

A Pharmacoeconomic Evaluation of Clozapine in One Patient

Alfred J. Rémillard and Jeffrey A. Johnson

ABSTRACT

Sandoz Canada Inc. began distributing clozapine in Canada under the Clozaril Support and Assistance Network (CSAN) in 1990. The costs associated with the required compliance to the CSAN program has prompted much debate regarding the ethical and clinical considerations in selecting patients to receive clozapine therapy. We undertook a one year cost-comparison analysis of clozapine therapy by assessing total mental health care costs for a patient with an extensive hospitalization history who was prescribed clozapine. Average yearly hospitalization costs were \$17,413. The average yearly cost associated with clozapine therapy for this patient, with no hospital admissions was \$8,411. The total health care cost for the year following initiation of clozapine was \$17,828, compared to a cost of \$68,423 in the year prior to clozapine, or \$27,754 in an estimated average year. This case is representative of costs savings that can be achieved by using clozapine and breaking the institution-dependency of many schizophrenic patients.

Key Words: clozapine, neuroleptics, pharmacoeconomics

Can J Hosp Pharm 1993;46:115-119

RÉSUMÉ

Sandoz Canada Inc. a commencé à distribuer de la clozapine au Canada en 1990, par l'entremise du Clozaril Support and Assistance Network (CSAN). Les coûts associés au respect des exigences du programme CSAN ont suscité une vive controverse notamment au sujet des critères déontologiques et cliniques relatifs au choix des patients qui recevraient de la clozapine. Les auteurs ont évalué le coût du traitement à la clozapine pendant un an en déterminant le coût total des soins de santé mentale d'une personne qui présentait des antécédents d'hospitalisation prolongée et à qui le médicament avait été prescrit. Les frais d'hospitalisation annuels se situent en moyenne à 17 413 \$. Le coût annuel moyen du traitement à la clozapine pour l'intéressé, sans séjour à l'hôpital, se chiffre à 8 411 \$. Le coût total des soins de santé offerts durant l'année suivant le début du traitement à la clozapine s'est établi à 17 828 \$, contre 68 423 \$ pour l'année précédant le traitement, ou une moyenne estimée à 27 754 \$ par année. Ce cas illustre bien les économies qu'il est possible de réaliser en recourant à la clozapine et en aidant les schizophrènes à briser les liens de dépendance que bon nombre d'entre eux créent avec l'établissement où ils sont hospitalisés.

Mots clés: clozapine, neuroleptique, pharmacoeconomie

Alfred J. Rémillard, Pharm.D., is Associate Professor, College of Pharmacy, University of Saskatchewan, Saskatoon, Saskatchewan.
Jeffrey A. Johnson, is currently a M.Sc. Candidate, College of Pharmacy, University of Saskatchewan, Saskatoon, Saskatchewan.

INTRODUCTION

The introduction of chlorpromazine in 1952 proved to be a major breakthrough in psychiatry. Many patients suffering from chronic psychotic disorders were finally given the opportunity to be deinstitutionalized.¹ However, the initial excitement was short-lived. The limitations of antipsychotic therapy became apparent as approximately 20% of schizophrenic patients failed to respond, and all agents were associated with significant if not disabling neurologic side effects.^{1,2}

Clozapine, a tetracyclic dibenzodiazepine antipsychotic agent, has

generated much enthusiasm. Patented in Switzerland over 30 years ago, and clinically evaluated in the 1970s, clozapine is considered an "atypical" neuroleptic.¹ These agents have greater selectivity for a dopamine receptor sub-type, and reduced likelihood for causing extrapyramidal adverse effects, and perhaps tardive dyskinesia.³ In a pivotal study, Kane et al. reported that 30% of treatment-resistant schizophrenics were categorized as responders to clozapine therapy.⁴ However, the promising benefits of clozapine were soon tempered by the recognition that this agent was associated with a significant risk of

agranulocytosis with an incidence of 1-2% of the treated population.^{1,3} To ensure safety, Sandoz Canada began distributing clozapine in 1990 under the Clozaril Support and Assistance Network (CSAN). The program requires patients receiving clozapine to provide weekly blood samples to assure normal white blood cell counts prior to dispensing the next supply of the medication.

