Underprescribing of Clozapine and Unexplained Variation in Use across Hospitals and Regions in the Canadian Province of Québec

Eric Latimer [1,2], Willy Wynant [2], Robin Clark [3], Ashok Malla [1,2], Erica Moodie [1], Robyn Tamblyn [1], Adonia Naidu [1]

Abstract

Background: Clozapine remains the antipsychotic of choice for people who, having met the criteria for a diagnosis of schizophrenia or a related psychotic disorder, do not respond adequately to other antipsychotic medications. Utilization rates appear highly variable across jurisdictions, with an overall tendency toward underuse. This paper describes patterns of clozapine use in the province of Québec, Canada. **Methods:** Individuals with a diagnosis of schizophrenia were identified using linked government medical claims and hospitalization records for 2003 and 2004. Linked data on their filled prescriptions in 2004 were then used to determine clozapine-use rates at the level of the province, the region, and the hospital at which individuals received most of their services. Individual predictors of clozapine use were identified using logistic regression. **Results:** Only 6.7% of the 29,155 individuals identified with schizophrenia received clozapine for six months or longer in 2004. Utilization rates ranged from 3.9 to 9.0% among regions with 1,000 or more people with schizophrenia. Over 8% of 61 hospitals did not prescribe clozapine at all. People with schizophrenia taking clozapine experienced 3.4 fewer days of hospitalization per year than those not taking clozapine—representing a cost offset of about $1,800 per year. Medication costs were higher, however, by about $3,000 per year. **Conclusions:** Given the increasingly clear benefits of clozapine for people who do not respond to other antipsychotics, measures to increase access to clozapine for people who can benefit from it are likely to be cost effective and are urgently needed.

Key Words: Antipsychotics, Clozapine, Epidemiology, Evidence-Based Treatment, Schizophrenia

Introduction

About one-fifth to one-third of people who meet the criteria for a diagnosis of schizophrenia respond poorly to first-line antipsychotic therapy (1, 2), with a commonly accepted estimate of 30% (3, 4). Recent guidelines continue to recommend a trial with clozapine for people who have not responded to trials of two other antipsychotics (5), as its benefits for people with medication-resistant schizophrenia, even in comparison with other second-generation antipsychotics, have been confirmed in recent trials (6, 7). Clozapine monotherapy of adequate dosage and duration has proven effective for one- to two-thirds of people with medication-resistant schizophrenia (8). Clozapine has also been associated with a significant reduction in the rate of suicide (9, 10) and in hospitalizations (11, 12), the latter making it a cost savings in some settings (13). It has a number of side effects, however, most significantly metabolic side effects (14). Less than 1% of patients develop potentially fatal agranulocytosis, the risk of which must be managed by means of systematic blood testing (15). In part for this reason, not all treatment-resistant patients are willing to take clozapine (16). The uncertainty surrounding many of these

[1]McGill University, Montreal, Canada
[2]Douglas Institute, Montreal, Canada
[3]Center for Health Policy and Research, University of Massachusetts Medical School, Shrewsbury, MA

Address for correspondence: Eric Latimer, PhD, Douglas Institute, Perry 3C, 6875 LaSalle Blvd., Verdun, QC H4H 1R3
Phone: 514-761-6131, x2351; Fax: 514-762-3049;
E-mail: eric.latimer@mcgill.ca

Submitted: January 12, 2011; Revised: May 2, 2011;
Accepted: May 13, 2011

Clinical Implications

Given the increasingly clear benefits of clozapine for people who do not respond to other antipsychotics, measures to increase access to clozapine for people who can benefit from it are likely to be cost effective and are urgently needed. The implementation of three complementary measures could increase appropriate prescribing of clozapine. First, clozapine clinics could be established within each psychiatry department together with, at the provincial level, a clozapine resource center similar to one that used to exist in British Columbia and that supplemented the monitoring established at the national level by the Clozapine Support and Assistance Network (CSAN) (34). The local clozapine clinic would require that granulocyte counts of all patients prescribed clozapine were tested according to a prescribed schedule, and that the results were sent back both to the physician and to the provincial clozapine resource center. The provincial center would alert physicians to low or abnormal values. Experience with such a center in British Columbia, initially funded by the provincial government but later dismantled ostensibly for cost reasons, indicates that prescribers often contacted it for help in interpreting test results (34). A centralized facility also would help ensure that more subtle factors, such as the tendency toward benign neutropenia of people of African descent, are taken into account in interpreting trends in granulocyte counts (2). Second, ensuring that all people with schizophrenia who are unstable have access to Assertive Community Treatment (ACT) or Intensive Case Management (ICM) teams could facilitate continued engagement in treatment (35). Third, physician education, audit and feedback mechanisms could be implemented to help motivate physicians to use clozapine when indicated, although more research is needed on how to make these maximally effective (36).

proportions makes it difficult to know the overall proportion of people with schizophrenia one would expect to see on clozapine in an optimal treatment system (16).

