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Research Article

The Impact of Pharmaceutical Support Programs on Persistence: Clinical, Human and Economic Impact of Clozapine Support Programs in Quebec, Canada

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Abstract

Objective: Though clozapine products have the same clinical benefits, Patient Support Programs (PSPs) may have an impact on treatment persistence. This study aimed to evaluate the impact of clozapine PSPs on treatment persistence, from the Quebec perspective.

Methods and analysis: An 18-month persistence study was conducted using data from the Régie de l' Assurance Maladie du Québec (RAMQ) for patients who initiated clozapine. The persistence rate on clozapine was compared with and without PSPs, which were used to model potential hospitalization, suicide attempts, emergency room consultations, physician visits, and clozapine withdrawal symptoms and their respective costs as well as drug acquisition. Mean annual per-patient costs (2023 Canadian dollars) for clozapine were calculated, considering persistence rates and healthcare resource utilization with and without clozapine from literature. The one-year economic impact was calculated based on the estimated prevalence of TRS patients on clozapine in Quebec.

Results: Persistence rates were better when clozapine was paired with a PSP, and there was a statistical difference in persistence rates between products. The persistence rates of 122 patients on CSAN and GenCAN, two PSPs in Quebec, were 69% and 55% (p=0.049), respectively, as opposed to the 25% reported persistence rate. Despite higher annual treatment costs based on list prices (+$2,097 per patient), the improved persistence on CSAN compared to GenCAN translates into annual savings of $3,324 per patient or $23.4 million for the Quebec healthcare system.

Conclusion: PSPs offer an important advantage in improving clozapine persistence, and there are significant differences in clozapine persistence between PSPs.

Keywords: Persistence; Schizophrenia; Canada; Clozapine; Patient support program; Adherence; Burden; Cost

Abbreviations

CSAN: Clozaril Support and Assistance Network; ER: Emergency Room; PSP: Patient Support Program; RAMQ: Régie de l'Assurance Maladie du Québec; SCZ: Schizophrenia; TRS: Treatment-Resistant Schizophrenia

Introduction

Schizophrenia (SCZ) is a complex, chronic psychiatric disorder characterized by a myriad of symptoms, including delusions, hallucinations, disorganized speech or behavior, and impaired cognitive ability [1]. Although SCZ only affects around 1% of the population it imposes a disproportionate burden on society and the health care system [1,2]. The most recent Canadian study on this topic estimated that, in 2004, the total economic burden attributed to SCZ, including both direct and indirect costs was 6.85 billion dollars [3]. Despite significant improvements in the past decades in pharmacological SCZ treatments, about 30% of patients have Treatment-Resistant SCZ (TRS), usually defined as treatment failure despite adequate trials with at least 2 different antipsychotic medications other than clozapine [4,5]. Clozapine is the only treatment approved for these patients in Canada [5,6] however of those who initiate clozapine a substantial proportion (some estimates suggesting almost 75%, in the first year) discontinue therapy for various reasons such as adverse events, or low compliance challenges [7]. Since clozapine is the only approved treatment in Canada for treatment-resistant schizophrenia, and there is a high relapse rate when patients stop taking medication, non-persistence to clozapine is detrimental since it is associated with increased hospitalizations, mortality, suicide, delayed remission, poorer prognosis, worsening psychiatric symptoms, unemployment, and poor quality of life [8-11].

Canada is among the five countries (with the United States, United Kingdom, Australia, New Zealand, and Japan) that require that each manufacturer of clozapine implement a Patient Support Program (PSP) that includes a patient registry that assures compliance with laboratory monitoring for agranulocytosis. While various clozapine brands may offer the same clinical benefits from an ingredient perspective, proprietary differences in the PSP's operations and offerings may have an impact on treatment persistence, having a substantial economic impact on the health care system. Indeed, the positive impact of PSPs has been seen in other therapeutic areas as

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they have shown to have a positive impact on patient adherence to growth hormone treatment, improved adherence to acne treatment with an isotretinoin regimen, and improved adherence in patients with relapsing-remitting multiple sclerosis, as examples [12,13]. The objective of this study was to evaluate if PSP programs help with clozapine persistence and to estimate, from the Quebec health care system perspective, the clinical, human, and economic impact associated with clozapine persistence.