The cost associated with clozapine and the required compliance to the CSAN program, or the parallel Clozaril Patient Management System in the United States, has prompted much debate regard-

ing the ethical and clinical considerations involved in permitting patients to receive clozapine.^{5,6} Recently a moratorium has been placed on clozapine therapy in Ontario, limiting public funding of clozapine in that province. Other provinces are rumored to be planning to impose the same restrictions. Unfortunately, formulary decision makers focus on drug costs alone, and global health care costs are disregarded. Economic evaluations of clozapine therapy in treatment-resistant schizophrenics have been carried out in the United States.^{7,8}

We present a case report of a treatment refractory patient who benefited from clozapine therapy. We then evaluated the economic impact of the patient's treatment one year later.

CASE

A 60 year-old male was admitted to the psychiatric unit with increasingly aggressive as well as bizarre behavior, such as placing his head in the toilet bowl and delusional and persecutory thoughts. He felt there were worms in his head and that people were trying to do him harm. He was hearing and responding to voices which varied in content: some hostile, others friendly. Past neuroleptic history included a variety of agents both oral and depot (trifluoperazine, chlorpromazine, haloperidol, flupenthixol, and fluphenazine). During this admission a number of antipsychotic agents including chlorpromazine, haloperidol, and pimozide were tried with little effect on his aggressive and inappropriate behavior and delusional state. On day 52 of admission, the patient was started on clozapine 25 mg twice daily. This dose was gradually increased over the next three weeks to a maximum dose of 400 mg daily. At the end of the titration period the patient exhibit-

ed less aggressive behavior and became more co-operative. The hallucinations and delusions continued. At this dose the patient began to develop noticeable sialorrhea. The dose was decreased to 375 mg/day with a subsequent reduction in saliva production. The patient was discharged from hospital on day 77, and was prescribed clozapine 375 mg per day in divided doses. He has, subsequently, been managed in a private care home with no hospital visits. To ensure safety and efficacy of clozapine, an extensive protocol was developed to comply with Sandoz's CSAN. On a weekly basis, a phlebotomist collected blood samples from the patient, and a home care nurse would visit the patient to assess any clinical change, obtain the laboratory results and communicate them to the appropriate individuals. The patient was assessed monthly by a psychiatrist.

METHODS

When the patient reached the one year post-discharge mark, we undertook a cost comparison of clozapine therapy. Four components of complete mental health care costs were identified: drug therapy, hospitalization, monitoring (home care and phlebotomy), and physician billing.

We first calculated the annual cost of the clozapine protocol. This protocol included three major services: pharmacy (drug cost, dispensing fee), laboratory (collecting, analyzing blood sample), and home care (time spent, travel). The cost of the clozapine protocol was then compared to standard drug therapy. Annual costs of selected neuroleptics currently available on the Saskatchewan Health Services Formulary Services were estimated for comparable doses using chlorpromazine equivalents.^{9,10} Since our patient had a very extensive and diverse medication history

which resulted in unused portions of medications, an accurate figure representing his drug cost prior to clozapine could not be obtained. For this reason, we chose for comparison the cost of standard neuroleptic therapy reported in the literature and estimated at \$500 per year.⁷

Other health care costs were calculated from hospitalization, home care, and psychiatrist services. Hospitalization information and costs were obtained from the Saskatchewan Hospital Services data base. This included location, duration of stay, and cost of hospitalization since 1985. Psychiatrist billings were calculated using Medical Care Insurance Commission rates for the province of Saskatchewan. For inpatient status, we assumed daily physician visits, and monthly assessment as an outpatient. This patient required level three care which is defined as someone with advanced physical or mental illness that is stable, but requires intensive personal or nursing care. Due to limited space for clients in private care homes, this patient's room was maintained during his inpatient stays by continued payments. As such, the cost of private home care was included in all comparison groups.

