

Clozapine for Refractory Schizophrenia: The Illinois Experience

Robert W. Buckman, Ph.D., and Randy D. Malan, R.Ph.

Based upon the Illinois Department of Mental Health and Developmental Disabilities' computerized clinical information system, with its integration of client-specific clinical data, a 5-year retrospective study was designed to determine the clinical effectiveness and economic impact of the use of clozapine for treatment-resistant schizophrenia. The study sample consisted of 518 hospitalized, treatment-resistant patients. At the end of 5 years, 78% were well maintained on clozapine. Two hundred forty-three patients had been discharged to the community, and 62 had been transferred for treatment of medical or surgical problems. Clozapine treatment was discontinued in 115 patients (22%). The drug was well tolerated, with a very low incidence of agranulocytosis. Cost savings resulting from the discharge of the 243 clozapine-treated patients amounts to approximately \$20 million per year. A disease management algorithm has been developed allowing physicians to begin clozapine treatment for patients not successfully treated with 2 prior antipsychotic agents. Adherence to this protocol throughout the state's mental health system would result in even greater savings.

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Based upon the Illinois Department of Mental Health and Developmental Disabilities' (IDMHDD) computerized clinical information system, with its integration of client-specific clinical data, a 5-year retrospective study was designed to determine the clinical effectiveness and economic impact of the use of clozapine for treatment-resistant schizophrenia. The 5-year (1990-1995) retrospective study focused in particular on the clinical effectiveness and economic impact of clozapine therapy for patients with drug-resistant schizophrenia. At that time, of the state's population of approximately 11.4 million people,¹ an estimated 97,000 to 229,000 had schizophrenia and schizoaffective disorders, for an overall incidence of 0.85% to 2%.^{2,3} During the 5 years of the study, the average cost to the state for each hospitalized schizophrenic patient was \$242.50 per day, or about \$88,000 per year (data on file, IDMHDD, 1995).

Clozapine is the only agent proven to be effective for treating schizophrenic patients who are resistant to typical

neuroleptic agents. Clozapine has been described as the most significant advance in pharmacologic therapy for schizophrenia since chlorpromazine.⁴ This atypical antipsychotic differs from earlier drugs in mechanism of action, chemical effects, and side effect profile. It is relatively free of extrapyramidal symptoms, appears not to cause tardive dyskinesia, and has little effect on prolactin levels. Moreover, clozapine works remarkably well for both the positive and the negative symptoms of schizophrenia. Since its introduction in the United States in 1989, it has become the gold standard for treating drug-resistant patients.

With clozapine came new hope for treating patients with refractory schizophrenia, however, it was more expensive than traditional antipsychotic agents. Therefore, the IDMHDD study investigated whether clozapine therapy for treatment-resistant schizophrenic patients led to overall cost savings as a result of decreased hospitalization and improved function in the community.

FIVE-YEAR CLOZAPINE EXPERIENCE

Between 1990 and 1995, we identified 951 treatment-resistant schizophrenic patients in our hospitalized patient population. Clozapine was approved for treating 647, but 129 were waiting for laboratory tests when the study began, leaving 518 clozapine-treated patients as the study sample. Brand-name Clozaril was used exclusively.

By the end of the 5-year study, the data revealed that 403 (78%) of the 518 patients were doing well on clozapine therapy, with their symptoms controlled. Of these 403

From the Clinical Pharmacology Advisory Committee, The Drug Formulary, Department of Public Aid, State of Illinois (Dr. Buckman), and Pharmacy Services, Disability and Behavioral Health Services, Illinois Department of Human Services, Springfield (Mr. Malan).

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Reprint requests to: Robert W. Buckman, Ph.D., 1325 Heatherton Drive, Naperville, IL 60563-2230 (e-mail: buckman@naper.com).

patients, 243 (60%) were successfully treated with clozapine and were discharged from the hospital and were back in the community; 62 (15%) were successfully treated and transferred because of surgical or medical problems and were in the process of being discharged; and 99 (25%) had improved substantially on clozapine therapy but remained hospitalized. A total of 115 patients (22%) had discontinued clozapine therapy for a variety of reasons.

