Evaluation of an Interchangeability Switch in Patients Treated With Clozapine: A Retrospective Review

Silvia Alessi-Severini, Ph.D.; Patricia L. Honcharik, Pharm.D.; Karleen D. Simpson, B.Sc. (Pharm); Michael K. Eleff, M.D.; and David M. Collins, Ph.D.

Received Nov. 10, 2005; accepted Jan. 30, 2006. From the Faculty of Pharmacy (Drs. Alessi-Severini, Honcharik, and Collins and Ms. Simpson) and the Department of Psychiatry, Faculty of Medicine (Dr. Eleff), University of Manitoba; and the Department of Pharmaceutical Services–Psychiatry, Health Sciences Centre (Dr. Honcharik), Winnipeg, Manitoba, Canada.

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Corresponding author and reprints: Dr. Silvia Alessi-Severini, Faculty of Pharmacy, University of Manitoba, Winnipeg, Manitoba, R3T 2N2, Canada (e-mail: alessise@ms.umanitoba.ca).

Objective: To report the findings of a switch from brand-name to generic clozapine in a Canadian outpatient population.

Method: The medical records of 58 outpatients diagnosed with schizophrenia and other psychotic disorders and stabilized on brand-name clozapine therapy were reviewed retrospectively. Patients were switched from brand-name to generic clozapine on their next dispensing supply after September 29, 2003. Data regarding clozapine dose regimens, physicians' visits, hospitalizations, and adverse events were collected from the patients' charts for the 6 months preceding and the 6 months after the switch from brand-name to generic clozapine. Relevant measurement changes in those data associated with the switch are evaluated.

Results: No significant changes in dose, number of physician's visits, or hospitalization rates were observed as a consequence of the switch from brand-name to generic clozapine. In addition, there were no reported increases in the frequency of the most common adverse events, including decreases in white blood cell counts. None of the patients received a "nonrechallengeable" status, and no discontinuation of clozapine therapy occurred for any reason (toxicity or treatment failure) in the 6 months after the formulation switch.

Conclusion: In the current outpatient population, retrospective evaluation of the conversion from brand-name clozapine to the first generic alternative available on the Canadian market did not reveal any significant treatment changes.

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Clozapine is a potent antipsychotic agent that has been available on the Canadian market since 1991 for the management of patients with treatment-resistant schizophrenia. Because of the significant risk of granulocytopenia and agranulocytosis associated with the use of clozapine, Health Canada (Ottawa, Ontario, Canada) has mandated that the distribution of this agent be regulated through a system that requires hematologic testing every 1 or 2 weeks prior to the dispensing of the next period's supply[1,2]; as a consequence, prescriptions for clozapine are written for a maximum supply of 2 weeks. Regular blood testing is mandatory, and results are forwarded to the prescribing physician, the dispensing pharmacist, and the manufacturer, the latter responsible for monitoring patients' hematologic status through a patient registry. Clozapine must be discontinued in patients who have been issued a "nonrechallengeable" status (white blood [cell] count [WBC] $< 2.0 \times 10^9$/L and/or an absolute neutrophil count [ANC] $< 1.5 \times 10^9$/L).

Prior to February 2003, clozapine had been available in Canada as a single-source product (Clozaril, manufactured and marketed by Novartis Pharmaceuticals Canada, Inc., Dorval, Quebec, Canada), and its distribution was handled by a single registry, the Clozaril Support and Assistance Network, for the hematologic monitoring of patients on Clozaril therapy. The first generic form of clozapine became available in Canada on February 19, 2003,