Four total annual costs were calculated for comparison purposes:

- (1) the year following clozapine therapy;
- (2) the year prior to clozapine therapy;
- (3) an average year based on the six year hospitalization history on standard neuroleptic therapy; and
- (4) a year of standard neuroleptic therapy with no hospitalization.

RESULTS

The yearly cost associated with the clozapine protocol for this patient was \$8,411 (Figure 1). Figure 2

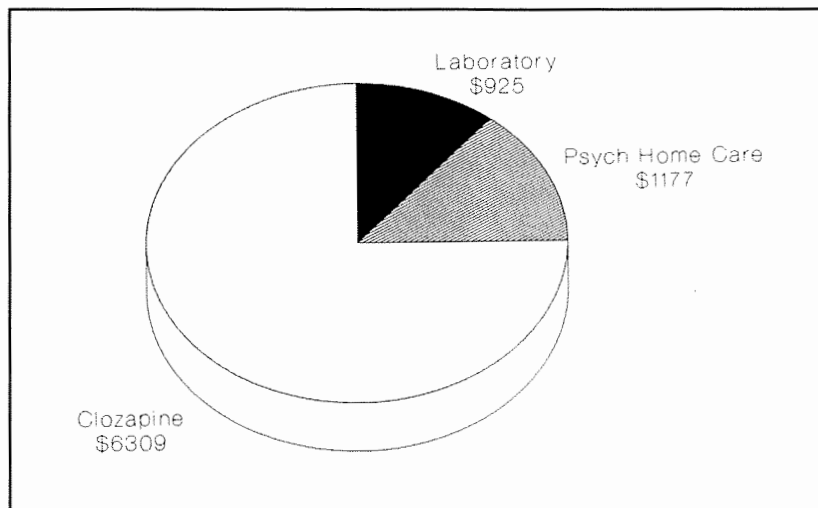


Figure 1: Clozapine Protocol Costs (\$8,411 per year)