In the majority of cases, patients discharged to the community were aged 21 to 65 years—the most productive period of life. Every patient discharged not only saves the State of Illinois approximately \$88,000 per year in hospitalization costs but also represents a gain of a functioning, working citizen. With clozapine therapy, schizophrenic symptoms may be controlled to such an extent that many patients can continue their education, obtain jobs, live independently, and pursue normal activities.

The data also demonstrated that clozapine benefited difficult-to-treat patients regardless of gender or ethnic group and dramatically reduced their term of institutionalization. Many of the patients discharged on maintenance clozapine therapy had long histories of hospitalization. For example, the 72 white women in this study had been hospitalized, on average, for 1081 days before starting clozapine therapy; they remained hospitalized on clozapine therapy for another 460 days before discharge. For 14 African American women, institutionalization averaged 827 days with another 400 days on clozapine therapy; for 5 Hispanic women, 714 days plus 460 on clozapine therapy; and for 2 Asian women, 165 days plus 28 more on clozapine therapy. The data are similar for men: 120 white men averaged 1198 days institutionalized plus 319 more on clozapine therapy before discharge; 24 African American men averaged 971 days hospitalized plus 182 on clozapine therapy; and 3 Hispanic men averaged 2952 days institutionalized and only 349 more once clozapine therapy began.

Of the original study group of 518, only 115 patients discontinued clozapine therapy, about one third doing so only after 6 months of treatment. Some patients felt so well that they thought they did not need to continue treatment; some of them required rehospitalization. In other cases, community physicians took patients off clozapine therapy, unaware that treatment is for life and that these patients are refractory to other antipsychotic drugs. Only between 11% (data on file, IDMHDD, 1995) and 26%⁵ of clozapine-treated patients stop therapy because of lack of treatment effectiveness.

ADVERSE REACTIONS

We examined the relative risk of developing adverse reactions, including sedation, extrapyramidal symptoms, anticholinergic effects, and cardiovascular symptoms, for

low- and high-potency antipsychotic agents. We found that clozapine is similar to other low-potency agents in frequency of sedation, anticholinergic effects, and cardiovascular symptoms and has a lower incidence of extrapyramidal effects. Serious side effects of clozapine are preventable or controllable when the drug is used effectively and the patient monitored properly. Titrating the dosage slowly can help reduce the frequency of adverse reactions.

The most serious potential adverse reaction to clozapine therapy is agranulocytosis, which is not dose related. In the total study population, the incidence of agranulocytosis was only 0.9% (data on file, IDMHDD, 1995). More recently, it has declined nationally to approximately 0.38% among clozapine-treated patients because of very close monitoring of white blood cell counts through the Clozaril National Registry.⁶ Although the possibility of agranulocytosis necessitates frequent monitoring—with attendant expense—monitoring also means regular contact with the patient and, therefore, closer supervision.

When selecting the clozapine dosing regimen, it is also important to consider the patient's age, weight, gender, and ethnic background, as well as medical conditions and concomitant pharmacotherapy. We are very concerned about polypharmacy, because inappropriately administered concomitant medications can pose serious problems and increase the risk of adverse effects. Extreme caution is needed when selecting concomitant drugs for clozapine-treated patients. We find it best not to add other medications to clozapine unless absolutely necessary.

When switching a patient from another antipsychotic agent to clozapine, the safest method is to gradually reduce the dose of the other agent while slowly increasing the dose of clozapine. When cross-tapering is used, other antipsychotics can be given safely with a clozapine dose of up to 350 mg per day. Every effort should be made to wean patients from all other drugs before clozapine reaches 350 mg per day, the therapeutic maintenance dose. After reaching 350 mg daily, only rarely is it necessary to supplement clozapine with standard antipsychotic medications.

