

# Violence and Schizophrenia: Clozapine as a Specific Antiaggressive Agent

Peter Buckley, MD, James Bartell, MA, Karl Donenwirth, MA, Shin Lee, MD, Frank Torigoe, MA, and S. Charles Schulz, MD

**Pharmacological management of persistent aggression in patients with schizophrenia is a difficult clinical dilemma. Clozapine has been shown to be an effective agent in this regard. This study sought to compare the symptomatic response on the Brief Psychiatric Rating Scale (BPRS) between hostile schizophrenic patients and patients without aggression. While dramatic improvements were evident in aggression, both groups were indistinguishable with respect to BPRS response. These results suggest that clozapine may have a selective antiaggressive effect.**

Despite continued education and advocacy, public opinion remains focused on the notion that there is a close and overwhelming relationship between violence and serious mental illness.<sup>1,2</sup> In contrast, accruing scientific literature attests to the low level of violent behavior among the mentally ill in general and supports the proposition that violence is observed among only a small subgroup of patients.<sup>3</sup> This pattern also holds true for schizo-

phrenia, wherein aggression is seen among only 3 to 10 percent of patients and is, for the most part, usually of low lethality.<sup>3,5</sup> Violence is a broad term and definitions vary greatly, encompassing homicidal behavior to minor physical assault. For patients with schizophrenia, aggressive behavior is most often defined and thought of as physical assault (of other patients or staff) or damage to property.<sup>4</sup> Violence tends to occur during periods of exacerbation of symptoms and may be precipitated by persistent, distressing delusions or command hallucinations.<sup>4,5</sup>

Although in the minority, violent schizophrenic patients who are notoriously difficult to treat, are more likely to have neuroleptic-refractory illness and, largely because of their behavioral disturbances, tend to reside long-term in foren-

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Dr. Buckley is Medical Director, Northcoast Behavioral Healthcare System, and is affiliated with the Department of Psychiatry, Case Western Reserve University, Cleveland, OH; J. Bartell, K. Donenwirth, Dr. Lee, and F. Torigoe are also affiliated with Northcoast Behavioral Healthcare System; and Dr. Schulz is also affiliated with the Department of Psychiatry, Case Western Reserve University. This paper was presented at the 33rd annual meeting of the American College of Neuropharmacology, December 1994, San Juan, Puerto Rico. Address correspondence to: Peter Buckley, MD, Northcoast Behavioral Healthcare System, 1756 Sagamore Road, Northfield, OH 44167.

sic and state facilities. The use of high-dose neuroleptic therapy has proved ineffective and may even exacerbate aggression as a consequence of akathisia.<sup>6</sup> Alternative pharmacologic approaches include augmentation with lithium or carbamazepine, use of beta-blockers or benzodiazepine treatments.<sup>7</sup> Early carbamazepine studies as an adjunct to neuroleptics are most frequently reported, but are difficult to interpret because of pharmacokinetic interactions.<sup>8</sup> Although individual patients may benefit and show a quiescence of disturbed behavior, studies to date have been largely inconclusive and inconsistent; specifically, no single agent can be recommended as a primary treatment for aggression in schizophrenic patients.

Clozapine has now emerged as the primary pharmacologic treatment for severe, "neuroleptic-refractory" forms of schizophrenia. The U.S. multicenter study demonstrated superior efficacy of clozapine over chlorpromazine<sup>9</sup>: 30 percent of neuroleptic-refractory patients who received clozapine for six weeks showed substantial improvement (in both positive and negative symptoms) in contrast with just 4 percent of the chlorpromazine-treated group. The introduction of clozapine therapy into state hospitals and institutional settings has met with dramatic (and heretofore generally unexpected) reductions in aggressive behavior.<sup>10-15</sup> In a recent study of data derived from New York's state hospitals, Volavka and colleagues<sup>12</sup> were able to evaluate the relative effect of clozapine on aggression and on psychosis by comparing response on the hostility subscale with respect to the global rating

of psychosis on the Brief Psychiatric Rating Scale (BPRS). Their results suggested a selective amelioration of aggression by clozapine that was in excess of the global improvement on the BPRS. An alternative, complementary approach that explores the role of clozapine in aggressive or violent behavior is to compare the symptomatic response to clozapine of schizophrenic patients with and without aggressive behavior.