Material and Methods

Persistence rate of clozapine

An analysis of longitudinal data from IQVIA Canada's Régie de l'Assurance Maladie du Québec (RAMQ) data, covering the period from October 2018 to February 2021 was conducted (Figure 1). The study selection criteria were (1) 'de-novo' prescription, defined as a non-user of clozapine in the 12-months prior to initiation, and (2) patients who initiated clozapine treatment between October 2018 and August 2019 and who were followed for the subsequent 18 months. The study focused on patients in the first year of treatment as this is associated with the highest rate of non-persistence. Further, it is noted that part of the 545-day analysis period which ended Feb 2021 evaluated patients during the COVID-19 epidemic. Additionally, patients receiving clozapine could have more challenges with persistence given this was a period with reduced access to health care facilities, during shutdowns, that occurred during the COVID-19 epidemic. Within Canada, there are only three clozapine products approved, within Quebec two of these products dominate the market, which was shown in this data set as only two clozapine products were identified in the RAMQ data set clozapine (Viatris Inc) with a PSP branded as GenCAN and clozapine (HLS Therapeutics Inc), with a PSP branded as Clozaril Support and Assistance Network (CSAN) [6,14]. Persistent patients were defined as any patient who did not discontinue clozapine. Discontinuation was defined as the absence of a claim for more than the number of days supplied on the treatment plus a 30-day grace period. The discontinuation date was the date at the end of the days supplied of the last claim. Patients were considered censored if their last claim happened before the last day of clozapine supplied plus a 30-day grace period. The censor date was the date at the end of days supplied of the last clozapine. Given literature suggests that ~75% of patients who start clozapine treatment will discontinue in the 1st year of treatment, 18 months were thus deemed to be an adequate duration for assessment [7]. Persistence within the 545-day post-index period (18 months) was analyzed using a time-to-event model. A Kaplan-Meier model was used to estimate persistence across medications. A Cox Proportional Hazards model was used to determine the association between index medication, age, and sex. P-values and hazard ratios for each of these variables were reported. Each covariate was treated as categorical. A likelihood ratio chi-square test statistic was used to calculate p-values for the model. A p-value less than 0.05 were deemed statistically significant.

Economic impact of clozapine persistence

Schizophrenia is a mental health condition known for its association with high levels of disability and health care utilization [3]. An extensive literature review was performed using the PubMed, Embase, and Google Scholar electronic databases to retrieve the main cost drivers associated with the non-persistence of clozapine treatment. Costs and health care resources considered were those related to treatment acquisition, hospitalization, suicide attempts, Emergency Room (ER), physician visits, and clozapine withdrawal symptoms (Table 1), Supplementary material. Cost and health care resource use estimates were obtained from the most reliable Quebec or Canadian governmental sources (RAMQ, Ontario Case Costing, Canadian Institute for Health Information) and the published literature [15-20]. Any costs estimated before 2023 were inflated to 2023 Canadian dollars using the all-item Quebec Consumer Price Index [21]. A mean cost per patient was modeled by applying the resulting persistence rates and the health care resource utilization data before and after clozapine initiation (i.e., with and without clozapine), which were based on recently published literature [7,22-25]. A mean annual cost was calculated for a patient on brand clozapine and a patient on generic clozapine. The mean annual cost per patient was subsequently used to estimate the overall economic impact of clozapine retention for Quebec based on the proportion of TRS patients treated with clozapine in the province. This was done using a step wise approach (Table 2).

Results

Persistence rate

A total of 122 patients were included in the persistence analysis: 39 on CSAN and 83 on GenCAN, the only two PSP programs within the RAMQ data analyzed. Groups were comparable in terms of age and gender. The 18-month persistence rate of the CSAN PSP was 69% (31% non-persistent), vs. while the persistence rate of GenCAN was 55% (45% non-persistent) (Figure 2). The risk of non-persistent for patients on the GenCAN PSP was 32.5% higher than patients on the HLS PSP (p= 0.049). Both the CSAN and GenCAN PSP appear to have marked improvement in patient persistence over the published reported rate, which is as low as 25% [7].