when Gen-Clozapine (manufactured and marketed by GenPharm, Inc., Etobicoke, Ontario, Canada) received Notice of Compliance from the Therapeutic Products Directorate of Health Canada.[3] The Gen-Clozapine Access Network, a second distribution system responsible for the monitoring of patients treated with Gen-Clozapine, was established as a consequence of the approval of Gen-Clozapine. Federal approval of Gen-Clozapine was granted on the basis of comparative bioavailability data with the brand-name product, Clozaril, and the Notice of Compliance for Gen-Clozapine was issued by the Therapeutic Products Directorate with a Declaration of Bioequivalence with the Canadian Reference Product, Clozaril. Guidelines for bioequivalence of oral dosage formulations, not in modified-release forms, showing complicated characteristics (such as nonlinear pharmacokinetics, long half-life, narrow therapeutic index, or high toxicity) were published by Health Canada in the document known as "Report C" in 1992.[4] Bioequivalence criteria applicable to Gen-Clozapine included the requirement that the ratios of the log transformed area under the curve $(AUC)_{0-t}$ and C_{max} of the test-to-reference formulation and the relative 95% CI were to be between 80% and 125%. These standards were to be met on parameters calculated from both measured data and potency-corrected data. Studies were to be conducted in healthy volunteers in both fasted and fed states. Please note that "Report C" guidelines are currently under review by the Therapeutic Products Directorate. Modifications have been proposed for drugs that are defined as "critical dose." (Clozapine would be included in this category.)[5]

According to the Canada Health Act, "decisions respecting interchangeability and drug lists remain in the domain of the institution responsible for the costs of the products which includes hospitals, provincial governments and other third party payers."[6] As a result, provincial jurisdictions conduct independent evaluations of new generic products for the designation of interchangeability. The policy of reimbursing only the "lowest-cost alternative" in an interchangeable category is one of the cost-saving strategies most widely implemented by provincial drug programs across Canada.

Because of the significant cost savings that were anticipated following the introduction of generic clozapine, the Provincial Drug Programs in Manitoba granted Gen-Clozapine a designation of interchangeability with Clozaril, effective September 15, 2003.[7] However, a 2-month grace period before implementation of the lowest-cost alternative reimbursement policy was announced to allow a seamless switch of patients from one registry to the other.[8] Manitoba was the first Canadian province to implement interchangeability for clozapine. At the time of the writing of this article, only British Columbia, New Brunswick, and the NIHB (Non-Insured Health Benefits) drug plan (which covers First Nations and Inuit populations), have listed Gen-Clozapine as interchangeable with Clozaril in their respective formularies. Alberta and Saskatchewan have listed it as noninterchangeable but have encouraged the use of the generic alternative in new patients, while patients previously using Clozaril were "grandfathered in" to continue receiving reimbursement for the brand-name product.

The consequence of a designation of interchangeability, combined with the implementation of the lowest-cost alternative reimbursement policy, is always a significant switch from the brand-name product to the generic version. This switch affects those patients who are clients of various government-sponsored drug programs.

Switching formulations from one brand to another has often been anticipated by physicians and patients with apprehension. However, despite the often-raised concerns, there is generally no objective evidence of clinically significant differences on switching from a brand-name product to a generic alternative. Reports of reduced efficacy or increased toxicity are often anecdotal in nature. The interchangeability switch of clozapine was complicated by the need to register patients, physicians, and pharmacists with the new monitoring program. This necessity raised concerns regarding additional administrative burden and patients' safety in cases of miscommunication between the 2 parallel registries. Furthermore, concerns regarding the bioequivalence of the 2 formulations were prompted by the publications of case reports[9] and 1 randomized trial[10] describing increased symptoms or marked psychotic decompensation in hospitalized patients switched from Clozaril to a generic clozapine (Zenith Goldline Pharmaceuticals, Inc., Miami, Fla.) in the United States. In contrast, other reports had concluded that no significant differences were detected between formulations in terms of symptom control, adverse events, WBCs, and doses when inpatients were converted from Clozaril to a generic product (Zenith Goldline Pharmaceuticals, Inc., Miami, Fla., and Mylan Pharmaceuticals, Inc., Morgantown, W.Va.).[11,12] The validity of the published results has been questioned on the basis of the sponsorship (brand-name vs. generic manufacturer) of the studies. The importance of conducting independent studies to assess the interchangeability of the 2 different formulations of clozapine in the clinical setting has been more recently emphasized.[13]

The current study reports the findings of a systematic evaluation of an interchangeability switch between the brand-name product, Clozaril (Novartis Pharmaceuticals Canada, Inc.) and a generic clozapine formulation (GenPharm, Inc.) in a Canadian outpatient population.