Accordingly, rates of clozapine prescribing are highly variable. Rates as high as 25 to 60% have been documented in China, while among U.S. Veterans Administration patients with schizophrenia in New York the percentage being treated with clozapine alone at the end of the 90s has been reported to be 1% (17). Rates between 10 and 25% have been documented in Victoria, Australia and Maryland, U.S. (18), and Auckland, New Zealand (19). A sixteen-fold variation in clozapine-use rates has been reported in the Greater Manchester area (20).

Such variations may be partly explained by differences in patient characteristics. Patients who are younger, male and (in the U.S. at least) white are more likely to be administered clozapine (2, 21). The very wide variations observed across treatment systems, however, whether one considers differences across countries or across small geographic areas, suggest that factors unrelated to patient characteristics play a large role.

Studies of clinical charts suggest that clozapine is often not prescribed to people for whom it appears appropriate (16, 22). The combination of variability in use and a tendency toward underprescribing must be a source of concern given evidence that clozapine is the most effective drug currently available for patients with treatment-refractory schizophrenia.

The province of Québec, Canada, offers a useful setting in which to observe both the overall level of clozapine use for people with schizophrenia, and the extent to which clozapine prescribing varies across small areas for reasons not related to differences in patient characteristics. In 2004, the year for which data were analyzed, virtually all people with schizophrenia in Québec had medication coverage under a public plan. Irrespective of the plan people were insured under, physicians had no direct financial incentive to prescribe one drug or another—their remuneration was and remains unaffected by the medications they prescribe. Moreover, psychiatric care was and remains sectorized, which means that even patients with more severe schizophrenia are not normally transferred from one psychiatry department to another. Differences in utilization rates across regions or hospitals should, therefore, be due largely to differences in physician prescribing preferences rather than in patient case mix.

This paper aims, accordingly, to describe patterns of clozapine use in patients with schizophrenia and to examine to what extent they are likely attributable to unexplained differences in physicians' prescribing preferences. In order to determine whether the use of clozapine might be cost effective in Québec as it has been reported to be in other jurisdictions, we also compared days hospitalized between patients taking clozapine and those not taking clozapine, and the overall costs of antipsychotic use.

Methods

Analytic Population

All individuals in the province of Québec, Canada (population in 2004: 7.7 million) who filled at least one prescription for an antipsychotic medication while covered by a public plan, in 2003 or 2004, were identified from the province's central administrative database for pharmaceuticals (maintained by Québec's Health Insurance Board, known by its French acronym RAMQ). Their pharmaceu-

tical data were linked with hospitalization records (provincial Med-Echo database, which contains detailed records of each hospitalization in the province of Québec), as well as with medical claims (database held by the RAMQ, which records almost all medical services provided in the province). This procedure yielded 29,622 individuals who were at least 18-years-old in 2004, who were alive at the end of 2004, and who were given a diagnosis of schizophrenia (*ICD-9* codes 295.0–295.9) on either a physician claim or a hospitalization record during 2003 or 2004. Among these 29,622 individuals, 467 were eliminated following data cleaning procedures (checks on prescription duration and consistency between cost, quantity and duration fields on prescription records), leaving 29,155 individuals in the analysis. These represented 0.4% of the Québec population.

Patient Demographics

Patient demographic data including sex, date of birth and administrative region of residence were obtained from a linked patient characteristics dataset. Age in 2004 was represented using a set of categorical variables (18–29, 30–39, 40–49, 50–64 and 65+). Québec is organized into seventeen administrative regions, each with a different health authority. The region in which each patient lived was identified; regions were classified as rural, semi-rural or urban.

Physician Specialty

Prescription data include a physician identifier. The specialty of the prescribing physician was obtained from a linked RAMQ database. A total of 6,348 physicians prescribed antipsychotic medications to patients in the dataset.

Clozapine Use

A patient was identified as using clozapine if: 1) they filled consecutive prescriptions for clozapine for a period of at least six months during 2004 (allowing interruptions for hospitalizations); and, 2) had no more than ten days without a clozapine prescription during the six-month period. (Shorter durations of clozapine use were expected to reflect trials of clozapine, rather than continuous use.)