Economic impact of clozapine persistence

When considering the RAMQ's list prices for the two brands of

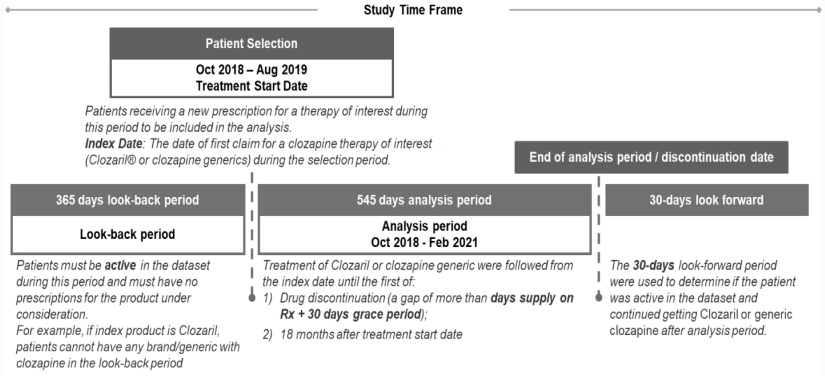

Figure 1: Persistence analysis details.

Table 1: Summary of Cost and Health Care Resource Utilization Inputs (Per Patient Per Year).

Parameter	Input	Source
Annual treatment acquisition	Brand clozapine: $6,895 (List Price) - used for CSAN PSP	[18, 24, 35]
	Generic clozapine: $4,826- used for No PSP and GenCAN PSP	
Hospitalization	Mean total cost: $17,019	[15, 19, 25]
	Mean admission frequency with clozapine: 1.05	
	Mean admission frequency without clozapine: 3.17	
Suicide attempts	Mean cost of a suicide attempt: $14,161	[7,17,24]
	Mean cost of a death by suicide: $6,860	
	Mean baseline # of suicide attempts: 0.12	
	% reduction in suicide attempts - continued clozapine: 93.1%	
	% reduction in suicide attempts - discontinued clozapine: 51.7%	
	% death by suicide in TRS schizophrenia patients: 25.0%	
Emergency room visits	Cost per visit: $417	[16, 19, 25]
	Mean visit frequency with clozapine: 0.25	
	Mean visit frequency without clozapine: 1.07	
Physician visits	Cost per visit: $86	[19, 23]
	Mean visit frequency with clozapine: 2.37	
	Mean visit frequency without clozapine: 6.14	
Clozapine withdrawal	Mean cost of withdrawal-associated psychosis: $8,870	[19, 20, 22]
	Mean cost of other withdrawal symptoms: $312	
	% with withdrawal-associated psychosis after stopping clozapine: 20%	
	% with other withdrawal symptoms after stopping clozapine: 50%	

Table 2: Number of Clozapine-treated Schizophrenia Patients in Quebec.

	Value	Source
Population of Quebec 10+ years old	7813598	Statistics Canada (2022) [36]
Prevalence of SCZ	0.01	Government of Canada - Schizophrenia in Canada (2020) [37]
Percentage of SCZ patients with TRS	0.3	Lally (2016) [38]
Total number of TRS patients in Quebec	23441	Calculation
Percentage of TRS patients receiving clozapine in Quebec	0.3	Farooq (2011) [39]
Total number of TRS patients receiving clozapine in Quebec	7032	Calculation

