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Prescribing and deprescribing trends in schizophrenia: an overview of inpatients in Belgium and in the Canadian province of Québec

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Abstract

Although switching to antipsychotic monotherapy improves patient outcomes in schizophrenia, antipsychotic deprescribing is rarely performed and its use varies between countries, as do psychotropic prescribing patterns. This study aimed to determine factors associated with antipsychotic deprescribing at discharge after a psychiatric hospitalisation and to compare psychotropic prescribing patterns between Belgium and Québec, Canada. Data on adult inpatients with schizophrenia were collected retrospectively in seven hospitals. At discharge, the number of antipsychotics had decreased in 22.2% of the 63 Canadian patients and 9.9% of the 516 Belgian patients. A number of factors increased the likelihood of antipsychotic deprescribing: a hospitalisation in the Canadian hospital (aOR=4.13, 95% CI 1.48-11.5), living in a residential facility (aOR=2.51, 95% CI 1.05-4.39), ≥2 previous antipsychotic trials (aOR=15.38, 95% CI 3.62-65.36), having an antipsychotic side effect (aOR=1.86, 95% CI 1.01-3.44), and being in a general hospital (aOR=2.28, 95% CI 1.09-4.75). Patients on a long-acting injectable antipsychotic (aOR=0.51, 95% CI 0.26-0.98), with prior clozapine use (aOR=0.36, 95% CI 0.13-0.95), greater antipsychotic exposure (aOR=0.35, 95% CI 0.2-0.61) and more hypno-sedatives (aOR=0.65, 95% CI 0.43-0.98), were less likely to be deprescribed. Specific deprescribing interventions could target patients who are less likely to be deprescribed.

1. Introduction and background

Antipsychotic monotherapy is the only licensed type of drug treatment for schizophrenia in Europe and Canada [1,2]. Antipsychotic polypharmacy (APP), i.e. the simultaneous use of two or more antipsychotics by one patient, is common worldwide for treatment augmentation or to treat comorbid psychiatric conditions (e.g. anxiety, sleep disorders)[3-5]. There is no high-quality evidence to support greater efficacy of APP over antipsychotic monotherapy[6-8]. Patients on APP experience more adverse effects than those on antipsychotic monotherapy, show poorer treatment adherence and potentially have a greater risk of hospital readmission, thereby increasing healthcare costs [9-11]. All schizophrenia prescribing guidelines therefore recommend antipsychotic monotherapy for a first episode, and switching to another monotherapy where there is a lack of efficacy or poor tolerability [12]. In situations of treatment resistance, clozapine is the first choice of treatment because of its superior efficacy [13]. Clozapine augmentation with another antipsychotic should only be considered when symptoms persist after an appropriate trial of clozapine, because there is little evidence to support its use [14]. In many cases, other psychotropic medications are also prescribed to patients with schizophrenia. Off-label use of these medications and potentially inappropriate prescribing are common in this population, and increase the risk of medication-related harms, warranting consideration of deprescribing these potentially deleterious treatments [15-17].

Deprescribing is the process of identifying and discontinuing medications for which existing or potential harms outweigh potential benefits within the context of an individual patient's care goals, functioning, values and preferences[18]. While deprescribing may encompass reducing the dose or completely stopping the medication, antipsychotic deprescribing in schizophrenia refers to reducing the number of antipsychotics. Indeed, an appropriate dose of antipsychotics that ensures the blockade of at least 65-70% of D2 receptors is needed to reduce psychotic symptoms. Dose reduction is therefore not always appropriate, especially during an exacerbation (e.g. during acute psychiatric hospitalisation)[19]. Moreover, the daily dose of antipsychotic cannot be reduced to below a certain threshold during maintenance without recurrence of symptoms and/or rehospitalisation [20]. However, switching from APP to antipsychotic monotherapy leads to improvement in attention and executive functions, and fewer side effects and has been shown to reduce the risk of relapse, possibly by improving treatment adherence [21-23].