METHOD

This retrospective chart-review study was approved by the Biomedical Research Ethics Board at the University of Manitoba. Data were collected in full compliance

Table 1. Demographic Characteristics of the Study Population (N = 58)[a]

Variable	Value
Age, y, mean ± SD (range)	40.8 ± 11.3 (21–66)
Gender	
Male	41 (71)
Female	17 (29)
Diagnosis	
Schizophrenia	53 (91)
Schizoaffective disorder	3 (5)
Bipolar mood disorder	1 (2)
Psychosis	1 (2)
Length of illness, y[b]	
1–5	7 (12)
5–10	41 (71)
> 10	10 (17)
Comorbidity	
Type 2 diabetes	7 (12)
Hypertension	2 (3)
Hyperlipidemia	1 (2)
Smoking status	
Smoker	18 (31)
Not known	40 (69)

[a]Values are N (%) unless otherwise stated.
[b]Range equals 1–25 years.

Table 2. Patient Distribution According to Prescribed Pharmacotherapy (N = 58)

Variable	N (%)
Antipsychotic monotherapy (clozapine only)	43 (74)
Antipsychotic combination therapy (clozapine + concomitant antipsychotic)	15 (26)
Length of clozapine therapy	
< 1 y	7 (12)
1–3 y	15 (26)
> 3–5 y	26 (45)
> 5 y	10 (17)
Duration of clozapine therapy at preswitch dose	
2–6 mo	11 (19)
> 6–12 mo	5 (9)
> 1–3 y	24 (41)
> 3 y	18 (31)
Polypharmacy, no. of additional prescriptions	
1	14 (24)
2	12 (21)
3	7 (12)
4 or more	9 (16)

with Privacy of Health Information Act legislation in the province of Manitoba. All outpatients attending the Health Sciences Centre psychiatric clinics who had been stabilized on the same dose of clozapine for at least 2 months before the date of the interchangeability switch were included in the study. As a result of an administrative decision made at the Health Sciences Centre, all patients treated with brand-name clozapine (Clozaril, Novartis Pharmaceuticals Canada, Inc.) were converted to the generic clozapine formulation (GenPharm, Inc.) on their next dispensing supply after September 29, 2003. Data on patients' histories for the 6 months before and after the switch were collected and recorded in a purpose-designed database (Microsoft Access 2000, Microsoft Corp., Redmond, Wash.). Patients were assigned a study number, and any identifying information was destroyed at the end of the study period.

Data collected included dose regimens, number of physician/therapist visits, number of hospitalizations and ER visits, physician's notes on patient progress, information on adverse events, and comedication regimens. Blood test results were also collected, and patients' hematologic status was recorded in order to capture any variation during the time of the study. Additional information regarding smoking, compliance, and lifestyle changes that could have affected clozapine absorption and disposition at the time of the conversion from the brand-name to the generic product was also collected when available. Statistical analysis by paired t test, when appropriate, was conducted for the numerical measures available before and after the interchangeability switch. Significance level was set at .05.

RESULTS

Demographics

Ninety-two charts were reviewed for 58 patients (male, N = 41; female, N = 17; age range, 21–66 years [mean ± SD = 40.8 ± 11.3 years]) who met the inclusion criteria (Table 1). The majority (N = 53) had a diagnosis of schizophrenia, 3 had schizoaffective disorder, 1 had bipolar mood disorder, and 1 was diagnosed with psychotic disorder not otherwise specified. Length of illness for the study population ranged from 1 to 25 years, and in 51 patients (88%) it was > 5 years (Table 1). Patients' comorbidity included 7 cases of type 2 diabetes. Other documented comorbidities included hypertension, hyperlipidemia, epilepsy, hypothyroidism, and type 1 diabetes (Table 1).

Pharmacotherapy

Ten patients had been taking clozapine for more than 5 years; and 41, for a period of 1 to 5 years; only 7 patients had been on clozapine therapy for less than 1 year (Table 2).