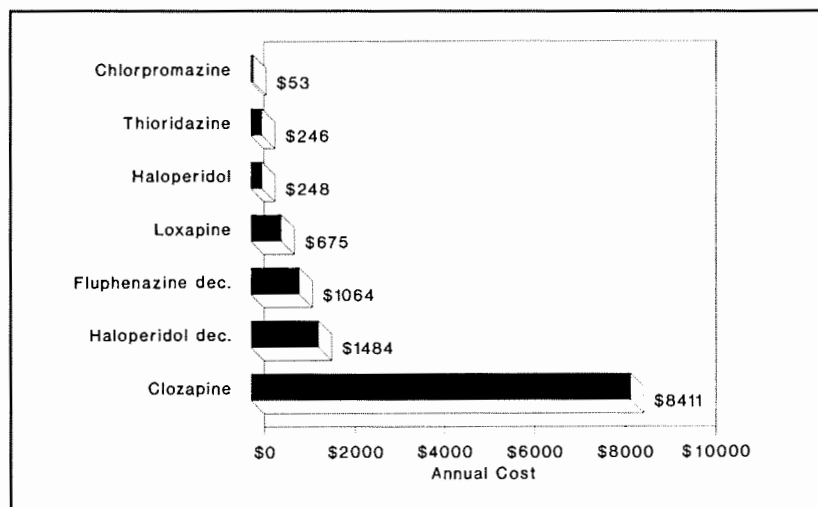


Figure 2: Neuroleptic Drug Costs¹⁰

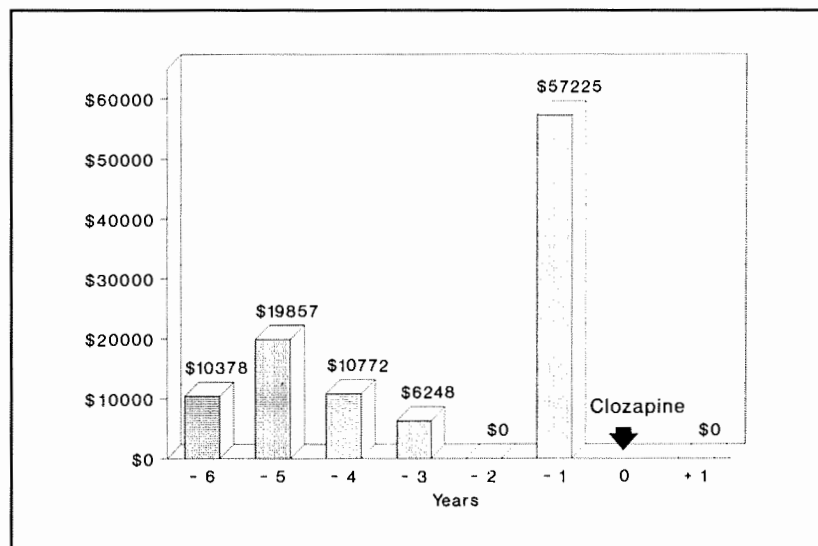


Figure 3: Hospitalization Costs

compares the selected neuroleptic agents to the clozapine protocol. The annual cost of the neuroleptics are probably underestimated. Most chronic schizophrenic patients require home care nurse visits for monitoring and for administration of depot medications. These costs were not included in the total.

Figure 3 shows all the hospitalization costs for this patient who had an extensive inpatient history. Records dating back to 1985 report an average of two admissions and 61.3 hospital days per year. The mean annual hospitalization costs were \$17,413.

Table I illustrates the total health care costs for this patient prior to and after clozapine therapy. Since clozapine was initiated a year ago, the patient has remained out of the hospital and annual health care costs were estimated to be \$17,828. In the 12 months prior to clozapine, the patient was hospitalized for 185 days, and total health care costs were estimated to be \$68,423. For the average of six years prior to clozapine, total health care costs were estimated to be \$27,754.

DISCUSSION

Since the initiation of clozapine therapy, the annual health care cost for this patient was estimated to be \$17,828. This includes an extensive protocol involving phlebotomy and home care nursing visits. Other institutions may choose to have the patient take on more responsibility, and reduce cost by having them go to the laboratories themselves and have only psychiatrists follow-up on monthly visits with no home care nurse visits. However, as seen in Figure 1, the medication itself is responsible for 75% of the protocol cost so the other important services do not have a major financial impact.

Looking back over the six years since 1985, the average annual

Table I. Comparison of total health care costs

Comparison Years	Home Care	Drugs	Psychiatrist	Hospitalization	Total
Clozapine Treatment 91/92	\$8,880	\$8,411	\$ 537	\$0	\$17,828
Standard Treatment 1990	\$8,880	\$ 500	\$1,818	\$57,225	\$68,423
Standard Treatment, "Average Year"	\$8,880	\$ 500	\$ 961	\$17,413	\$27,754
Standard Treatment, No Hospitalization	\$8,880	\$ 500	\$ 537	\$0	\$ 9,917

cost for health care for this patient was \$27,754. Since starting clozapine, the health care system has saved an estimated \$9,926, a 36% reduction in costs. These savings might also be an underestimate since, in the most recent year, the patient had required more frequent hospital admissions, at a total cost of \$68,423.

Two economic evaluations of clozapine therapy have recently been published in the American literature. Revicki et al reported on a cost-effective analysis of clozapine therapy compared to conventional neuroleptic therapy.⁷ Data on the use of hospital and non-hospital mental health services, including outpatient treatment, support services and residential services, were collected from psychiatric records and administrative data sources. Information was collected for one year prior to and two years after clozapine therapy was started. Total mental health costs in the year prior to the index admission date were \$80,440 and \$73,067 for the clozapine and conventional group, respectively. Cost did not change in the first posttreatment year for the clozapine group, however, these patients required fewer hospital admissions than the conventional neuroleptic group. By the second year, total health care costs had decreased by \$24,573 in the clozapine group compared to \$8,189 in the neuroleptic group, and this despite the fact clozapine patients underwent prolonged in-

itial hospitalization for monitoring and evaluation, regardless of clinical necessity.⁷