Psychotropic prescribing patterns can differ greatly between countries and are influenced by physician preferences, culture, norms and environment (e.g. health system)[24,25]. In the treatment of schizophrenia, APP rates have been reported to be higher in Europe than in North America [5]. Moreover, Canada has been the leader in deprescribing policies in the last few decades, and Canadian researchers have developed several programmes and algorithms for deprescribing psychotropics[26]. A comparison between Belgian prescribing and deprescribing patterns for psychotropic drugs and those of a Canadian hospital could therefore help to identify key differences. This may inspire future policies to improve the use of psychotropics in schizophrenia. In addition, most prior studies have focused on outpatient prescribing patterns and lacked an overview of the deprescribing that occurs during a psychiatric

hospitalisation. Identifying patients who are less likely to be deprescribed naturally (i.e. without a specific intervention) could therefore help to develop targeted hospital-based deprescribing strategies.

This study aimed: (1) to determine factors associated with antipsychotic deprescribing after a psychiatric hospitalisation, and (2) to compare psychotropic prescribing patterns on admission and at discharge in several Belgian hospitals and a Canadian hospital.

2. Materials and methods

2.1. Setting and data sources

Retrospective data were collected in 2020-2021 in a tertiary care hospital in Montréal, Québec, Canada, and in six Belgian hospitals [27]. Prescribing patterns were extracted from local prescribing software and other characteristics (e.g. demographics, comorbidities) from patient medical records. All drugs were encoded according to the Anatomical Therapeutic Chemical (ATC) classification.

2.2. Study population

The data extracted concerned individuals between 18 and 64 years old, discharged from psychiatric units after an acute hospitalisation (i.e. less than one year) between November 2018 and November 2019, with a prescription of at least one antipsychotic on admission and a diagnosis of schizophrenia or schizoaffective disorder (DSM-5 295.xx). In the event of multiple hospitalisations during this period, only the last hospitalisation was analysed.

2.3. Factors potentially associated with antipsychotic deprescribing at hospital discharge

A range of factors, in addition to country, were considered to identify patients with a higher probability of antipsychotic deprescribing. Factors for which data were collected include demographics, disease and hospitalisation characteristics, comorbidities, antipsychotic treatment, and co-treatment. These factors were taken into account as they are associated with the use of APP[27,28], and may therefore increase or reduce the likelihood of deprescribing[29]. The full list of these factors is available in the online Appendix (eTable 1).

Low-dose antipsychotics (i.e. clotiapine ≤40 mg, levomepromazine ≤ 100 mg, prothipendyl ≤80 mg, quetiapine ≤50 mg), trazodone ≤100 mg, benzodiazepine receptor agonists (BZRAs), and sedating antihistamines were considered hypno-sedative drugs when taken at night to induce sleep.

Group homes, nursing homes or supervised residential facilities for individuals with mental disorders were referred to as residential facilities.

2.4. Comparison of antipsychotic and psychotropic prescribing patterns at admission and discharge from psychiatric hospitalisation

2.4.1. Antipsychotics

The prevalence of APP was compared between the two countries, both on admission and at discharge from hospital. Low-dose antipsychotics are frequently used for indications other than psychosis, particularly for the management of insomnia. While the combination of an antipsychotic for psychosis with a low-dose sedating one for sleep disorders is technically APP, clinicians do not always consider it as real APP. Thus, the prevalence of patients based on an alternative definition of antipsychotic polypharmacy, excluding patients on this combination, was also examined. Types of antipsychotics and routes of administration were compared. Antipsychotic exposure was expressed using the ratio of the prescribed daily dose (PDD) to the defined daily dose (DDD) of the World Health Organisation. The PDD/DDD ratio was calculated using the sum of the PDD/DDD ratio of each prescribed antipsychotic in case of APP.

2.4.2. Clozapine

Clozapine prescribing patterns on admission and at discharge were also compared. Patients were considered eligible for clozapine if they had an insufficient response to at least two separate trials of an antipsychotic at a minimal dose of 400 mg of chlorpromazine equivalence, for at least six weeks[13]. The prevalence and evolution of clozapine antipsychotic polypharmacy was compared, and is defined as the combination of clozapine with at least one other antipsychotic.

2.4.3. Other psychotropics

The prevalence of antidepressants, mood stabilizers, BZRAs, trazodone or sedating antihistamines and anticholinergics was compared on admission and at discharge. Anticholinergics refer to drugs indicated for the treatment of extrapyramidal symptoms which are available in either Belgium or Canada (i.e. procyclidine, trihexyphenidyl, biperiden, benztropine).

