Clozapine Treatment in a Population of Adults With Mental Retardation

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Background: There is a paucity of data on the use of clozapine in patients with mental retardation and comorbid psychiatric illness. The authors describe their recent clinical experience using clozapine in treatment-refractory patients with mental retardation and severe psychiatric illness.

Method: A retrospective review was performed on the records of all patients admitted to a university-affiliated, specialized inpatient psychiatry service who were selected for clozapine therapy from March 1994 through December 1997 (N = 33). Patients had DSM-IV diagnoses of schizophrenia, schizoaffective disorder, bipolar disorder, delusional disorder, or psychotic disorder NOS and were considered treatment resistant. All had deficits in functioning well beyond those expected for their degree of cognitive deficits and adaptive delays.

Results: Of 33 initial patients, 26 remained on clozapine therapy for a follow-up duration of 5 to 48 months (mean = 24.8 months). Evaluation at follow-up revealed Clinical Global Impressions-Improvement (CGI-I) scores from 1 to 4 with a mean ± SD improvement of 2.0 ± 0.8 (much improved). The mean ± SD rating of the CGI-Efficacy Index was 5 ± 2.6 (decided improvement and partial remission of symptoms with no interference from side effects). The 6 patients who were not maintained on clozapine therapy over the study period did not significantly differ from the clozapine group in gender, race, age, side effects, or diagnosis. One patient was lost to follow-up. Side effects were mild and transient with constipation being the most common (N = 10). There were no significant cardiovascular side effects and no seizures. No patients discontinued treatment due to agranulocytosis.

Conclusion: The current investigation lends support to the conclusion that clozapine appears to be safe, efficacious, and well tolerated in individuals with mental retardation and comorbid psychiatric illness.

(J Clin Psychiatry 2000;61:22–25)

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Clozapine is an atypical antipsychotic that has proven efficacy in the management of treatment-resistant schizophrenia. Patients who require antipsychotics but have tardive dyskinesia or who are otherwise intolerant of traditional neuroleptics benefit from treatment with clozapine. In addition, clozapine has been used successfully in the treatment of refractory mood disorders and schizoaffective disorders.[1–3] Finally, clozapine use has also been reported in individuals with neurologic disease or traumatic brain injury, primarily to treat symptoms of psychosis or agitated behavior.[4,5] Individuals with mental retardation can suffer from severe and persistent mental illnesses, including schizophrenia, schizoaffective disorder, and psychotic mood disorders.[6,7] In addition, traditional neuroleptics are used to target severe aggression, self-injurious behavior, and marked agitation in persons with mental retardation who do not meet the threshold for a specific DSM-IV diagnosis. Like their nonretarded peers, persons with mental retardation who are also mentally ill can present with treatment resistance, negative side effects of neuroleptics, and tardive dyskinesia.

Clinical experience with the use of clozapine in persons with mental retardation is limited. Serious side effects (including agranulocytosis), the need for weekly monitoring for the first 6 months, frequent blood draws, the paucity of published efficacy studies, and the expense of the drug and monitoring program have discouraged clinicians from using this agent in persons with mental retardation. Additionally, clinical research on the safety and efficacy of clozapine routinely uses mental retardation as an exclusion criterion. Nonetheless, in those studies published, clozapine has been found to be efficacious and well tolerated in individuals with mental retardation and comorbid psychiatric illness.[8–14]

Recently, Buzan et al.[15] published a comprehensive review of the existing literature and reported their own clinical experience with the use of clozapine in 10 adults with mental retardation. They concluded that clozapine was well tolerated and efficacious for the treatment of psychosis and mania and that it might improve aggression and self-injurious behavior, independent of psychiatric diagnosis.

Because clozapine appears to be an important pharmacologic tool in the treatment of serious psychiatric illness in the cognitively impaired, further prospective random-

ized clinical trials warrant consideration. In support of more systematic study of clozapine in the mentally retarded and to encourage clinicians to consider using clozapine in this patient population, the current study reports our clinical experience with the use of clozapine in 33 adults with mental retardation, all of whom also have serious psychiatric illnesses.

METHOD

This study reports the findings of a retrospective chart review on a group of treatment-resistant, psychiatrically ill (DSM-IV criteria) patients with mental retardation who received clozapine in a naturalistic manner from March 1994 through December 1997. Consent for a trial of clozapine was obtained after medication education regarding the risks and benefits of clozapine, including the risk of fatal agranulocytosis. Consent was obtained from the patients themselves and the patients' guardians, if applicable.