Linking Of Physicians and Patients to Hospitals

Clozapine prescribing requires regular blood monitoring and in Québec this would normally be carried out in connection with a hospital outpatient clinic—the hospital outpatient clinic corresponding to that patient's geographic sector. Because of the blood monitoring required, physicians who prescribe clozapine usually are specialists who are associated with one or more hospitals. In order to be able to determine the hospital(s) at which physicians normally practice, each patient hospitalization record with a principal psychiatric diagnosis (*ICD-9* codes 290.X–319.X: psychoses, neurotic disorders, and other nonpsychotic mental disorders) was linked to a physician if that particular patient was identified as having a *single* prescribing physician based on patient psychotropic prescription data. A physician was considered to normally practice at a particular hospital if 80% or more of his or her patients' hospitalizations occurred at that hospital. Patients who did not have any hospitalization record during 2004, but whose antipsychotics were prescribed by a single physician, were assigned to their prescribing physician's hospital if that physician had been assigned to a hospital. If they had more than one prescribing physician, they were assigned to a hospital if all of those prescribing physicians were assigned to the same hospital. Thus, some physicians whose patients had no hospitalizations, or hospitalizations not concentrated in a particular hospital, were not associated with any particular hospital; and, as a result, their patients could not be considered to have been treated at a particular hospital either.

Grouping of Hospitals by Size

Hospitals were grouped into small, medium and large size categories. Size was based on the number of physicians who prescribe antipsychotic medications to patients with schizophrenia within a particular hospital. Based on the distribution of the number of such physicians at each hospital, small hospitals were defined as having 1–5 physicians, medium hospitals 6–10 physicians and large hospitals 11 or more physicians.

Classification of Hospitals by Urbanicity

Due to confidentiality restrictions, we could only know the administrative region hospitals were located in, not their specific identity. Hospitals were classified as urban if they were in Montreal, Québec City, Laval (a northern suburb of Montreal) or Montérégie (most hospitals in the Montérégie region are located in the Greater Montreal area).

Data Analysis

The overall rate of clozapine use was calculated for the entire population, and values of other variables were compared between the entire population and the sub-group of patients that were linked to a hospital. Rates of clozapine use were then calculated by region, and by hospital for patients for whom a hospital could be assigned. Overall rates of clozapine use, as well as the percentage of physicians identified as prescribers of antipsychotics who prescribe clozapine, were reported by hospital size. We calculated the Pearson correlation between the percentage of physicians who prescribe clozapine and the percentage of patients who take clo-

zapine. We used logistic regression to identify patient, hospital and physician variables associated with patient use or non-use of clozapine. Finally, we compared hospitalization days in 2004 between patients on clozapine who had only one physician prescriber, and those not on clozapine who also had only one physician prescriber; we also calculated total costs of antipsychotic medications in 2004 for patients taking clozapine, patients not taking clozapine, and patients taking second-generation antipsychotics other than clozapine.

Data analyses were carried out using Stata version 9.0. Ethics approval was obtained from the Douglas Institute Research Ethics Board.

Results

Overall Clozapine-Use Rates

Table 1 provides comparative statistics for the population of patients we identified as having schizophrenia, and for the subset who could be assigned to a hospital. The age and sex distributions in the subset are similar to those in the entire population, although patients included in the subset tend to be slightly younger. A significantly greater proportion of patients in the subset saw at least one psychiatrist in 2004. Overall use rate for clozapine among patients with schizophrenia we identified was 6.7%, a bit less than the 8.2% calculated for those in the subset of patients that we could assign to a hospital.

Table 1 Descriptive Statistics

	All Patients (N=29,155) %	Patients Assigned to a Hospital (N=18,367) %
Patient Age		
18–30	15.0	16.6
30–39	16.8	17.8
40–49	27.1	27.8
50–64	26.5	26.2
65+	14.6	11.6
Male	56.0	57.1
At Least One Psychiatrist	67.7	86.9
Clozapine Use	6.7	8.2
Hospital		
Small		8.0
Medium		32.0
Large		60.0
Urban		69.4

Clozapine-Use Rates by Hospital, Region and Hospital Size

Of the 6,348 physicians who prescribed an antipsychotic one or more times in 2004, fewer than 10% (601) could be linked to a single or principal hospital. A total of 18,367 patients (63% of the total) were assigned a hospital. Among patients who could be associated with a hospital through their physician or physicians, 60% were seen at a hospital that had more than 10 physicians who prescribed antipsychotics to patients with schizophrenia. In contrast, 10% were seen at hospitals that had five or fewer such physicians.

Figure 1 shows how hospitals are distributed according to the percentage of patients associated with them who are taking clozapine on an outpatient basis. As may be seen, this percentage varies greatly across hospitals, ranging from nearly 22% to 0, the latter in more than 8% of hospitals.

Table 2 shows the percentage of patients with schizophrenia who were taking clozapine by region, as well as the distribution of specialties of the prescribing physicians by region. Clozapine-use rates vary almost threefold across regions, ranging from 3.9 to 10.8%, with the largest region—Montreal—exhibiting a rate of 7.2%, slightly above the provincial average of 6.7%.

