have demonstrated that clozapine has antiaggressive effects. A retrospective analysis of 331 schizophrenic patients assessed the effects of clozapine on hostility and aggression. At baseline, 31.4% of patients showed overt physical aggression, and after an average of 47 weeks of treatment with clozapine, this rate had fallen to 1.1%. The antiaggressive effects of clozapine were relatively specific and could not be explained by sedation or general antipsychotic effects. These effects were more pronounced than the effects on other symptoms and were also present in those patients who showed the highest pretreatment levels of hostility and aggression. Clozapine may also be of benefit in the treatment of schizophrenic patients with comorbid substance abuse. After 6 months of treatment with clozapine, substance abusers and nonabusers with schizophrenia or schizoaffective disorder showed similar improvements on measures of psychopathology and psychosocial functioning.

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The image of the aggressive schizophrenic patient is a common perception in the public's mind; however, violent behavior occurs in only a small minority of these patients.¹ When it occurs, violence in patients with schizophrenia may have serious implications for patients and their caregivers. The association between aggressive behavior and schizophrenia is also of increasing importance, as more patients are cared for in the community.

Aggressive behavior is a frequent reason for psychiatric admission. Post hoc analyses of the data obtained in the Epidemiologic Catchment Area (ECA) study examined the relationship between psychiatric disorders and violent behavior in the community over a period of 1 year.^{2,3} Schizophrenia and major affective disorder increased the percentage of respondents reporting violent behavior (Table 1). Substance abuse very significantly elevated the probability of violent behavior. Moreover, the greater the

number of psychiatric diagnoses, the more likely it was that the person would report violence.

As highlighted in the ECA study,^{2,3} there is a strong association between substance abuse and violent behavior. Data from the U.S. Department of Justice (1992) revealed a high proportion of positive urine tests for illicit substances following arrests for assault (59%), homicide (48%), robbery (65%), and sex offenses (37%).⁴ Statistics for 1996 confirm an association between use of marijuana, cocaine, and opiates in men arrested for any reason.⁵ Comorbid substance abuse in schizophrenia is also a major problem. Schizophrenic patients are approximately 5 times more likely to have any substance use or dependence than the rest of the population (Table 2).⁶ Thus, schizophrenia alone elevates the risk for violent behavior, and the risk is elevated many times over if there is comorbid substance abuse.

The pharmacologic management of this group of patients is a challenge. Typical antipsychotics, anticonvulsants, benzodiazepines, and β -blockers have been used with varying results. Until recently, it was assumed that if there was no reduction in violent behavior following administration of a typical antipsychotic, the patient was receiving an inadequate dose of medication. Thus, in a recent study of 155 newly admitted patients with schizophrenia, the greater the Positive and Negative Symptom Scale (PANSS) paranoid/belligerence cluster score, the

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Table 1. Percentage of Respondents Reporting Violent Behavior in the Past Year^a

Diagnostic Group	Men		Women	
	Patients, N	% Violent	Patients, N	% Violent
No disorder	3728	2.74	4143	1.11
Anxiety disorder	484	8.87	960	3.25
Major affective disorder	100	13.87	221	9.39
Major affective disorder or schizophrenia	142	11.30	266	10.03
Alcohol or drug disorder	591	21.08	15	21.7

^aAdapted from reference 2, with permission.

Table 2. Substance Use Disorder in Schizophrenic Patients^a

Comorbid Disorder	Schizophrenia		
	%	SE	Odds Ratio
Any substance abuse or dependence	47.0 ^b	4.0	4.6
Any alcohol diagnosis	33.7 ^b	4.4	3.3
Any alcohol dependence	24.0 ^b	3.7	3.8
Alcohol abuse only	9.7	2.7	1.9
Any other drug diagnosis	27.5 ^b	3.2	6.2
Any other drug dependence	12.9 ^b	2.6	4.2
Other drug abuse only	14.6 ^b	3.0	6.9

^aData from reference 6.

^bp < .001 (prevalence in schizophrenic vs nonschizophrenic patients).

greater the dose of neuroleptic.⁷ However, increasing the dose to control aggressive behavior may be counterproductive since it can induce akathisia and extrapyramidal side effects. These side effects increase both the degree and extent of agitation and aggression.