SCZ: Schizophrenia; TRS: Treatment-Resistant Schizophrenia

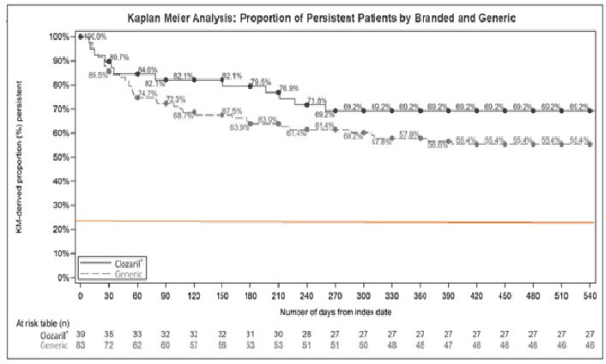

Figure 2: Persistence analysis results.

clozapine the improved persistence rates from the literature show that both CSAN and GenCAN are helping to reduce annual health care costs through improved persistence by $13,801 and $10,476 respectively, per patient. Further, there appear to be differences in persistence between these two registries, the mean total annual cost being $35,120 compared to $38,445 for CSAN *vs.* GenCAN clozapine respectively (9% reduction for CSAN clozapine compared to GenCAN clozapine in terms of absolute percentage or $3,324 annual savings per patient) (Table 3). Although the list price of the CSAN product is higher(+$2,097 per patient, per year), the additional persistence with CSAN clozapine compared to GenCAN clozapine results in savings especially in terms of hospitalization costs (-$4,980 per patient, per year). When considering the total population of TRS patients on clozapine in Quebec and using list prices, the PSPs are contributing to an annual savings of $97.1 million and $73.7 million respectively for CSAN and GenCAN clozapine. The additional persistence seen between the two programs resulted in additional annual savings of $23.4 million for the Quebec health care system.

Table 3: Results by PSP Group - Total Annual Costs.

	No PSP	CSAN PSP	GenCAN PSP
Retention rate	25%	69%	55%
Treatment costs	$1,207	$4,771	$2,674
Hospitalization costs	$44,900	$28,951	$33,931
Emergency room visit costs	$361	$211	$258
Physician visit costs	$444	$302	$346
Cost associated with suicide	$561	$291	$375
Cost associated with clozapine withdrawal	$1,448	$595	$861
Total cost per patient with TRS	$48,921	$35,120	$38,445
Cost for the Quebec health care system	**$344,024,256**	**$246,973,240**	**$270,351,192**

TRS: Treatment-Resistant Schizophrenia

Retention rates of PSPs were obtained from the persistence study while the retention rate without PSP was obtained from literature given PSP is mandatory for all clozapine patients in Canada [7].

All costs are annual weighted average costs per patient. These costs were estimated using the persistence rates and costs for patients on clozapine (i.e., persistent) and patients off clozapine (i.e., non persistent), as shown in Table 1.

Discussion

This is the first study we are aware of that evaluates the impact of PSP on patient persistence for clozapine. The findings of this

persistence study demonstrated that clozapine PSPs improve persistence between 30% and 44% in absolute percentage compared to no clozapine PSP. This results in estimated savings ranging between $10,476 and $13,801 per patient when considering treatment acquisition and health care resource costs. When extrapolating these savings to the whole Quebec population, savings up to $97.1 million per year can be realized for the Quebec health care system.

A strength of this study was that the persistence analysis was based on data from a claim database (RAMQ) representing the population of interest (i.e., patients on clozapine in the province of Quebec). Such data are also longitudinal, which allows for adequate and accurate patient follow-up [26,27]. This was important considering the outcome of interest of the current study (i.e., drug persistence at 18 months). Additionally, claim data cover all insured patients in a given jurisdiction, which typically represents a large sample size of individuals and all types of patients seen in real-world practice that may not be represented in clinical trials [26,27]. The cost and health care resource utilization inputs were based on a comprehensive literature review to ensure all information relevant to treating patients with TRS in Quebec was considered and, accordingly, all cost estimates used in the calculations were obtained from Canadian-specific resources only.