At the time of the switch from brand-name to generic clozapine, 43 (74%) of the 58 patients were on antipsychotic monotherapy with clozapine. The remaining 15 patients were maintained on combination therapy with clozapine and quetiapine (3 patients), clozapine and risperidone (3 patients), clozapine and zuclopenthixol/flupenthixol (4 patients), clozapine and chlorpromazine (2 patients), clozapine and pimozide (2 patients), and a combination of clozapine, risperidone, and olanzapine (1 patient) (Table 2).

Other medications most commonly prescribed to this outpatient population were anticholinergic agents (e.g., benztropine, procyclidine), anticonvulsants (e.g., topiramate, valproic acid), antidepressants (e.g., fluoxetine,

Table 3. Clozapine Doses, Hospitalizations, and ER Visits Recorded in the Preswitch and Postswitch Periods (N = 58)

Variable	Mean (SD)	Range	p Value
Clozapine doses, mg/d			
Before switch	391.8 (161.9)	100–700	…
2 months after switch	388.8 (163.6)	100–700	NS
4 months after switch	389.7 (163.3)	100–700	NS
6 months after switch	392.5 (164.7)	100–700	NS
Hospitalizations	N (%)		
6 months before switch	10 (17.2)		…
6 months after switch	5 (8.6)		NS
ER visits			
6 months before switch	7 (12.1)		…
6 months after switch	3 (5.2)		NS

Abbreviations: ER = emergency room, NS = nonsignificant.
Symbol: … = not applicable.

paroxetine, sertraline), and anxiolytics (e.g., benzodiazepines, zopiclone). Comorbidity was treated according to diagnosis (e.g., metformin and/or glyburide for type 2 diabetes). As a result, 72% of the population (42/58) was receiving 1 or more additional prescriptions in combination with clozapine at the time of the switch (Table 2).

Clozapine Doses

Clozapine doses at the time of the switch ranged from 100 mg/day to 700 mg/day (mean ± SD = 391.8 ± 161.9 mg/day) (Table 3). The duration of therapy at the dose prescribed at the time of the switch ranged from 9 weeks to 7 years; 42 patients had been stabilized on the same dose for longer than 1 year (Table 2). Doses at 2 months after the switch (range: 100–700 mg/day; mean ± SD = 388.8 ± 163.6 mg/day) were not significantly different from those observed prior to the switch. A similar pattern was observed at 4 months after the switch (range: 100–700 mg/day; mean ± SD = 389.7 ± 163.3 mg/day), with no significant difference observed between preswitch and postswitch periods. In addition, doses 6 months after the switch (range: 100–700 mg/day; mean ± SD = 392.5 ± 164.7 mg/day) were also not significantly different from the preswitch doses (Table 2).

Clozapine Dose Adjustments: Details

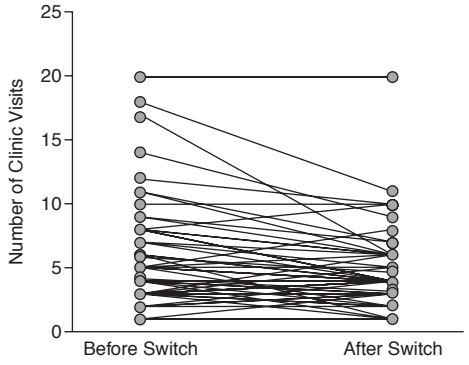
Only 2 patients required a dose adjustment within 2 months of the switch to generic clozapine. In one case, the dose was decreased from 450 mg/day to 400 mg/day (Patient #29), and in the other the dose was increased from 400 mg/day to 425 mg/day (Patient #65). Patient #29 had been taking 450 mg/day for 4.5 months when he was switched; 2 months after the switch, the patient reported symptoms of "hangover" during the day and complained about not being able to tolerate the new brand of clozapine. He had asked if he could be switched back to the original brand. At this time, the dose was reduced to 400 mg/day and divided up, with 300 mg to be taken at night and 100 mg to be taken in the morning. The records indicated that the dose had been increased to 450 mg/day from 400 mg/day in May 2003 (4 months prior to the switch) and that the patient had suffered from persistent orthostatic hypotension ever since. However, no dose reduction was recommended at that time, as the patient was still experiencing hallucinations. No additional comments were reported in this case. This patient did not appear to have been taking other medications at the time of the switch from brand-name to generic clozapine. It is not known if the patient was a smoker trying to quit at the time of the switch, and no plasma concentrations of clozapine were reported in the chart. No problems were recorded in this case with the 400 mg/day dose of generic clozapine at 6 months after the switch.