Table 3 shows clozapine-use rates, as well as the percentage of physicians who prescribe clozapine among physicians who prescribe antipsychotics to patients with schizophrenia, by hospital size. The average percentage of patients taking clozapine tends to increase with hospital size. The percentage of physicians prescribing clozapine is greater on average among larger hospitals than among small and medium-sized hospitals. Nonetheless, the variation by hospital size is much smaller than the variation across individual hospitals or even across regions. Table 3 also reports the correlation between the proportion of physicians who prescribe clozapine in a hospital and the proportion of patients who take clozapine in that hospital. This correlation is large overall (0.59), especially among smaller hospitals (0.76).

Predictors of Clozapine-Use Rates

Table 4A shows parameter estimates from a logistic regression of being on clozapine or not, on patient-level and hospital-level predictors, for people who could be linked to a hospital, while Table 4B does the same using the entire population under study and, thus, without hospital-level predictors. Compared to patients below age 30, those between 30 and 49 are significantly more likely to be receiving clozapine, whereas those above 65 are significantly less likely. Males are more likely to be receiving clozapine. People seen in medium-sized and large hospitals are more likely to receive clozapine; only if hospital size is not controlled for, being seen by a psychiatrist is strongly associated with being on clozapine.

Figure 1 Use of Clozapine by Hospital (N=61 hospitals)

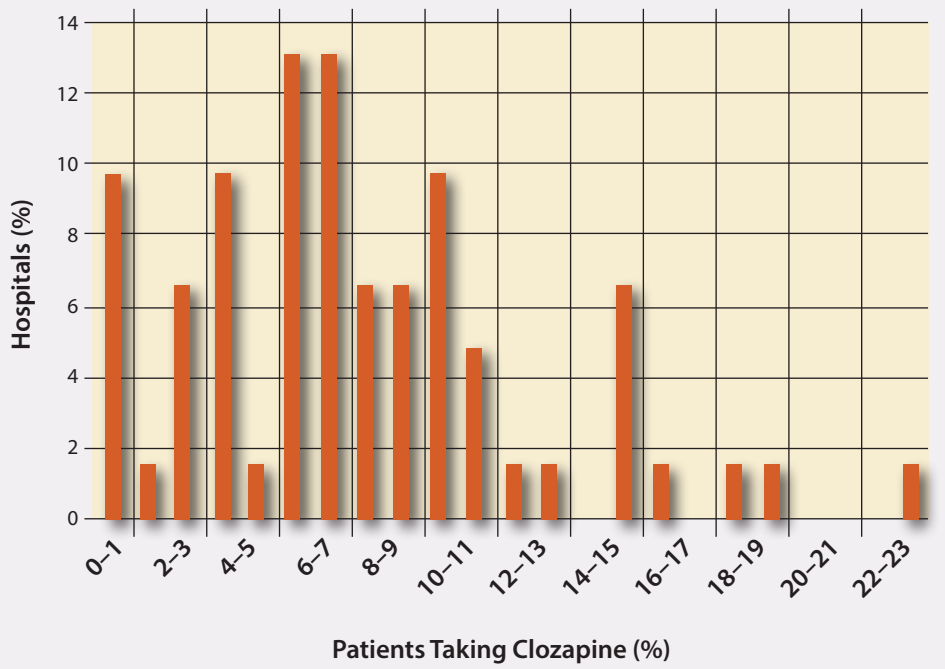

Table 2 Regional Differences in Clozapine Prescribing (N=29,155)

Region*	Patients with Schizophrenia (N)	Percent Taking Clozapine	GP Prescriber Only (%)	Psychiatrist Prescriber Only (%)	Other Prescriber(s)† (%)
A	1,952	3.9	59.2	31.6	9.2
B	1,178	4.1	8.3	70.8	20.9
C	340	5.0	11.8	70.6	17.6
D	2,637	5.1	4.4	63.0	32.6
E	893	5.8	38.5	23.1	38.4
F	1,286	6.7	48.8	26.7	24.5
G	368	6.8	4.0	80.0	16.0
H	1,010	7.0	7.0	64.8	28.2
I	3,919	7.1	2.9	77.7	19.4
J	964	7.1	16.2	58.8	25.0
K	12,185	7.2	5.4	75.0	19.6
L	905	8.6	0	75.6	24.4
M	1,261	9.0	8.8	60.2	31.0
N	231	10.8	44.0	32.0	24.0

*Three regions with 20 or less patients were excluded; †both a GP and psychiatrist may have prescribed clozapine during 2004, or else the drug may have been prescribed by another specialist.