Despite these strengths, this study also has some limitations. As claims data are for administrative and reimbursement purposes only, there is often limited information on patient outcomes, such as actual health care resource utilization [26-28] which is why these estimates were retrieved from the published literature. Claim data are also vulnerable to data quality issues (e.g., data entry errors) [26-28]. Additionally, there is no reported prevalence of patients with TRS on clozapine in Quebec and this number had to be estimated using data on other relevant parameters that were available publicly or in the literature. Other clinical, environmental, and socioeconomic factors can also affect drug persistence, though these could not be considered in the current analysis. Another limitation is that, since all clozapine patients in Canada are required to be on a PSP, it was not possible to evaluate the real-world clozapine persistence without PSP using the RAMQ database. As such, the persistence rate reported in the literature was used to compare clozapine groups [7]. Lastly though we used data from published literature, no data regarding health care resource utilization of persistent and non persistent TRS patients to clozapine was available. As such, data for clozapine and non-clozapine users were used as a proxy. All the limitations noted above add some uncertainty around the economic impact associated with clozapine persistence estimated in this study. Of note, this study did not consider productivity loss associated with medical visits, hospitalizations, and suicide attempts. As such, the economic impact would have been greater from a Quebec societal perspective.

Even though clozapine is the only medication available for treatment-resistant schizophrenia, its use remains sub-optimal in Canada at about 8%, and it has been reported it can be five (5) to nine (9) years to initiate clozapine the only product indicated for treatment of TRS [29]. Canada is one of five countries that require risk mitigation programs as a condition of clozapine regulatory approval. Each of these countries has different levels of programs that are offered as part of this regulatory requirement. In Canada, the impact of patient registries is recognized within the product monograph, and it remains one of the only products in Canada that may not be substituted for a different brand by a pharmacist without the implicit consent of the treating physician [6,14]. Beyond the core regulatory aspects dictated by Health each program has evolved to have their own proprietary monitoring systems to help ensure compliance and patient safety. While all the programs in Canada seem to offer some of the same core services there are differences in services and how the service offering is deployed. While further review of what PSP attributes make the most significant impact on persistence, this study clearly showed that PSPs have an important impact on patient persistence and that there may be differences in patient persistence depending on the depth and breadth of such PSP offerings. In that, the literature reports persistence at one year of 25%, and this study showed persistence rates of 55% and 69% for GenCAN and CSAN respectively [7,30-33].

Conclusion

The resources required to initiate and maintain a patient on clozapine are higher than other antipsychotics since most clozapine is initiated in the hospital setting. Assuring that discharged patients maintain persistence is a critical success factor for the management of these patients. Such efforts will reduce the pain and suffering of the patient, improve treatment benefits, and reduce health care costs [34-40].

This study shows that PSP may be a valuable tool for improving patient persistence. It also highlights that differences in servicing offerings of PSPs also have an impact on persistence, and thus on the health care system [41-50].

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Supplementary Files

Treatment Acquisition Costs

The unit costs of clozapine products were all retrieved from the RAMQ's Listedes medicaments, except for CSAN (clozapine) 50 mg and 200 mg, which were retrieved from Alberta's Drug Benefit List [18,35]. In most patients, clozapine's antipsychotic activity can be expected within the therapeutic range of 300-600 mg/day in divided doses [6]. According to a pharmacoeconomic evaluation of clozapine in TRS and risperidone in chronic SCZ published by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA), the mean daily dose of clozapine is 500 mg [24] (Table 1).

Hospitalization Costs

TRS patients are high consumers of health care resources, especially in terms of hospital admissions. In a recent study conducted by Jo, et al. [22] Using the Health Insurance Review Agency database in the Republic of Korea to investigate the real-world effectiveness of clozapine for patients with TRS (n=998), the mean annual number of admissions per patient was 3.17 before initiating clozapine and 1.05 after the initiation of clozapine [25].

The mean cost of inpatient stay for TRS was estimated by combining hospital and physician fees during the stay. The hospital fees were obtained from the Patient Cost Estimator, which is provided by the Canadian Institute for Health Information (CIHI) [15]. A weighted average cost per hospital stay was calculated using the mean inpatient cost in Québec for SCZ diagnosis codes for each age group. Of note, this cost may be an underestimate, as it includes all SCZ diagnosis codes and not only TRS. Physician fees during the inpatient stay were also considered, using the RAMQ's Manuel des medicine specialists [19]. Specifically, a consult with a psychiatrist was assumed at hospital admission, and a control visit with a psychiatrist was assumed for the subsequent inpatient days using a mean length of stay of 22.2 days, as per the Patient Cost Estimator [15,19] (Table 2).