The new atypical antipsychotics are thought to have antiaggressive effects and decrease substance abuse in schizophrenic patients. In particular, clozapine is associated with a low incidence of extrapyramidal symptoms. Data from a number of studies with these newer agents will be highlighted in this article.

EFFECTS OF CLOZAPINE ON VIOLENT BEHAVIOR

Several open, uncontrolled studies have demonstrated the antiaggressive effects of clozapine (Table 3).⁸⁻¹⁸ The number of violent episodes in 100 patients in a state psychiatric hospital decreased over the first 6 months of clozapine treatment and remained fairly constant over the next 12 months.⁹ Similarly, in 139 schizophrenic patients, 12 weeks of treatment was associated with a significant reduction of seclusion.¹⁵ Rabinowitz and coworkers have demonstrated that the number of verbally and physically aggressive incidents significantly decreased after clozapine treatment in 47 schizophrenic patients.¹⁸ Of particular note is the rapid effect of clozapine on aggression in these studies, with a beneficial effect occurring within the first 6 months of treatment and in some cases within the first few weeks.

Table 3. The Antiaggressive Effects of Clozapine in Open, Uncontrolled Studies^a

Reference	Patients, N	Diagnosis	Daily Dose (mg) ^b	Specific Antiaggressive Effect ^c
Wilson ⁸ ; Wilson and Claussen ⁹	100	Mixed	463	NA
Maier ¹⁰	25	Schizophrenia or schizoaffective disorder	450	NA
Volavka et al ¹¹	331	Schizophrenia	383-520	Yes
Michals et al ¹²	9	Brain injured	400	NA
Ratey et al ¹³	5	Mixed	NA	Yes
Ebrahim et al ¹⁴	27	Schizophrenia	558	NA
Chiles et al ¹⁵	139	Schizophrenia or schizoaffective disorder	350	Yes
Buckley et al ¹⁶	11	Schizophrenia	NA	Yes
Dennis et al ¹⁷	89	Schizophrenia	NA	NA
Rabinowitz et al ¹⁸	47	Schizophrenia	350	Yes

^aAbbreviation: NA = not available.

^bAverage or typical daily dose.

^cSpecific antiaggressive effect in the sense that it is, at least in part, independent of the general antipsychotic effect.

To further assess the effects of clozapine on hostility and aggression in schizophrenia, we conducted a retrospective analysis of the database maintained by the New York Office of Mental Health (OMH).¹¹ The OMH developed this database to assess the safety and efficacy of clozapine; a total of 21 hospitals participated.

The inclusion criteria were inpatient status, DSM-III-R diagnosis of schizophrenia, treatment resistance defined as a history of failed treatment with at least 3 neuroleptics in at least 2 chemical classes in doses of at least 1000 mg/day of chlorpromazine (or equivalent), and no good functioning in the past 5 years. The cohort consisted of 331 schizophrenic patients with an average age of 35.7 years and a current mean duration of hospitalization of 1930 days.

Patients were assessed using the Brief Psychiatry Rating Scale (BPRS; 18 items, 1-7 scoring), which was completed by psychiatrists who received minimal training on its administration. To improve reliability of the BPRS ratings, the OMH distributed detailed instructions.¹⁹ The BPRS was administered at baseline, 6 weeks, 12 weeks, and at the study endpoint (average = 47 weeks).

One of the BPRS items is hostility, which is defined as animosity, contempt, belligerence, and disdain for other people outside the interview situation. Severity of hostility is defined using 7 anchor points. A severity score of 1 to 5 indicates that the patient did not express overt physical aggression (low hostility). Severity scores of 6 and 7 indicate a patient who exhibited overt physical aggression (high hostility).

At baseline, 31.4% of patients showed overt physical aggression, and after an average of 47 weeks of treatment with clozapine this rate had fallen to 1.1% (Table 4). In

Table 4. Number of Patients With High and Low Levels of BPRS Hostility After Receiving Treatment With Clozapine^a

Hostility	Baseline		6 Weeks		12 Weeks		Endpoint	
	N	%	N	%	N	%	N	%
High ^b	70	31.4	15	6.7	6	3.1	2	1.1
Low ^c	153	68.6	208	93.3	185	96.9	181	98.9

^aAdapted from reference 11, with permission. Abbreviation: BPRS = Brief Psychiatric Rating Scale.

^bBPRS score 6–7 (patient acted on anger).

^cBPRS score 1–5 (hostility absent or limited to feelings of anger).