Table 3 Hospital Level Analyses (N=18,367)

Hospital Size*	Average Number of Patients with Schizophrenia	Proportion of Patients Taking Clozapine (A)†	Proportion of Physicians Prescribing Clozapine (B)†	Correlation between A and B
Small (N=18)	81	0.06	0.58	0.76
Medium (N=25)	235	0.07	0.56	0.25
Large (N=18)	613	0.09	0.66	0.44
Overall	301	0.07	0.60	0.59

*Small hospitals have 1 to 5 physicians prescribing antipsychotics to people with schizophrenia, medium 6 to 10 and large 11 or more; †average proportion across hospitals by size.

Hospital-Utilization Rates and Medication Costs Associated with Clozapine Use

Finally, we calculated that 1,788 patients on clozapine who had one physician prescriber experienced an average of 7.87 days hospitalized in 2004 (standard deviation [SD]=23.44), compared to 11.24 (SD=32.04) for 24,123 patients not on clozapine who also had a single physician prescriber. Considering all patients in our analyses, patients on clozapine incurred $6,928 (SD: $3,312) in antipsychotic drug costs, compared to $2,276 (SD: $2,519) for all those not on clozapine, and $2,641 (SD: $2,448) for those on atypical antipsychotics other than clozapine.

Discussion

Our findings extend several previous results concerning patterns of use of clozapine and provide further evidence of the need for policies that ensure access to clozapine for people who have treatment-resistant schizophrenia.

The estimate of the overall clozapine utilization rate in the Canadian province of Québec, 6.7%, appears relatively low in comparison with most other estimates reported in the literature and much below expectation if treatment guidelines were followed. As indicated in the introduction, such estimates range widely, but most exceed 10%. A U.K. modeling exercise designed to estimate the number of suicides that would be averted and the value of the resources that would be freed if clozapine were used optimally in that country set 12% as a benchmark for optimal use (4).

The most telling indication that 6.7% is an unduly low rate is the wide variation across regions and, even more, across hospitals in the percentage of people with schizophrenia taking clozapine. Even among regions with 1,000 or more schizophrenia patients, the rate of clozapine prescribing varies more than twofold: from 3.9 to 9%. Among patients we could associate with a particular hospital, in the case of nearly one hospital out of 9, less than 2% of patients with schizophrenia were being administered clozapine. At the other extreme, for 13% of hospitals, more than 13% were being administered clozapine.

Possible differences in patient characteristics cannot account for such variation across hospitals and across regions. Our analysis does confirm, consistent with previous studies, that male patients and patients aged 30 to 49 are more likely to receive clozapine than female patients and those younger than 30. Patients older than 65, as one would expect given the effects of clozapine on the elderly, are much less likely to receive clozapine than younger patients. But neither the sex nor even the age distribution could vary enough across hospital sectors or regions to account for the large variation in clozapine-use rates that we have observed. More importantly, sectorization of care in Québec implies that there is little movement of patients with schizophrenia from one hospital to another in order to receive care from a different hospital. The main circumstance where this can occur is when someone has been declared not criminally responsible on account of mental disorder and sent to a designated hospital other than the one they were initially seen at—a relatively uncommon occurrence.

The data suggest, rather, what anecdotal information from psychiatrists in Québec also indicates: hospital psychiatry departments in Québec are marked by a "clozapine culture." In some, the culture is to not use clozapine at all; in some others, to use it frequently. Indeed, data in Table 3 confirm, not surprisingly, that clozapine prescribing is higher where a greater proportion of those psychiatrists who prescribe antipsychotics also prescribe clozapine. It is another

Table 4A Predictors of Clozapine Use among People Linked to a Hospital (N=18,367)

Predictors of Being on Clozapine	Odds Ratio	Std Err	Z	P>|Z|	95% CI	Test for Trend
Patient Age*						
30–39	1.28	0.11	2.83	0.01	1.08, 1.52	
40–49	1.28	0.1	3.06	0	1.09, 1.50	
50–64	0.88	0.08	-1.4	0.16	0.75, 1.05	
65+	0.25	0.04	-8.24	0	0.18, 0.35	p<0.01
Male Patient	1.24	0.07	3.74	0	1.11, 1.39	
Psychiatrist	1.06	0.09	0.76	0.45	0.91, 1.25	
Urban Hospital	0.95	0.06	-0.75	0.45	0.85, 1.08	
Hospital Size						
Medium	1.36	0.18	2.35	0.02	1.05, 1.75	
Large	1.76	0.22	4.6	0	1.38, 2.24	p<0.01

Goodness of Fit: Pearson χ^2=162.7; p=0.0007

Table 4B Predictors of Clozapine Use, Complete Sample (N=29,155)

Predictors of Being on Clozapine	Odds Ratio	Std Err	Z	P>|Z|	95% CI	Test for Trend
Patient Age*						
30–39	1.24	0.1	2.81	0.01	1.07, 1.44	
40–49	1.22	0.09	2.83	0.01	1.06, 1.40	
50–64	0.81	0.06	-2.78	0.01	0.69, 0.94	
65+	0.26	0.03	-10.1	0	0.20, 0.33	p<0.01
Male Patient	1.2	0.06	3.7	0	1.09, 1.33	
Psychiatrist	1.89	0.11	10.68	0	1.68, 2.12	

Goodness of Fit: Pearson χ^2=20.04; p=0.0943. *In both tables, age 18–29 represents the reference category.

instance of small-area variation in medical practice, a ubiquitous phenomenon in medical care (23).