Patient #65 had been taking a stable dose of 400 mg/day for more than 2 years and doing relatively well. However, the physician's comments recorded in the chart noted that he had been experiencing occasional auditory hallucinations while taking the 400 mg/day dose. The increase of the clozapine dose to 425 mg/day that occurred 2 months after the switch was not accompanied by any specific comment. The patient was a smoker and had a history of multiple-substance abuse. However, no specific information was available on his smoking and drug abuse patterns around the time of the formulation switch. He had also been taking sertraline at the stable dose of 50 mg/day for more than 2 years. No change in this prescription was noted during the study period. Assessment of this patient's compliance with medications at the time of the switch was not available. No information was reported on clozapine plasma levels in this instance.

Dosage adjustments made subsequent to the 2 months postswitch period (i.e., at 4 months and at 6 months) were also noted and reported. Only 1 additional patient (Patient #36) had his dose increased within the 4 months after the switch (from 300 to 350 mg daily). This patient had had his dose of 275 mg/day increased to a 300 mg/day dose in July 2003 (3 months before the switch) because of increased paranoid symptoms and hallucinations. The dose of concomitant chlorpromazine was also increased (from 25 mg/day to 50 mg/day) 1 month before the clozapine switch. It was increased again to 75 mg/day 4 months after the clozapine switch to control further exacerbation of paranoid symptoms. The patient was reported stable at 6 months following the switch to generic clozapine.

Three further patients had dose adjustments within the 6 months after the switch: 2 had their doses increased from 400 to 450 mg/day (Patient #9 and Patient #69), and 1 had a dose increase from 300 mg/day to 350 mg/day (Patient #13). Patient #9 had been taking quetiapine and was in the process of tapering off the drug at the time of switching from brand-name to generic clozapine. Patient #13 had the dose changed during a visit to the Crisis Stabilization Unit as a result of deterioration because of compliance problems. A dose increase from 350 mg/day to

Figure 1. Number of Clinic Visits Recorded for Each Patient in the 6 Months Before Switch and in the 6 Months After Switch



400 mg/day of clozapine had been recorded for Patient #69 only 3 months before the interchangeability switch. This patient's dose was increased again, to 450 mg/day, about 6 months after the switch. He was taking trazodone and bupropion concomitantly, but no change in their dosages was noted. He had been complaining about insomnia and agitation.

Concomitant Antipsychotic Medications

Concomitant antipsychotic therapy was modified in 2 patients in the period after the interchangeability switch. Patient #5, who had apparently been managed with clozapine 100 mg/day in combination with quetiapine 500 mg/day for about a year, had consistently reported obsessional symptoms and concerns about gaining weight. About 2 months after the clozapine switch, his quetiapine dose was increased to 600 mg/day. No additional comments were added to the chart at that time. Similarly, it was reported that Patient #72 had his quetiapine dose increased from 500 mg/day to 600 mg/day about 2 months after the switch, with no specific reason being documented. This patient had also been taking lorazepam: the dose had been decreased from 2 mg/day to 0.5 mg/day during the time of the switch; no specific comments were recorded concerning this dose adjustment. In neither of these cases were clozapine doses modified.

Clinic Visits

The number of physician or therapist visits recorded for each patient during the 6 months prior to the switch (mean ± SD = 5.8 ± 4.1) was compared with the number of visits recorded during the 6 months after the switch (mean ± SD = 4.7 ± 3.1). The difference did not achieve statistical significance and corresponded to the expected frequency associated with patients' routine monitoring (Figure 1).

Physician's notes were screened for comments regarding possible relapse of psychotic symptoms following the switch from brand-name to generic clozapine, as well as relevant changes in comedication regimens. No evidence of deterioration was recorded that could be unequivocally linked to the formulation switch of clozapine.

Minor changes in nonantipsychotic comedications were consistent with the expected clinical management of nonpsychotic symptoms (e.g., anxiety), medication side effects (e.g., salivation and constipation), and comorbidity.