The study group consisted of 33 individuals who were a subset of patients admitted to a community-based, university-affiliated inpatient psychiatry service that specializes in the treatment of individuals with both mental retardation and mental illness. Patients are admitted to this unit when they require acute psychiatric care due to an exacerbation of their mental illness. Patients who were selected for clozapine therapy had diagnoses of schizophrenia, schizoaffective disorder, bipolar disorder, delusional disorder, or psychotic disorder NOS. Psychiatric diagnoses were made by consensus between outpatient and inpatient treating psychiatrists using DSM-IV criteria. A detailed review of each patient's medication history revealed that they had failed treatment with at least 3 traditional neuroleptics used either alone or in combination with mood stabilizers. To our knowledge, none had received previous trials with another atypical agent. All patients had deficits in functioning that went beyond those expected for their degree of cognitive deficits and adaptive delays. All of these patients had been chronically mentally ill for greater than 10 years, with lifetime hospitalization rates ranging from 1 to 30 years, with a mean of 10.9 years.

The original sample consisted of 17 men and 16 women with a mean ± SD age of 40.2 ± 9.7 years (range, 23–55 years; Table 1). The majority of the group were diagnosed with mild mental retardation: 19 (57.6%) mild, 13 (39.4%) moderate, and 1 (3.0%) severe. Twenty-two patients were African American and 11 were white. Nine (27.3%) were smokers. Pearson chi-square analysis revealed no significant interactions for diagnosis by cognition, age, or race.

Clozapine was titrated in a standard way, starting with 25 mg/day and increasing by 25 mg/day in divided doses until a total dose of 150 mg/day was reached. After administration of 150 mg/day for 4 days, the daily dose continued to be increased in a similar fashion until a total of 300 mg/day was achieved. Patients were maintained at 300 mg/day and assessed for clinical improvement. Most patients were taking other psychotropic medications prior to the initiation of clozapine. Benzodiazepines and antidepressants were tapered and stopped. Anticonvulsants were maintained, although valproic acid was substituted for carbamazepine. In most cases, traditional neuroleptics were maintained initially but then tapered and discontinued as clozapine was increased. Further dose increases were made in a naturalistic way, depending on clinical necessity. Final dosages of clozapine ranged from 75 to 600 mg/day, with a median dose of 400 mg/day. Two patients received relatively low doses (75 mg/day and 125 mg/day) as they had a markedly positive clinical response that did not require further dosage increases.

Table 1. Demographic and Clinical Characteristics of Study Population

DSM-IV Diagnosis	Cognitive Performance			Gender		Race	
	Mild	Moderate	Profound	M	F	White	African American
Schizophrenia	2	7	0	5	4	3	6
Schizoaffective disorder	11	4	1	10	6	7	9
Bipolar I disorder	3	1	0	0	4	0	4
Delusional disorder	2	0	0	1	1	0	2
Psychotic disorder NOS	1	1	0	1	1	1	1

RESULTS

Treatment Response

Upon admission and initiation of clozapine therapy, all patients were severely ill, with Global Assessment of Functioning (GAF) scores ranging from 10 to 30. The Clinical Global Impressions (CGI)-Severity of Illness scale scores ranged from 1 to 7, with a mean severity of 4.4. All patients showed enough clinical improvement with clozapine therapy to allow discharge into the community. The mean ± SD length of hospitalization was 39.9 ± 16.6 days. CGI-Improvement (CGI-I) at follow-up revealed scores from 1 to 4, with a mean ± SD improvement of 2.0 ± 0.8 (much improved). The mean ± SD score on the CGI-Efficacy Index (CGI-E) was 5 ± 2.6 (decided improvement and partial remission of symptoms with little or no interference from side effects). Patients were principally discharged on clozapine therapy alone (N = 20). The remainder of subjects (N = 13) were discharged taking clozapine and another agent: either clozapine plus valproic acid alone (N = 9), or clozapine and a tapering dose of either a traditional neuroleptic (N = 3) or a benzodiazepine (N = 1). This is in contrast to pretreatment conditions in which the original sample of 33 patients were taking 4 or more psychotropic medications, excluding those used to treat side effects.