CLINICAL IMPROVEMENT

Over a period of 1 year, we evaluated 189 patients discharged on clozapine therapy who were evaluated using the Brief Psychiatric Rating Scale (BPRS),⁷ and other patients who were evaluated by other means. The results are shown in Figure 1. The average admission BPRS score was 64; the average discharge score, 37. From admission values, BPRS scores were down by 22% after 2 months of clozapine therapy, by 28% after 3 months, by 33% after 6 months, and by 42% after 12 months (data on file, IDMHDD, 1995). The substantial benefits of clozapine therapy as reflected in lower total BPRS scores clearly signify patient improvement.

Figure 1. Improvement in Brief Psychiatric Rating Scale (BPRS) Scores of Patients Discharged on Clozapine Therapy

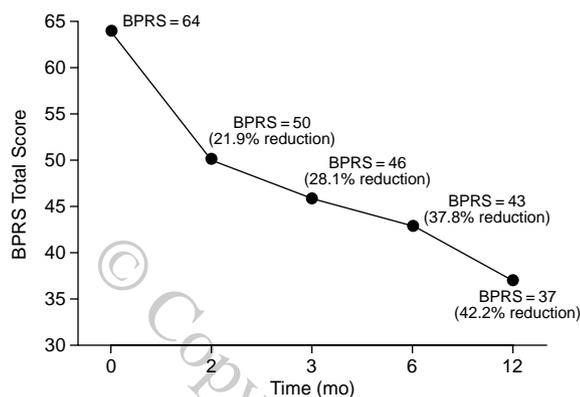
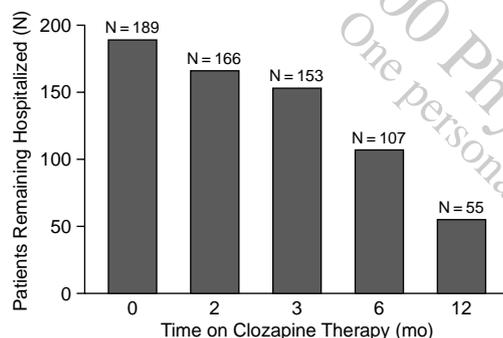


Figure 2. Reduction in Number of Patients Remaining Hospitalized After Initiation of Clozapine Therapy

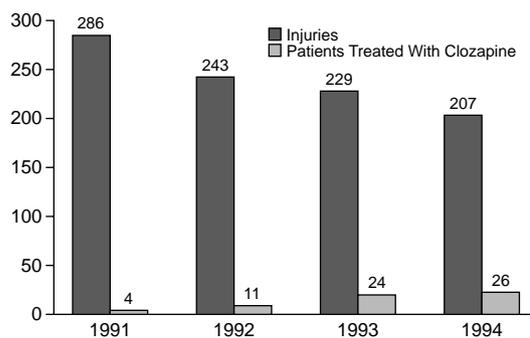


Also, it should be noted that the number of patients remaining in the hospital diminished at each time of evaluation (Figure 2). The significance of this decreasing number of hospitalized patients can only be reflected in the clinical fact that these patients were drug refractory and destined to living out their lives in a state institutional setting. After 12 months of clozapine therapy, only 55 (29%) of the original 189 patients remained. Another means to appreciate the value of clozapine is to indicate that 71% of these drug-resistant patients were released, under complete clozapine maintenance therapy, to their respective communities.

In addition, the number of injuries resulting from aggressive behavior declined in 1 hospital location between 1991 and 1994 as the number of patients on clozapine therapy increased (Figure 3). That decline has had a significant impact on the institution's budget through reductions in workers' compensation and other costs associated with injuries to employees and patients.