The lifetime suicide rate for people with schizophrenia has been estimated in a meta-analysis at 5.6%, with suicide tending to occur in the early years of illness (24). Being on clozapine has been estimated to reduce the risk of suicide by about 59% (25), compared to not being on it, thus to about 3.3%. If we use the conservative estimate from our data of 29,155 people with schizophrenia in the province of Québec, and assume that rates of clozapine use were to double to 13.4%, then the number of suicides over the lifetimes of the group newly placed on clozapine (n=1,953) could be reduced from about 109 to about 64—a difference of 45.

Clozapine has also been found to reduce hostility in people who exhibit persistent violent behavior (5, 26), to reduce the desire for substance use (27), and to benefit people with refractory mood disorders (28, 29). Further still, a large recent cohort study from Finland reports that clozapine, in spite of its metabolic and other side effects, is associated with lower all-cause mortality than other antipsychotics (30)—the only drug to exhibit a significantly lower mortality (-26%) than the authors' reference drug, perphenazine. Although this finding, derived from an observational study, is subject to some biases (31), it is consistent with the well-established result concerning suicide and suggests that the metabolic side effects of clozapine have limited impact on mortality. Finally, time to discontinuation tends to be longer for clozapine than other antipsychotics (7, 32), and, relatedly, treatment adherence (both persistence in refilling prescriptions as intended, and compliance with the prescribed

dosage and schedule) tends to be higher (33).

The optimal rate of prescribing clozapine is, therefore, likely to be relatively high, much higher than that observed in Québec. If other studies confirm lower all-cause mortality associated with the use of clozapine, it may even be arguably appropriate to prescribe it as a first-line treatment (30), at least in circumstances that remain to be determined.

The tendency to underprescribe clozapine undoubtedly arises in large part from the risk of agranulocytosis and the associated need for systematic blood monitoring. Prescribers who perceive poor access to a convenient and reliable mechanism for blood monitoring of clozapine patients may understandably be reluctant to initiate clozapine treatment.

The implementation of three complementary measures could increase appropriate prescribing of clozapine. First, clozapine clinics could be established within each psychiatry department together with, at the provincial level, a clozapine resource center similar to one that used to exist in British Columbia and that supplemented the monitoring established at the national level by the Clozapine Support and Assistance Network (CSAN) (34). The local clozapine clinic would require that granulocyte counts of all patients prescribed clozapine were tested according to a prescribed schedule, and that the results were sent back both to the physician and to the provincial clozapine resource center. The provincial center would alert physicians to low or abnormal values. Experience with such a center in British Columbia, initially funded by the provincial government but later dismantled ostensibly for cost reasons, indicates that prescribers often contacted it for help in interpreting test results (34). A centralized facility also would help ensure that more subtle factors, such as the tendency toward benign neutropenia of people of African descent, are taken into account in interpreting trends in granulocyte counts (2). Second, ensuring that all people with schizophrenia who are unstable have access to Assertive Community Treatment (ACT) or Intensive Case Management (ICM) teams could facilitate continued engagement in treatment (35). Third, physician education, audit and feedback mechanisms could be implemented to help motivate physicians to use clozapine when indicated, although more research is needed on how to make these maximally effective (36).

Would the implementation of such a set of measures be cost effective? Consistent with the literature, we found that people with schizophrenia who take clozapine spent 3.4 fewer days in the hospital than people who do not—a conservative estimate given that our comparison was with all people with schizophrenia, not just those who might have been prescribed clozapine. We also found, however, that people who received clozapine had much higher average costs of antipsychotics, by about $4,300 compared to people on second-generation antipsychotics other than clozapine. Although this figure is likely biased by the fact that the population of people with schizophrenia not on clozapine differs from the subgroup not on clozapine, but for whom clozapine prescribing would be appropriate, it is plausible that the monitoring of clozapine patients would increase treatment adherence and, thus, medication costs. (Results not shown indicate that including all psychotropic drugs in the comparisons merely increases all amounts by about $350 and, thus, has no material effect on the cost differences.) Since 2004, clozapine has become generic and its cost is now reduced by about 30%—so that the cost difference today would likely be about $3,000 (instead of $4,300). In addition, however, higher treatment adherence with clozapine is likely associated with increased monitoring visits and clinician contacts, the costs of which we are not able to estimate. The estimate of a reduction of 3.4 days in hospital days is also most likely conservative; however, as the refractory patients for whom clozapine prescribing might be indicated, but who are not on clozapine, likely have more hospital days than the average schizophrenia patient not on clozapine. Be that as it may, 3.4 days represents about $1,800 per year in Québec (37), which would only partly offset the extra cost of medications. A modeling study that would also take into account reductions in suicide rates, increases in quality of life, and potential increases in economic productivity (for people with schizophrenia and their families) would be required to assess the cost effectiveness of clozapine in our setting in a comprehensive way. Even given our finding that clozapine increases medication costs, the results by Duggan et al. (4) suggest that a comprehensive modeling study would conclude that clozapine is cost effective.