Follow-up in the community showed a sustained clinical improvement. Twenty-six of 33 patients remained on clozapine therapy for a follow-up duration of up to 48 months (range, 5–48 months; mean = 24.8 months). CGI-I at time of follow-up for those who remained on clozapine therapy showed global improvements from 1 to 4, with a mean improvement of 2.2 (much improved). When the therapeutic effect of clozapine therapy was measured by the CGI-E, the mean rating was 5 (decided improvement and partial remission of symptoms with no interference from side effects). Rehospitalizations were reviewed. Eleven of the 26 patients who remained on clozapine therapy required one rehospitalization during the follow-up period, typically for adjustment of their clozapine dosage or addition of a mood stabilizer.

Side Effects

Side effects were mild and in no case required discontinuation of the initial medication trial. No patients had seizures while on clozapine therapy. There were no significant cardiovascular side effects or drop attacks. Constipation was the most common complaint occurring in 10 (30.3%) of 33 patients. One patient (3.0%) had tachycardia, 1 (3.0%) had hypotension, and 6 (18.1%) complained of sedation, which was early and transient. Hypersalivation was present in 4 individuals (12.1%) and incontinence was a problem for 5 (15.1%). All individuals receiving clozapine tolerated weekly venipuncture without protest or inconvenience. Significant weight gain was not observed during the course of the patients' hospitalizations.

Clozapine Discontinuation

No patients discontinued clozapine therapy secondary to agranulocytosis. Two patients had a good clinical response to the medication but could not be compliant with oral medications, and thus the medication was stopped. Clozapine was discontinued in 4 patients due to lack of significant clinical efficacy. One patient was lost to follow-up. The 6 patients who were not maintained on clozapine therapy over the study period did not differ in gender, race, age, side effects, or diagnosis from the larger study group.

DISCUSSION

The current study reports the results of a retrospective chart review of 33 patients with both mental retardation and serious psychiatric illness. These patients were treated in a specialized inpatient unit using clozapine in a naturalistic way. All patients had consensus diagnoses of schizophrenia, schizoaffective disorder, delusional disorder, bipolar disorder, or psychotic disorder NOS. Of the patients with diagnoses of psychosis NOS, one had an affective syndrome secondary to a traumatic brain injury, and the other had subsyndromal aggression and affective dysregulation best characterized as psychosis NOS.

In keeping with previous reports in the literature, clozapine was found to be well tolerated and clinically efficacious. Of 33 patients discharged on clozapine therapy alone or in combination with a mood stabilizer or other psychotropic medication, 26 remained on clozapine therapy for a mean follow-up period of 24.8 months. Six patients stopped taking clozapine secondary to noncompliance with oral administration or insufficient clinical response. One patient was lost to follow-up.

It is of significant interest that, in general, clozapine was well tolerated and accepted by both the patients and caregivers. Given the complexity of prescribing and monitoring clozapine, along with the potential serious side effects associated with the drug, providers have a strong incentive to discontinue clozapine unless significant improvement in behavior and mental status is observed and maintained. Concerns that are traditionally posited as barriers to use of this agent in persons with mental retardation were unfounded. In addition, these individuals showed significant improvement on all measures, despite the potential overshadowing of their clinical syndromes by their cognitive delays.

Several limitations of the current investigation warrant consideration. Because the use of clozapine was not blinded, there may have been interpretation bias. However, in all cases, the patients had a significant, chronic, treatment-refractory psychiatric illness in addition to cognitive impairment. Thus, the apparent meaningful improvement on measures of life functioning lends support to the interpretation that clozapine was effective.

An additional limitation was the lack of a placebo control or non-clozapine pharmacologic active treatment group. However, it is not unreasonable to conclude that clozapine was effective in contrast to traditional neuroleptics, as each of the patients had failed numerous trials of typical antipsychotics alone or in conjunction with mood stabilizers. Another weakness of the current study is the failure to record weight at the time of follow-up evaluation. It is well established in the extant literature that weight gain is a significant side effect of clozapine therapy. Nonetheless, the majority of studied subjects remained on clozapine therapy, suggesting that weight gain was not a significant barrier to treatment. Despite these limitations, it is proposed that the current results support further systematic research, including controlled trials, that compare clozapine with other atypical antipsychotics as a treatment for persons with mental retardation and psychiatric illness.

Drug names: carbamazepine (Tegretol and others), clozapine (Clozaril and others), valproic acid (Depakene).

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