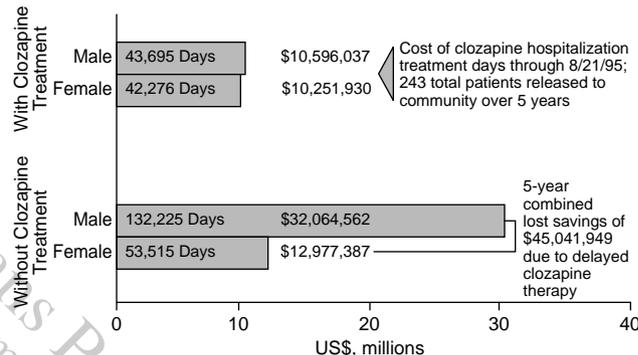
We expect the improved clinical functioning of clozapine-treated patients and the cost savings will be

Figure 3. Decline in Frequency of Injuries as Number of Patients Taking Clozapine Increased*



*Data collected from a single site.

Figure 4. Estimated 5-Year Cost of Delaying Clozapine Treatment*



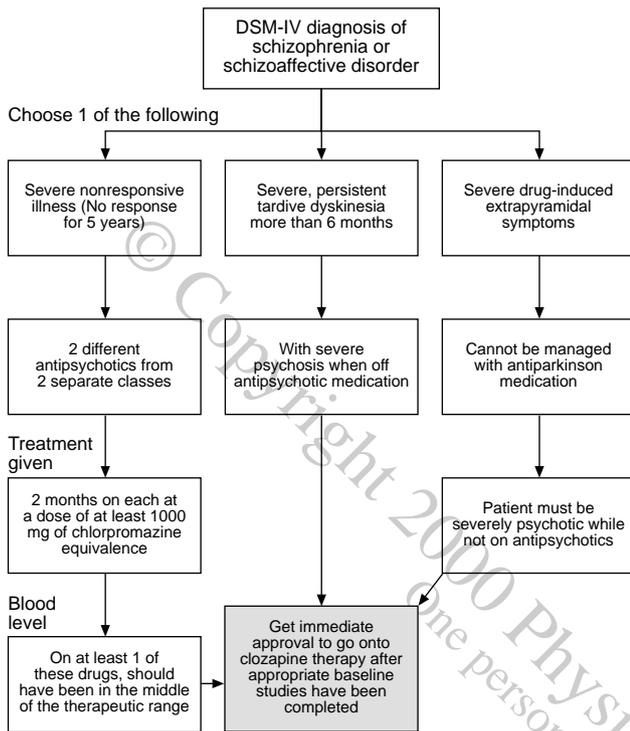
*Data on file, State of Illinois Department of Mental Health and Developmental Disabilities, 1995.

maintained into the future because of the low relapse rate associated with clozapine therapy. In 1994, the approximately 13,800 admissions to the State of Illinois mental health system included 10,200 recidivism patients. Among these patients, 3978 had schizophrenia or schizoaffective disorders, most (99%) treated with typical neuroleptic agents; only 50 were clozapine patients. Notably, a study of 304 patients who relapsed during 1994 revealed a relapse rate of 83.5% for patients taking traditional neuroleptic agents, but only 16.5% for patients taking clozapine (data on file, IDMHDD, 1995).

ESTIMATED COSTS OF DELAYING CLOZAPINE TREATMENT

In the 5-year study, 243 patients were treated successfully with clozapine and returned to the community. Before treatment with clozapine, these patients were treated with other agents for a collective total of 185,740 days (132,225 days for males and 53,515 days for females) (data on file, IDMHDD, 1995). At an average cost of

Figure 5. Treatment Algorithm for Chronic Refractory Schizophrenia Suggested by State of Illinois



\$242.50 per patient per day, the total cost of institutionalizing these patients prior to initiating clozapine was \$45,041,949 for the 5-year period (Figure 4).