Our analysis presents two significant limitations. First, we may not have captured all individuals with schizophrenia, as many individuals who meet the criteria for schizophrenia may have neither been hospitalized in 2003 or 2004, nor have had that diagnosis recorded on a medical claim (recording of diagnosis on medical claims in Québec does not affect physician billing and is not always made). However, we have certainly detected all individuals on clozapine, so our estimated rates of clozapine use may in fact be overestimated. Second, we were able to assign to a single hospital fewer than 10% of physicians who prescribed antipsychotics one or more times in 2004, although these accounted for 63% of patients. This will affect our results at the hospital level, and our classification by hospital size.

In conclusion, our findings highlight the need for the establishment of specific mechanisms to increase the rate of use of clozapine in the province of Québec. Given that there are no particular restrictions on clozapine use in that province, our finding also suggests the need to measure use levels in other mental health treatment systems as well.

Acknowledgments

We thank, in particular, the Régie de l'Assurance-Maladie du Québec (Québec Health Insurance Board) for providing data.

Funding

This project was funded by a grant from the Fonds de la recherche en santé du Québec (Québec Health Research Fund) (grant 6659).

References

1. Conley RR, Kelly DL. Management of treatment resistance in schizophrenia. Biol Psychiatry 2001;50(11):898-911.
2. Kelly DL, Kreyenbuhl J, Dixon L, Love RC, Medoff D, Conley RR. Clozapine underutilization and discontinuation in African Americans due to leucopenia. Schizophr Bull 2007;33(5):1221-1224.
3. Meltzer HY. Treatment-resistant schizophrenia--the role of clozapine. Curr Med Res Opin 1997;14(1):1-20.
4. Duggan A, Warner J, Knapp M, Kerwin R. Modelling the impact of clozapine on suicide in patients with treatment-resistant schizophrenia in the UK. Br J Psychiatry 2003;182:505-508.
5. Buchanan RW, Kreyenbuhl J, Kelly DL, Noel JM, Boggs DL, Fischer BA, et al.; Schizophrenia Patient Outcomes Research Team (PORT). The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. Schizophr Bull 2010;36(1):71-93.
6. Lewis SW, Barnes TR, Davies L, Murray RM, Dunn G, Hayhurst KP, et al. Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. Schizophr Bull 2006;32(4):715-723.
7. McEvoy JP, Lieberman JA, Stroup TS, Davis SM, Meltzer HY, Rosenheck RA, et al.; CATIE Investigators. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. Am J Psychiatry 2006;163(4):600-610.
8. Chakos M, Lieberman J, Hoffman E, Bradford D, Sheitman B. Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. Am J Psychiatry 2001;158(4):518-526.
9. Munro J, O'Sullivan D, Andrews C, Arana A, Mortimer A, Kerwin R. Active monitoring of 12,760 clozapine recipients in the UK and Ireland. Beyond pharmacovigilance. Br J Psychiatry 1999;175:576-580.
10. Meltzer HY, Alphs L, Green AI, Altamura AC, Anand R, Bertoldi A, et al.; International Suicide Prevention Trial Study Group. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). Arch Gen Psychiatry 2003;60(1):82-91.
11. Rosenheck R, Cramer J, Xu W, Thomas J, Henderson W, Frisman L, et al. A comparison of clozapine and haloperidol in hospitalized patients with refractory schizophrenia. Department of Veterans Affairs Cooperative Study Group on Clozapine in Refractory Schizophrenia. N Engl J Med 1997;337(12):809-815.
12. Hayhurst KP, Brown P, Lewis SW. The cost-effectiveness of clozapine: a controlled, population-based, mirror-image study. J Psychopharmacol 2002;16(2):169-175.
13. Aitchison KJ, Kerwin RW. Cost-effectiveness of clozapine. A UK clinic-based study. Br J Psychiatry 1997;171:125-130.
14. Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Lobos CA, et al. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. Schizophr Res 2010;123(2-3):225-233.