The second report was a two-year follow-up of the efficacy and costs associated with clozapine therapy.⁸ After initiating therapy, patients treated with clozapine were re-hospitalized 50% less often than those treated with conventional therapy. The average annual hospitalization costs decreased from \$73,403 in the year prior to clozapine, to \$58,941 in the first year, and \$28,367 in the second year for patients treated with clozapine. For patients who remained on conventional therapy, comparative hospital costs were \$72,121, \$67,934 and \$61,518.⁸

The focus of this report is the financial impact of clozapine therapy. Not emphasized, but equally important, is the quality of life. The patient's improvement on clozapine can best be summarized by his statement "I hope the doctor does not take me off the drug". In addition to the economic benefits, improvement in psychopathology and quality of life has been demonstrated in chronic schizophrenia patients.^{7,8,11} In an evaluation of 38 patients who received clozapine for six months or more, clozapine treatment was associated with a significant improvement in the quality of life.¹¹ In continued follow-up of nine to 38 months, 55% of the patients went on to hold paying or volunteer jobs or to return to school. A major factor in

the improved quality of life and work functioning was an 86% reduction in re-hospitalization for patients receiving clozapine.

In conclusion, clozapine represents a major advancement in the treatment of schizophrenia. It provides a viable alternative to previously treatment-resistant patients or those experiencing intolerable neurologic side effects with standard treatment.^{12,13} However, the risks of agranulocytosis and seizures at higher doses, as well as the cost, limits its potential as a drug of first choice. When comparing costs of drug therapies, the total health care cost must be considered and not just the drug costs.

We have shown in our case report that clozapine therapy reduced the total health care cost and may have also improved quality of life. To the best of our knowledge, this is the first report which has evaluated the economic impact of clozapine in Canada, which is vastly different from the American health care system. Despite the obvious limitations of drawing any major conclusion from a case report, it provides valuable information necessary to plan future large scale prospective studies which will substantiate the clinical utility and pharmacoeconomics of clozapine therapy. ☐

REFERENCES

- Baldessarini RJ, Frankenburg FR. Clozapine: a novel antipsychotic agent. *N Engl J Med* 1991; 324:746-54.
- Baldessarini RJ. Drugs and the treatment of psychiatric disorders. In: Gilman AG, Rall TW, Nies AS, Taylor P (eds). *The pharmacologic basis of therapeutics*. New York, NY: Pergamon Press; 1990:383-435.
- Ereshefsky L, Watanabe MD, Tran-Johnson TK. Clozapine: an atypical antipsychotic agent. *Clin Pharm* 1989; 8:691-709.
- Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine.

- Arch Gen Psychiatry* 1988; 45:789-96.
5. Pelonero AL, Elliott RL. Ethical and clinical considerations in selecting patients who will receive clozapine. *Hosp Community Psychiatry* 1990; 41:878-80.
 6. Maier GJ, Miller RD, Roach L. The real cost of clozapine: a patient buys freedom. *Hosp Community Psychiatry* 1992; 43:177-8.
 7. Revicki DA, Luce BR, Weschler JM, et al. Cost-effectiveness of clozapine for treatment-resistant schizophrenic patients. *Hosp Community Psychiatry* 1990; 41:850-54.
 8. Honigfeld G, Patin J. A two-year clinical and economic follow-up of patients on clozapine. *Hosp Community Psychiatry* 1990; 41:882-5.
 9. Neuroleptics. In: Bezchlibnyk-Butler KZ, Jeffries JJ (eds). *Clinical handbook of psychotropic drugs*. Toronto, Ontario: Hogrefe & Huber Publisher; 1991:14-27.
 10. Saskatchewan Health, Prescription Drug Services Formulary, Thirty-fourth Edition, 1992: January.
 11. Metzler HY, Burnett S, Bastani B, et al. Effects of six months of clozapine treatment on the quality of life of chronic schizophrenic patients. *Hosp Community Psychiatry* 1990; 41:892-7.
 12. Collins EJ, Lalonde P, Jones BD, et al. Clozapine in the treatment of refractory schizophrenia: Canadian policies and clinical guidelines. *Can J Psychiatry* 1992; 37:482-8.
 13. Meltzer HY. Treatment of the neuroleptic-nonresponsive schizophrenic patient. *Schizophr Bull* 1992; 18:515-42.
-