Comments recorded in the charts were also screened for possible difficulties encountered during the process of switching patients from one manufacturer's registry to the other or changes in patterns of patients' adherence to treatment following the switch. No specific concerns were documented with regard to either of these issues.

Hospitalizations

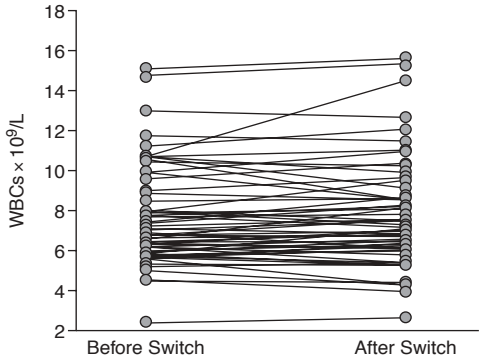
Rates of hospitalization were relatively low in this outpatient population. Ten hospitalizations (rate 17%) were recorded in the preswitch period, and 5 (rate 8.6%) after the switch (Table 3). Seven patients were hospitalized in the 6 months prior to the switch to generic clozapine: 3 had multiple (2) hospital admissions, while 4 patients were admitted once each (Table 3). Four patients were hospitalized during the 6 months after the switch: 1 patient (Patient #32) was hospitalized for 1 day for a reason not related to drug therapy (i.e., test flex sigmoidoscopy), and 3 patients were admitted for apparent clinical deterioration, with symptoms of decompensated schizophrenia. Two of these patients had been hospitalized twice in the 6 months prior to the switch. Patient #13 was hospitalized 5 months before the switch to initiate clozapine therapy. Two months later, this patient self-referred to the Crisis Stabilization Unit for a "place to stay": it was at this time that the dose was increased from 300 mg/day to 350 mg/day. This patient had been taking the 350 mg dose of clozapine for only 3 months before switching to the new formulation. The reason for the hospitalization after the switch was "noncompliance with clozapine therapy." Patient #15 was hospitalized twice before the switch and once after, in all instances because of symptoms of psychosis and auditory hallucinations. This patient, who had been diagnosed with type 2 diabetes in January 2003, was taking other medications in addition to clozapine, which included sertraline, enalapril, valproic acid, benzafibrate, and metformin. However, no changes in their dosages were prescribed during or after the time of the switch. The third patient (Patient #51) had been on clozapine therapy for 10 weeks before the switch and was hospitalized twice after the switch because of compliance problems (i.e., not taking the medication and missing blood work appointments). All postswitch hospitalizations occurred at least 3 months after the switch to the generic formulation. In all cases, no dose adjustments were made to the patients' clozapine regimens.

Table 4. Number of Adverse Events Reported in the Patient Population (N = 58) in the 6 Months Before Switch and 6 Months After Switch

Adverse Event	No. Before Switch	No. After Switch
Hypersalivation	10	7
Drowsiness/sedation	6	6
Tremor/muscle spasm	4	4
Decrease in WBCs/ANCs	5	3
Gastrointestinal (nausea, diarrhea, constipation, rectal bleeding)	3	2
Increased thirst and urination	0	2
Dizziness	2	1
Insomnia	0	1
Seizures	1	1
Weight gain	2	0
Headache	2	0
Orthostatic hypotension	1	0
Palpitation	1	0
Total	37	27

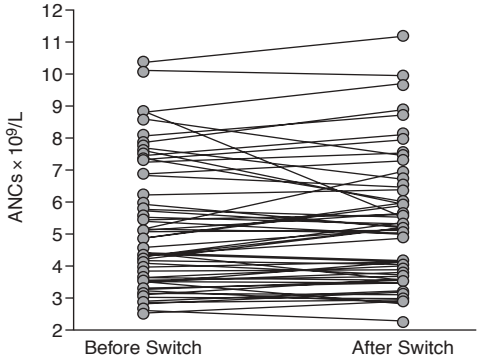
Abbreviations: ANCs = absolute neutrophil counts, WBCs = white blood [cell] counts.