15. Alvir JM, Lieberman JA, Safferman AZ, Schwimmer JL, Schaaf JA. Clozapine-induced agranulocytosis. Incidence and risk factors in the United States. N Engl J Med 1993;329(3):162-167.
16. Mortimer AM, Singh P, Shepherd CJ, Puthiryackal J. Clozapine for treatment-resistant schizophrenia: National Institute of Clinical Excellence (NICE) guidance in the real world. Clin Schizophr Relat Psychoses 2010;4(1):49-55.
17. Weissman EM. Antipsychotic prescribing practices in the Veterans Healthcare Administration--New York metropolitan region. Schizophr Bull 2002;28(1):31-42.
18. Conley RR, Kelly DL, Lambert TJ, Love RC. Comparison of clozapine use in Maryland and in Victoria, Australia. Psychiatr Serv 2005;56(3):320-323.
19. Wheeler A, Humberstone V, Robinson E, Sheridan J, Joyce P. Impact of audit and feedback on antipsychotic prescribing in schizophrenia. J Eval Clin Pract 2009;15(3):441-450.
20. Hayhurst KP, Brown P, Lewis SW. Postcode prescribing for schizophrenia. Br J Psychiatry 2003;182:281-283.
21. Leslie DL, Rosenheck RA. Benchmarking the quality of schizophrenia pharmacotherapy: a comparison of the Department of Veterans Affairs and the private sector. J Ment Health Policy Econ 2003;6(3):113-121.
22. Stroup TS, Lieberman JA, McEvoy JP, Davis SM, Swartz MS, Keefe RS, et al. Results of phase 3 of the CATIE schizophrenia trial. Schizophr Res 2009;107(1):1-12.
23. Wennberg JE. Practice variations and health care reform: connecting the dots. Health Aff (Millwood) 2004;Suppl Variation:VAR140-144.
24. Palmer BA, Pankratz VS, Bostwick JM. The lifetime risk of suicide in schizophrenia: a reexamination. Arch Gen Psychiatry 2005;62(3):247-253.
25. Hennen J, Baldessarini RJ. Suicidal risk during treatment with clozapine: a meta-analysis. Schizophr Res 2005;73(2-3):139-145.
26. Krakowski MI, Czobor P, Citrome L, Bark N, Cooper TB. Atypical antipsychotic agents in the treatment of violent patients with schizophrenia and schizoaffective disorder. Arch Gen Psychiatry 2006;63(6):622-629.
27. Green AI, Noordsy DL, Brunette MF, O'Keefe C. Substance abuse and schizophrenia: pharmacotherapeutic intervention. J Subst Abuse Treat 2008;34(1):61-71.
28. Suppes T, Webb A, Paul B, Carmody T, Kraemer H, Rush AJ. Clinical outcome in a randomized 1-year trial of clozapine versus treatment as usual for patients with treatment-resistant illness and a history of mania. Am J Psychiatry 1999;156(8):1164-1169.
29. Joober R, Boksa P. Clozapine: a distinct, poorly understood and under-used molecule. J Psychiatry Neurosci 2010;35(3):147-149.
30. Tiihonen J, Lonnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A, et al. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). Lancet 2009;374(9690):620-627.
31. De Hert M, Correll CU, Cohen D. Do antipsychotic medications reduce or increase mortality in schizophrenia? A critical appraisal of the FIN-11 study. Schizophr Res 2010;117(1):68-74.
32. Tiihonen J, Wahlbeck K, Lonnqvist J, Klaukka T, Ioannidis JP, Volavka J, et al. Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow-up study. BMJ 2006;333(7561):224.
33. Cooper D, Moisan J, Gregoire JP. Adherence to atypical antipsychotic treatment among newly treated patients: a population-based study in schizophrenia. J Clin Psychiatry 2007;68(6):818-825.
34. Black LL, Greenidge LL, Ehmann T, Ganesan S, Honer WG. A centralized system for monitoring clozapine use in British Columbia. Psychiatr Serv 1996;47(1):81-83.
35. Bond GR, Drake RE, Mueser KT, Latimer E. Assertive community treatment for people with severe mental illness: critical ingredients and impact on patients. Dis Manage Health Outcomes 2001;9(3):141-159.
36. Jamtvedt G, Young JM, Kristoffersen DT, O'Brien MA, Oxman AD. Audit and feedback: effects on professional practice and health care outcomes. Cochrane Database Syst Reviews 2006 April 19;(2):CD000259.
37. Jacobs P, Dewa C, Lesage A, Vasiliadis H-M, Escober C, Mulvale G, et al. The cost of mental health and substance abuse in Canada. Alberta, Canada: Institute of Health Economics; 2010. p. 42.