### Method

Thirty patients, 23 male and 7 female, who satisfied DSM-III-R criteria for schizophrenia were included in this study. All were selected for clozapine therapy at Western Reserve Psychiatric Hospital, a 300-bed state (Ohio) facility, on the basis of evidence of persistent psychosis, a prior history of failure to respond to three (or more) adequate trials of neuroleptics, and the absence of medical contraindications to treatment. Their mean age ( $\pm$ SD) was 41 ( $\pm$ 8) years and they had been hospitalized currently for 11 ( $\pm$ 7) years.

Data on the use of seclusion and restraint (S&R) were routinely completed jointly by physicians and nurses and were collated by the hospital's information and risk management services. Patients were classified into either violent or nonviolent groups on the basis of having spent at least 10 hours in S&R during the six months preceding clozapine therapy. The effect of clozapine on aggression was then assessed by comparing S&R data for the six months prior to and during treatment with clozapine. Symptoms were assessed by psychologists of master's level (or above) who administered to patients

## Management of Violence in Schizophrenic Patients

the 18-item version of the BPRS<sup>16</sup> at baseline and again after four months of clozapine therapy.

We used *t* test statistical procedures for comparisons between violent and nonviolent groups with respect to clinical and BPRS data. However, nonparametric statistics (Kruskal-Wallis test) were applied for analysis of S&R data that did not show a normal distribution.

### Results

Eleven patients, eight male and three female, recorded a mean of 100 hours (range 14–401) of S&R in the six months preceding clozapine therapy. By contrast, just over one hour (range 0–9) of S&R was recorded for the nonviolent group during the same period. In a pre-post comparison, the violent group showed a significant reduction in aggressive behavior during the first six months of clozapine therapy, as evidenced by less episodes of S&R (mean  $\pm$  SEM:  $6.4 \pm 2.6$  versus  $15.0 \pm 3.8$ ;  $\chi^2 = 4.8$ ,  $df = 1.0$ ,  $p < .03$ ) and less hours in S&R ( $37.9 \pm 15.8$  versus  $100.4 \pm 33.9$ ;  $\chi^2 = 3.8$ ,  $df = 1.0$ ,  $p = .052$ ). Although there was an evident overall reduction in aggression over the period of observation, there was variability in the extent of S&R among this small sample. For example, one patient registered 320 hours S&R pre-clozapine and 33 hours after clozapine therapy, while other patients showed less prominent reductions (e.g., 85 hours pre-clozapine to 29 hours post-clozapine); one patient did not improve during clozapine therapy.

Violent and nonviolent groups were indistinguishable with respect to age, gender,

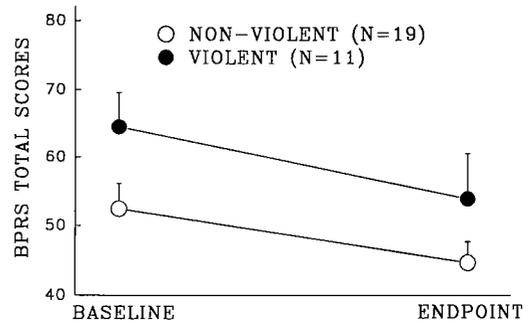


Figure 1. Response to clozapine in nonviolent and violent schizophrenic patients. Data represent mean values  $\pm$  SEM.

and length of stay. The violent patients were on a higher dose of clozapine than the nonviolent patients at endpoint evaluation ( $636 \pm 84$  versus  $526 \pm 94$ ,  $t = 3.1$ ,  $df = 28$ ,  $p < .004$ ). Comparison of BPRS total scores between violent and nonviolent groups (Fig. 1) revealed a higher baseline score in the violent patients ( $64.5 \pm 5.1$  versus  $52.4 \pm 3.7$ ,  $t = 1.9$ ,  $df = 28$ ,  $p = .07$ ); endpoint BPRS scores were similar ( $53.8 \pm 6.6$  versus  $44.6 \pm 3.0$ ,  $p = .4$ ) between both groups. Repeated measures analysis of variance did not show any time by group interaction over the course of clozapine therapy.