Figure 2. White Blood Cell Counts for Each Patient in the 6 Months Before Switch and in the 6 Months After Switch



Abbreviation: WBCs = white blood [cell] counts.

Figure 3. Absolute Neutrophil Counts for Each Patient in the 6 Months Before Switch and in the 6 Months After Switch



Abbreviation: ANCs = absolute neutrophil counts.

Emergency Room Visits

Three emergency room (ER) visits were recorded within the 6 months following the switch to generic clozapine (Patient #26, #28 and #90), compared with the 7 ER visits reported in the preswitch period. Two patients (Patient #26 and #28) who presented in the ER within the 6 months after the clozapine switch had complaints probably unrelated to antipsychotic therapy: infections and pain (in the scrotal area and in the leg, respectively). They were treated with antibiotics and analgesic medications. In neither case was clozapine therapy adjusted or comments regarding psychiatric symptoms recorded. In the third case, the patient (Patient #90) was treated in the ER for a cut that required sutures, secondary to a fall resulting from a seizure. This patient had a diagnosis of epilepsy and had been taking a relatively high dose of clozapine (650 mg/day) since January 2000. The patient had been also receiving valproic acid, citalopram, clonazepam, and topiramate. His clozapine dose had been increased to 700 mg/day about 3 months before the interchangeability switch, and at the same time his citalopram dose was increased from 10 mg to 20 mg/day. The patient admitted to smoking 2 packs of cigarettes a day. There was no specific information regarding any changes in his smoking pattern recorded after the time of the switch.

Adverse Events

The most frequent adverse events reported both before and after the switch were nocturnal drooling/hypersalivation, drowsiness/sedation, tremors/muscle spasms, and fall in WBCs/ANCs. No significant changes in the most frequently reported adverse events were noted in the 6 months following the switching of patients from brand-name to generic clozapine (Table 4). In 40 (69%) of the patients, there were no reports of adverse events after the clozapine switch.

Hematologic Monitoring

Information regarding blood testing was also collected as part of this study. The values of WBCs and ANCs in the 6-month period before the switch were compared with the values recorded for each patient in the 6-month post-switch period. No statistically significant differences were detected in the respective means ± SDs of WBCs and ANCs recorded before (WBC: $7.73 \pm 2.42 \times 10^9$/L; ANC: $5.08 \pm 1.95 \times 10^9$/L) and after (WBC: $7.85 \pm 2.63 \times 10^9$/L; ANC: $5.20 \pm 2.00 \times 10^9$/L) the switch to generic clozapine (Figure 2 and Figure 3).

No patient received a "nonrechallengeable" status, and no discontinuations of clozapine therapy for any reason (toxicity or treatment failure) were recorded within the 6 months after the switch of this patient population to generic clozapine.

DISCUSSION

Clozapine pharmacokinetics are characterized by considerable variability between individuals and can be affected by a variety of factors beside changes in formulation. Clozapine is metabolized primarily by the cytochrome P450 (CYP) hepatic isozymes CYP1A2 and CYP3A4, whose activity can be inhibited by a number of agents (e.g., selective serotonin reuptake inhibitors, valproic acid, caffeine) or induced by other agents (e.g., cigarette smoking, omeprazole). Clozapine plasma levels can increase in patients by 50% following a 5-day caffeine-free period. In addition, sudden smoking cessation can cause a significant elevation of clozapine plasma concentrations, leading to an increase in adverse events.[1]

A limitation of the current study is that data regarding factors that could have affected clozapine kinetics, particularly smoking habits, were not consistently available for this population. Eighteen patients were identified as definite smokers. However, it was not possible to determine from the patient charts whether or not anyone was in the process of quitting smoking during the time of the study. Furthermore, monitoring of clozapine levels was not conducted routinely in this patient population, and serum concentrations of clozapine were recorded only sporadically in the charts; as a consequence, it was not possible to document any consistent pattern of changes in clozapine serum levels. Nevertheless, this naturalistic investigation, which was based on the evaluation of objective measurements such as dose changes, number of clinic visits and hospitalization rates, did not identify any trend toward a reduced efficacy of clozapine therapy or an increased toxicity that could be attributed to the interchangeability switch.