Costs Associated with Suicide Attempts

In Krivoy, et al. [7] medical records of patients with SCZ who were hospitalized in the Geha Mental Health Center (Israel) between January 2002 and December 2008 were reviewed. The authors analyzed and compared demographic and clinical parameters between the 58 patients who continued and the 42 who discontinued clozapine treatment. The mean number of suicide attempts before the initiation of clozapine was 0.72 for a mean follow-up period of 6 years. During this period, patients who continued clozapine had a 93.1% reduction in the number of suicide attempts, while those who discontinued clozapine had only a 51.7% reduction in the number of suicide attempts.

The cost of a suicide attempt was retrieved from the study by Lebenbaum, et al. [14] which evaluated the cost-effectiveness of a suicide prevention campaign implemented in Ontario [17]. The costs of suicide attempts and death by suicide were reported. According to the pharmacoeconomic evaluation published by CCOHTA, 25% of suicide attempts in SCZ patients are fatal [24]. Consequently, a weighted average cost associated with a suicide attempt was calculated.

All inputs associated with suicide attempts are detailed in Table 3.

Emergency Room Costs

The number of ER visits was also retrieved from Jo, et al. [25] which reported an average of 1.07 ER visits per patient per year before initiating clozapine and 0.25 ER visits per patient per year after the initiation of clozapine. The cost of an ER visit was based on the mean hospital fees at the emergency department, which was retrieved from a report published by CIHI in 2020, and the physician fee in Québec for a simple visit at the emergency department (ER physician) [19,40] (Table 4).

Physician Visit Costs

The number of physician visits was retrieved from Butler, et al. [20] who conducted a real-world study to assess the feasibility and cost-effectiveness of clozapine initiation in a community in the UK [23]. They reported an average of 6.14 visits with a psychiatrist per year before clozapine initiation compared to 2.37 visits per year after clozapine initiation. The physician fee with a psychiatrist was retrieved from the RAMQ's Manuel des médecins specialists [19] (Table 5).

Costs Associated With Withdrawal Symptoms

The discontinuation of antipsychotics, especially clozapine, can cause a range of withdrawal symptoms, some of which can lead to deterioration in the clinical status of the patient. Indeed, the discontinuation of clozapine poses a real challenge for clinicians. Withdrawal symptoms include serotonergic symptoms (agitation, diaphoresis, clonus, hyperreflexia), cholinergic symptoms (nausea, vomiting, confusion, delirium, insomnia, and dystonia), and withdrawal-associated catatonia. The percentage of patients experiencing withdrawal symptoms (psychosis and other symptoms) was retrieved from Blackman, et al. [19], the hospital fees for withdrawal-associated psychosis were retrieved from the Ontario Case Costing (OCC) and control visits with a psychiatrist were also included during the inpatient stay (mean length of stay: 5.6 days). The unit cost of the control visits was retrieved from the RAMQ's Manuel des medicine specialists. According to Blackman (2022), the management of serotonin-like, cholinergic symptoms requires medications [22]. Consequently, one physician visit was assumed to prescribe medications, as well as one follow-up visit, as per the RAMQ's Manuel des medicines specialists [19] (Table 6).

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Supplementary Tables

Table 1: Treatment Acquisition Costs.