### Discussion

The results of the present study are consonant with earlier reports that highlight the efficacy of clozapine in the treatment of aggressive behavior in schizophrenic patients.<sup>10–15, 17</sup> Wilson,<sup>11</sup> in a six-month review of clozapine therapy in a state hospital, noted a significant reduction in aggression among 37 patients receiving clozapine. Although only three patients were discharged from the hospital, improvements in social functioning

such as increased privileges and better grooming were also noted. Similar findings were observed in other studies.<sup>17</sup> Ebrahim and colleagues<sup>15</sup> noted that 76 percent of their patients achieved a reduction in BPRS scores of 15 percent or greater; time in seclusion and restraint also decreased from a pre-clozapine level of 12.4 days to 0 days during six months of clozapine therapy. The improvement in seclusion and restraint in the present study is less impressive, both qualitatively and in statistical terms, and 1 of the 11 patients did not show an amelioration of aggression with clozapine treatment; another patient originally assigned to the nonviolent group (only eight hours of S&R in the previous six months on conventional antipsychotics) actually deteriorated in behavior, and clozapine was subsequently discontinued in favor of risperidone. Nevertheless, our results and the broad thrust of the available literature attest to clozapine's efficacy in ameliorating aggressive behavior in schizophrenic patients.<sup>17</sup> This effect may occur either as a consequence of a global improvement in psychosis, or through a specific antiaggressive effect (potentially related to clozapine's serotonergic antagonism), or some combination thereof. Violent patients here showed a response to clozapine that was comparable to (but no better than) that observed in the nonviolent patients, suggesting that the antiaggressive effect was not primarily linked to a preferential and superior antipsychotic effect in those aggressive patients. Moreover, the magnitude of the reduction in aggression in some (but not all) patients was well in excess of the modest improvement in BPRS symptomatology. This is consistent with the aggregated re-

sults of clozapine therapy in New York's state hospitals.<sup>12</sup> Patients in that study showed a global improvement in psychosis, as determined by serial BPRS evaluations, but there was also a selective and more prominent reduction in the hostility subscale of the BPRS.

It is postulated that clozapine's clinical potency may reside in its serotonergic antagonism.<sup>9, 17</sup> This may be relevant to the pathophysiology of aggression, which is characterized by a reduction in central serotonergic function.<sup>17, 18</sup> This is implied from observations of low cerebrospinal fluid levels of 5-hydroxyindoleacetic acid in violent offenders as well as the blunting of the prolactin response to fenfluramine (a 5HT<sub>2</sub> partial agonist) in sociopathic personalities.<sup>19-21</sup> It is unclear, however, how such a serotonergic explanation may be cogently articulated in the face of apparently irreconcilable findings of reduced serotonergic function in aggression and, paradoxically, clozapine's potent serotonergic antagonism. Moreover, fluoxetine, a serotonin re-uptake inhibitor, has been shown to reduce violent, self-injurious behavior.<sup>22</sup> One possible interpretation is that clozapine's effect on the serotonergic system is complex, with more recent research indicating selective binding 5HT<sub>6</sub> and 5HT<sub>7</sub> receptor subtypes.<sup>23</sup> Interestingly, a preliminary report on clozapine for intractable, borderline personality disorder also demonstrated a reduction in aggressive, self-injurious behavior,<sup>24</sup> suggesting that clozapine possesses a specific antiaggressive effect that is seen in its use in treating disorders other than schizophrenia.

Schizophrenic patients with aggression are difficult to treat and, despite enthusi-

## Management of Violence in Schizophrenic Patients

astic claims to the contrary, have largely shown inconsistent responses to putative antiaggressive pharmacologic agents. Although such patients do not appear to have a preferential antipsychotic response to clozapine, the reduction in aggression in most patients is of such magnitude and clinical significance as to endorse the use of clozapine in this population.