After initiation of clozapine therapy, males were institutionalized for 43,695 additional days and females for 42,276 additional days for a combined total cost of \$20,847,967 (data on file, IDMHDD, 1995). Therefore, had clozapine treatment been delayed, or had it been unavailable, the state would have missed the opportunity to save \$24,193,982 over the 5-year period.

Had these same 243 clozapine patients remained institutionalized, each would have cost the state about \$88,000 per year, or more than \$21 million total. At present, however, the cost to maintain a community-discharged schizophrenic patient on clozapine treatment is only about \$4300 per year, or about \$1 million total (data on file, IDMHDD, 1995). (This represents medication costs only; costs such as case management, group programs, and housing are not included.) Therefore, each group of 243 patients discharged to the community on clozapine maintenance saves the state more than \$20 million annually. Furthermore, with so many patients discharged back to the community, the state was able to shut down some of the costly wards used for institutionalized chronic schizophrenic patients, and convert others to acute care facilities. Currently, we are achieving a dis-

charge rate of nearly 75% of patients hospitalized with schizophrenia. That compares with a national average of less than 60%.

This study clearly demonstrated to state mental health professionals and others monitoring health care costs that the proper use of effective medications—not bricks and mortar—is the answer to caring for the state's large schizophrenic population. Based on the study data, it would seem economically prudent to treat and stabilize all eligible schizophrenic patients with clozapine and return them to the community on clozapine maintenance therapy as quickly as possible.

MANAGEMENT ALGORITHM

In the State of Illinois, clozapine is now used according to certain protocols. Figure 5 shows the algorithm that was developed for treating patients with chronic refractory schizophrenia. We have found, however, that physicians commonly follow the first part of the algorithm by using 2 different agents from 2 different classes of antipsychotics, but if the patient shows no improvement after that point, they often do not initiate clozapine therapy.

We now educate our physicians that if patients fail to respond to an 8-week course of a primary antipsychotic agent such as haloperidol, therapy should be switched to another antipsychotic agent such as risperidone—but if BPRS or other scores fail to show improvement after 8 more weeks, clozapine should be started without further delay. We also are trying to educate community-based physicians who care for patients discharged from state hospitals on clozapine therapy that the drug should not be discontinued even if patients insist that they feel better. From a clinical perspective, patients restarted on clozapine therapy after discontinuing it may not return to the same level of functioning as before the initial hospital discharge.

CONCLUSION

The State of Illinois study of the use of clozapine for treatment-resistant schizophrenia patients showed that 47% were successfully treated and discharged to the community and only 22% were treatment failures. Data from a group of 243 institutionalized patients suggest that their successful treatment with clozapine and discharge to the community—rather than hospitalization in state facilities—saved the state \$24 million over a 5-year period. Additional savings due to the low relapse rate associated with clozapine therapy have also been realized.

In the future, with the aid of clozapine therapy, institutional care may be only a stop along the road to recovery for many previously uncontrollable schizophrenic patients. Long-term institutionalization will still be an option—but one that will be needed for far fewer patients.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril), haloperidol (Haldol and others), risperidone (Risperdal).

REFERENCES

1. Illinois Department of Health. View statistics. Available at: <http://www.idph.state.il.us/health/est9096.htm>
2. Carpenter WT Jr, Buchanan RW. Schizophrenia. *N Engl J Med* 1994;330:681-690
3. Malan RD, Watanabe MD. Advances in therapy of schizophrenia. *US Pharmacist*; March 1996:HS13
4. Lieberman JA. Atypical antipsychotic drugs as a first-line treatment of schizophrenia: a rationale and hypothesis. *J Clin Psychiatry* 1996;57(suppl 11):68-71
5. Meltzer HY. Treatment of the neuroleptic-nonresponsive schizophrenic patient. *Schizophr Bull* 1992;18:515-542
6. Honigfeld G. The clozapine national registry system: forty years of risk management. *J Clin Psychiatry Monograph* 1996;14:29-32
7. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep* 1962;10:799-812

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