Treatment	Strength (mg)	Unit Cost	Mean Daily Dose (mg)	Mean Daily Cost**	Mean Annual Cost	Source
CSAN clozapine	25	$0.94	500	$18.89	$6,895	RAMQ. *Liste des médicaments*, Alberta Drug Benefit List, CCOHTA (2017) [18, 24, 35]
	50*	$1.88				
	100	$3.78				
	200*	$7.56				
GenCAN clozapine	25	0.66		$13.22	$4,826	
	50	$1.32				
	100	$2.65				
	200	$5.29				

*All costs were from RAMQ's Liste des medicaments, except for Clozaril® 50 mg and 200 mg (Alberta's Drug Benefit List)

**Assuming 5 tablets of 100 mg for both clozapine products.

CCOHTA: Canadian Coordinating Office for Health Technology Assessment; RAMQ: Régie De L'assurance Maladie Du Québec.

Table 2: Hospitalization Inputs.

Parameter	Value	Source
Hospital costs		
Hospital fees	$15,873	CIHI, Patient Cost Estimator (2018/2019). Québec, average all age groups, code 707. Costs adjusted to 2023 CAD [15].
Physician fees	$1,146	RAMQ. Manuel des médecins specialists.
		Codes 08970 (Visit principal) and 08972 (Visit de contrôle) [19]
.Mean length of stay	22.2	CIHI, Patient Cost Estimator (2018/2019) [15].
		Weighted average.
Mean total hospitalization cost	$17,019	Calculation
Admission Frequency		
With clozapine, mean per patient per year	1.05	Jo, et al. [25]
Without clozapine, mean per patient per year	3.17	

CIHI: Canadian Institute for Health Information; RAMQ: Régie De L'assurance Maladie Du Québec

Table 3: Suicide Attempt Inputs.

Parameter	Value	Source
Suicide Attempt Costs		
Suicide attempt	$14,161	Lebenbaum, et al. [17] Costs adjusted to 2023 CAD [21].
Death by suicide	$6,860	
Suicide Attempt Frequency		
Baseline - Number of suicide attempts (per year)	0.12	Krivoy, et al. [7]
% reduction in suicide attempts - continued clozapine	93.10%	
% reduction in suicide attempts - discontinued clozapine	51.70%	
% fatal suicide attempts in refractory schizophrenia patients	25.00%	CCOHTA (2017) [24]

CCOHTA: Canadian Coordinating Office for Health Technology Assessment

Table 4: Emergency Room Inputs.

Parameter	Value	Source
ER Costs		
Hospital fees	$362.26	CIHI 2020 - Costs adjusted to 2023 CAD [40]
Physician fees	$54.60	RAMQ. Manuel des médecins spécialistes. Code 15210 (Visite simple à l'urgence) [19]
Average cost per ER visit	**$416.86**	Calculation
ER Visit Frequency		
With clozapine, mean per patient (per year)	0.25	Jo, et al. [25]
Without clozapine, mean per patient (per year)	1.07	

CIHI: Canadian Institute for Health Information; ER: emergency room; RAMQ: Régie De L'assurance Maladie Du Québec

Table 5: Physician Visit Inputs.

Parameter	Value	Source
Physician Visit Cost		
Physician fees	$85.50	RAMQ. Manuel des médecins spécialistes. Code 08922 (Visite de contrôle, psychiatrie) [19]
Physician Visit Frequency		
With clozapine, mean per patient (per year)	2.37	Butler et al. [23]
Without clozapine, mean per patient (per year)	6.14	

RAMQ: Régie de l'assurance maladie du Québec

Table 6: Withdrawal Inputs.

Parameter	Value	Source
Cost of Withdrawal Symptoms		
Withdrawal-associated psychosis	$8,870	OCC. Acute inpatient 2017/2018. Codes F231,F232,F238,F239 (acute psychotic disorders). Manuel des médecins spécialistes. Codes 08970 (Visite principale) and 08972 (Visite de contrôle) - Mean LOS: 5.6 days [19, 20]
Other withdrawal symptoms	$312.45	Manuel des médecins spécialistes. Codes 08920 (Visite principale, cabinet) and 08922 (visite de contrôle, cabinet) [19]
Proportion of Patients Experiencing Withdrawal Symptoms		
% stopping clozapine experiencing withdrawal-associated psychosis	20%	Blackman et al. [22]
% stopping clozapine experiencing other withdrawal symptoms	50%	

OCC: Ontario Case Costing