Dose adjustments are commonly made in the pharmacologic treatment of psychiatric patients, but significant changes in clozapine dosages, together with the clinical assessment of patient response, represent an important indicator of formulation differences in the evaluation of interchangeability.[12] Clinical data were collected for each patient up to 6 months after the switch in order to capture all possible changes in patient response to therapy. Another naturalistic study of a clozapine interchangeability switch was conducted in an outpatient population in the United States: data were collected between 2 and 4 months after the switch, and, in this case as well, no deterioration of clinical status was noted.[14] It is accepted that symptoms of decompensation occurring after more than 8 weeks are unlikely to be attributable to bioequivalence problems with formulations.[10]

Because of the retrospective design of the study, the completeness of data addressing hospitalization and emergency room visits was difficult to ascertain. Nevertheless, it is unlikely that a significant increase in the postswitch rates of health care use, including physician's/therapist's visits, would have gone undetected in this patient population, and care was taken to record any additional information that was relevant to the evaluation of the switch, including substance abuse and compliance patterns. These data were extracted from the physician's/therapist's notes and the prescription renewals. Substance abuse was reported sporadically in this patient population and was not highly prevalent; interestingly, the only patient who received a dose increase in his clozapine regimen within the 2 months after the switch exhibited a history of multiple-substance abuse. Compliance with clozapine treatment can be easily determined on the basis of the 2-week prescription renewals that follow the mandatory blood test reports. However, it is challenging to ascertain whether the medication is actually taken as prescribed. In this study, it was noted that noncompliance, by patients' own admission, was the primary cause of decompensation symptoms and hospitalization (2 cases).

The exact mechanism of clozapine-induced agranulocytosis is unknown. This potentially life-threatening event, with an incidence of 0.8% and an average time to onset of 6 weeks after the initiation of clozapine therapy, is regarded as an idiosyncratic reaction. Genetic determinants appear to play an important etiologic role and are being extensively investigated.[15,16]

Because agranulocytosis is not dose-dependent, changes in WBCs/ANCs would not be expected to correlate with a change in clozapine formulation, even if there were differences in bioavailability between the formulations.[11] The results of this study did not reveal any significant change in patients' hematologic status and are consistent with previously reported findings.[11] Other adverse events reported were minor and typical of patients treated with clozapine. No trend was observed toward any increase in toxicity after the switch. Because of the frequency of patient monitoring, even transient symptoms would have been detected and recorded in the charts if deemed clinically significant.

In conclusion, the results of this fully independent study indicate that, for this Canadian outpatient population, the conversion from brand-name clozapine to the first generic alternative available on the Canadian market was not associated with any significant changes in treatment. No evidence of psychiatric decompensation or relapse that could be directly attributed to the switch from brand-name to generic clozapine was identified in this population. In addition, the change in formulation could not be linked to any significant increase in the incidence of adverse events.

According to a recent economic evaluation,[17] the projected savings associated with the switch to the generic product are estimated to be approximately 1241 Canadian dollars (or approximately 1045 U.S. dollars) per patient annually.

Since 2003, additional generic versions of clozapine have received Notice of Compliance from the Therapeutic

Products Directorate and have become available on the Canadian market. Individual provinces are making independent decisions regarding their formulary listings. It is hoped that the study reported here will be of assistance to clinicians, patients, and drug benefit payers considering the various formulations of clozapine.

Drug names: benztropine (Cogentin and others), bupropion (Wellbutrin and others), chlorpromazine (Thorazine, Sonazine, and others), citalopram (Celexa and others), clonazepam (Klonopin and others), clozapine (FazaClo, Clozaril, and others), enalapril (Vasotec and others), fluoxetine (Prozac and others), glyburide (Diabeta, Micronase, and others), lorazepam (Ativan and others), metformin (Riomet, Fortamet, and others), olanzapine (Zyprexa), omeprazole (Prilosec and others), paroxetine (Paxil, Pexeva, and others), pimozide (Orap), procyclidine (Kemadrin), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), topiramate (Topamax), trazodone (Desyrel and others), valproic acid (Depakene and others), zopiclone (Lunesta).

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