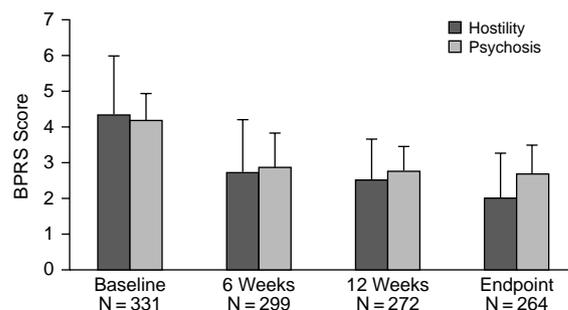
addition, the effect of clozapine on the psychosis factor, defined as the sum of 4 BPRS items, namely conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content, was compared with the effect on hostility. An improvement of both items by the study endpoint was evident, with a greater improvement in hostility (Figure 1).

A selective clozapine effect on hostility was defined as the change of hostility that was not associated with change of psychosis factor score. To test selectivity, 3 separate analyses of covariance (ANCOVAs) for repeated measures (6 weeks, 12 weeks, and endpoint) were performed. Each of the ANCOVAs demonstrated a highly significant change in hostility over time (time effect), therefore supporting the selective effect of clozapine on hostility. This effect was more pronounced than the effects of other symptoms, as a significant improvement ($p < .001$) of hostility occurred after the improvement of psychosis was accounted for at each timepoint. The effect was also present in those patients who showed the highest pretreatment levels of hostility and aggression.

SPECIFIC ANTIAGGRESSIVE EFFECT OF CLOZAPINE

It has been suggested that the antiaggressive effects of clozapine may be specific in that they are not mediated by sedation and are relatively independent of its general antipsychotic effect. This latter type of specificity may be defined as the reduction of aggressive or hostile behavior that is statistically independent of the reduction in psychosis. Data from a number of open, uncontrolled studies have indicated that the antiaggressive effects of clozapine are relatively specific and cannot be explained by sedation or general antipsychotic effects.^{11,13,15,16,18} However, data from controlled studies are not yet available.

A number of methodological, logistical, and ethical problems need to be considered when designing and implementing such studies. Problems encountered include patient selection bias (particularly consent bias), need for a long baseline period with an adequate number of aggressive events, assessment of antiaggressive effect, and evaluation of confounding variables such as the use of concomitant medication and environmental effects. We

Figure 1. Change in Hostility and Psychosis Factors Following Clozapine Treatment^a

^aData from reference 11.

are currently conducting a pharmacoepidemiologic study of the effect of the introduction of clozapine on violent criminal behavior in Finland. Finland is particularly suited for this study since it has a nationwide register of arrests and convictions, and large cohorts of clozapine-treated and control patients can be tracked longitudinally.

EFFECTS OF CLOZAPINE ON COMORBID SUBSTANCE ABUSE

In addition to the increased risk of violent behavior, there are a number of clinical implications of comorbid substance abuse in patients with schizophrenia. Comorbidity is associated with poor treatment response²⁰ and perhaps poor compliance. It is therefore important that the antipsychotic effectiveness of clozapine is not affected by comorbid substance use disorders.²¹

Anecdotal reports suggest that clozapine treatment may reduce the severity of substance use in psychiatric patients.^{22–24} Although schizophrenic patients with comorbid substance use disorders generally have a poorer prognosis, it has been demonstrated that clozapine actually may be of benefit in this group of patients. After 6 months of treatment, substance abusers and nonabusers with schizophrenia or schizoaffective disorder showed similar improvements on measures of psychopathology and psychosocial functioning.²⁵

CONCLUSION

Aggressive behavior in schizophrenic patients, although infrequent, is a serious problem. The introduction of the atypical antipsychotics has facilitated the pharmacologic management of these patients. Results from a number of studies suggest that clozapine may have a selective antiaggressive effect. Comorbid substance abuse in schizophrenic patients can have an impact on the effectiveness of the antipsychotic. Data from a small number of studies suggest that clozapine may also be of benefit in

these patients. A reduction in aggressive behavior and craving for illicit drugs or alcohol will improve the quality of life of schizophrenic patients, allowing them to live in the community and reducing the burden on health care systems.

Drug name: clozapine (Clozaril, Leponex).