### References

1. Editorial: Violence and mental illness. *Hosp Community Psychiatry* 45:786-7, 1994
2. Torrey EF: Evaluation of the relationship between violence and serious mental illness. *Hosp Community Psychiatry* 45:842-8, 1994
3. Tardiff H: The current state of psychiatry in the treatment of violent patients. *Arch Gen Psychiatry* 49:493-9, 1992
4. Buckley PF, Walshe D, Colohan H, *et al*: Violence and schizophrenia: a study of the occurrence and clinical correlates of violence among schizophrenia patients. *Ir J Psychol Medicine* 7:102-8, 1990
5. Taylor PJ: Schizophrenia and crime: distinctive patterns in association, in *Crime and Mental Disorder*. Edited by Hodgins S. Newbury Park, CA: Sage Publications, 1993
6. Barnes TRE, Hirsch SR: The use of high dose neuroleptics. *Br J Psychiatry* 164:81-6, 1994
7. Corrigan PW, Yudofsky SC, Silver JM: Pharmacological and behavioral treatments for aggressive psychiatric inpatients. *Hosp Community Psychiatry* 44:125-33, 1993
8. Schulz SC, Kahn EM, Baker EM, *et al*: Lithium and carbamazepine augmentation in treatment-refractory schizophrenia, in *The Neuroleptic Non-Responsive Patient: Characterization and Treatment*. Edited by Angrist B, Schulz SC. Washington, DC: American Psychiatric Press, 1990, pp 11-136
9. Kane J, Honigfeld G, Singer J, *et al*: Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 45:789-96, 1988
10. Maier GJ: The impact of clozapine on 25 forensic patients. *Bull Am Acad Psychiatry Law* 20:247-307, 1992
11. Wilson WH: Clinical review of clozapine treatment in state hospital. *Hosp Injurious Psychiatry* 43:700-3, 1992
12. Volavka J, Zito J, Vitra J, Czobor P: Clozapine effects on hostility and aggression in schizophrenia. *J Clin Psychopharmacol* 13:287-89, 1993
13. Ratey JN, Leveron C, Kilmer D, *et al*: The effects of clozapine on severely aggressive psychiatric inpatients in a state hospital. *J Clin Psychiatry* 54:219-23, 1993
14. Chiles J, Davidson P, McBride D: Effects of clozapine on use of seclusion and restraint of a state hospital. *Hosp Injurious Psychiatry* 45:269-71, 1994
15. Ebrahim G, Gibler B, Gacano CB, Hayes G: Patient response to clozapine in a forensic psychiatric hospital. *Hosp Community Psychiatry* 45:271-3, 1994
16. Overall JE, Gorham DR: The Brief Psychiatric Rating Scale. *Psychol Rep* 10:799-812, 1962
17. Buckley PF, Kausch O, Gardener G: Clozapine treatment of schizophrenia: implication for forensic psychiatry. *Clin Forensic Med*, in press, 1995
18. Eichelman B: Aggressive behavior: from the laboratory to clinic. *Arch Gen Psychiatry* 49:488-92, 1992
19. Linnoila VMI, Virkkunen M: Aggression, suicidality, and serotonin. *J Clin Psychiatry (suppl 10)* 53:46-51, 1992
20. Brown GL, Goodwin FK, Ballenger JC, *et al*: Aggression in humans correlates with cerebrospinal fluid amine metabolites. *Psychiatry Res* 1:131-9, 1979
21. O'Keane V, Moloney E, O'Neill H, *et al*: Blunted prolactin responses to *d*-fenfluramine in sociopathy: evidence for subsensitivity of central serotonergic function. *Br J Psychiatry* 160:643-46, 1992
22. Markowitz P, Calabrese J, Schulz SC, *et al*: Fluoxetine in the treatment of borderline and schizotypal personality disorders. *Am J Psychiatry* 148:1064-7, 1991
23. Roth BL, Craig SC, Choudhary MS, *et al*: Binding of typical and atypical antipsychotic agents to 5-hydroxytryptamine-6 and 5-hydroxytryptamine-7 receptors. *J Pharmacol Exp Ther* 268:1403-10, 1994
24. Frankenburg FR, Zanarini MC: Clozapine treatment of borderline patients: a preliminary study. *Compr Psychiatry* 34:402-5, 1993