REFERENCES

1. Volavka J. *Neurobiology of Violence*. Washington, DC: American Psychiatric Press; 1995
2. Swanson JW, Holzer CE, Ganju VK, et al. Violence and psychiatric disorder in the community: evidence from the Epidemiologic Catchment Area surveys. *Hosp Community Psychiatry* 1990;41:761-770
3. Swanson JW. Mental disorder, substance abuse, and community violence: an epidemiological approach. In: Monahan J, Steadman HJ, eds. *Violence and Mental Disorder Developments in Risk Assessment*. Chicago, Ill: The University of Chicago Press; 1994:101-136
4. Maguire K, Pastore AL, Flanagan TJ, eds. *Sourcebook of Criminal Justice Statistics 1992*. Washington, DC: US Dept of Justice, Bureau of Justice Statistics; 1993
5. *Sourcebook of Criminal Justice Statistics Online*. Washington, DC: US Dept of Justice, Bureau of Justice Statistics; 1997
6. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) Study. *JAMA* 1990;264:2511-2518
7. Troisi A, Pasini A, DeAngelis F, et al. Paranoid/belligerence and neuroleptic dosage in newly admitted schizophrenic patients. *J Clin Psychopharmacol* 1997;17:84-87
8. Wilson WH. Clinical review of clozapine treatment in a state hospital. *Hosp Community Psychiatry* 1992;43:700-703
9. Wilson WH, Claussen AM. 18-Month outcome of clozapine treatment for 100 patients in a state psychiatric hospital. *Psychiatr Serv* 1995;46:386-389
10. Maier GJ. The impact of clozapine on 25 forensic patients. *Bull Am Acad Psychiatry Law* 1992;20:297-307
11. Volavka J, Zito JM, Vitrai J, et al. Clozapine effects on hostility and aggression in schizophrenia [letter]. *J Clin Psychopharmacol* 1993;13:287-289
12. Michals ML, Crismon ML, Roberts S, et al. Clozapine response and adverse effects in nine brain-injured patients. *J Clin Psychopharmacol* 1993;13:198-203
13. Ratey JJ, Leveroni C, Kilmer D, et al. The effects of clozapine on severely aggressive psychiatric inpatients in a state hospital. *J Clin Psychiatry* 1993;54:219-223
14. Ebrahim GM, Gibler B, Gacono CB, et al. Patient response to clozapine in a forensic psychiatric hospital. *Hosp Community Psychiatry* 1994;45:271-273
15. Chiles JA, Davidson P, McBride D. Effects of clozapine on use of seclusion and restraint at a state hospital. *Hosp Community Psychiatry* 1994;45:269-271
16. Buckley PF, Kausch O, Gardner G. Clozapine treatment of schizophrenia: implications for forensic psychiatry. *J Clin Forensic Med* 1995;2:9-16
17. Dennis JL, McBride D, Peterson PD, et al. Clozapine therapy in a state hospital: patient care and policy implications. *Adm Policy Ment Health* 1996;24:39-52
18. Rabinowitz J, Avnon M, Rosenberg V. Effect of clozapine on physical and verbal aggression. *Schizophr Res* 1996;22:249-255
19. Woerner MG, Mannuzza S, Kane JM. Anchoring the BPRS: an aid to improved reliability. *Psychopharmacol Bull* 1988;24:112-117
20. Bowers MB Jr, Mazure CM, Nelson JC, et al. Psychotogenic drug use and neuroleptic response. *Schizophr Bull* 1990;16:81-85
21. Buckley PF. Substance abuse in schizophrenia: a review. *J Clin Psychiatry* 1998;59(suppl 3):26-30
22. Albanese MJ, Khantzian EJ, Murphy SL, et al. Decreased substance use in chronically psychotic patients treated with clozapine [letter]. *Am J Psychiatry* 1994;151:780-781
23. Yovell Y, Opler LA. Clozapine reverses cocaine craving in a treatment-resistant mentally ill chemical abuser: a case report and a hypothesis. *J Nerv Ment Dis* 1994;182:591-592
24. Marcus P, Snyder R. Reduction of comorbid substance abuse with clozapine [letter]. *Am J Psychiatry* 1995;152:959
25. Buckley P, Thompson P, Way L, et al. Substance abuse among patients with treatment-resistant schizophrenia: characteristics and implications for clozapine therapy. *Am J Psychiatry* 1994;151:385-389