2.5. Statistical analysis

Quantitative variables between Belgium and Canada were compared with t-tests or Mann-Whitney tests, depending on their distribution. Fisher tests were used to evaluate the difference in categorical variables between Belgium and Canada. Changes in the prevalence of drug prescriptions between admission and discharge were examined with McNemar tests. A multivariable logistic regression was used to identify factors associated with antipsychotic deprescribing after psychiatric hospitalisation, with multiple imputation for missing data. A backward stepwise elimination based on the Akaike information criterion was used to select the final model, in which p-values <0.05 were considered significant. The statistical analyses were performed using R software version 4.0.3.

2.6. Ethics

The study protocol was approved by the central ethics committee of UCLouvain (Belgium), as well as by the ethics committees of each hospital involved (No. 2019/27NOV/530).

3. Results

3.1. Characteristics of the Belgian and Canadian populations

The characteristics of the Canadian (N=63) and Belgian (N=516) populations were very similar, with a mean age of 40 (SD=12), the majority of the patients living in the community (79.4% and 70.4% respectively, p=0.339) and a median length of hospitalisation of 28 (IRQ 15.5-55.5) and 27 (IQR 13-52) days, respectively (p=0.427). However, 81% of the Canadian patients were admitted involuntarily, compared with 20.2% of the Belgian patients (p<0.001). Conversely, 42.3% of the Belgian patients had a legal guardian while 7.9% of the Canadian had one (p<0.001) (Table 1).

3.2. Factors associated with antipsychotic deprescribing at hospital discharge

Between hospital admission and discharge, 22.2% of the Canadian and 9.9% of the Belgian patients had antipsychotic deprescribing; i.e., a reduction in the number of antipsychotics. In addition, being hospitalised in the Canadian hospital significantly increased the likelihood of antipsychotic deprescribing (adjusted odds ratio (aOR)=4.13, 95% CI 1.48-11.5).

Living in a residential facility (aOR=2.51, 95% CI 1.05-4.39), two or more previous antipsychotic trials (aOR=15.38, 95% CI 3.62-65.36), having an antipsychotic side effect during the hospital stay (aOR=1.86, 95% CI 1.01-3.44), and being hospitalised in a general hospital (aOR=2.28, 95% CI 1.09-4.75) also significantly raised the probability of antipsychotic deprescribing at hospital discharge.

Conversely, patients on a long-acting injectable (LAI) antipsychotic (aOR=0.51, 95% CI 0.26-0.98), with prior clozapine use (aOR=0.36, 95% CI 0.13-0.95), a higher antipsychotic exposure (aOR=0.35, 95% CI 0.2-0.61), and a higher number of hypno-sedative drugs at discharge (aOR=0.65, 95% CI 0.43-0.98) were less likely to be deprescribed (Figure 1).

3.3. Comparison of psychotropic prescribing patterns

3.3.1. Antipsychotic prescribing patterns

The prevalence of APP was similar in Belgium and Canada on hospital admission (47.9% and 49.2%, respectively, p=0.894)(Table 2). However, 32.3% of the 31 Canadian patients admitted on APP were switched to monotherapy during their stay, while this occurred in only 13.4% of the 247 Belgian patients admitted on APP (p=0.02). The proportion of patients admitted on monotherapy and discharged on APP was not statistically different between hospitals of the two countries (34.2% in Belgium vs. 28.1% in Canada, p=0.9).

The types of antipsychotics used were comparable on admission, but significantly more patients were discharged on a combination of a first-generation antipsychotic with a second-generation antipsychotic in the Belgian hospitals (62.3% of the patients on APP) compared with the Canadian one (30% of the patients on APP) (p<0.001) (Table 2).

In addition, more Canadian patients were discharged on an LAI antipsychotic. The majority of those discharged on APP from the Canadian hospital had a combination of an LAI with an oral antipsychotic (86.7%), whereas this type of combination was only prescribed to 46.2% of the Belgian patients discharged on APP (p<0.001) (Table 2).

A similar proportion of patients were being treated with clozapine on hospital admission in both populations (11.1% in Canada vs. 9.3% in Belgium, p=0.648). Although a comparable proportion of patients were eligible to clozapine in the two countries (39.7% in Canada vs. 28.2% in Belgium, p=0.775), significantly more patients had clozapine introduced in Canada (14.3%) than in Belgium (1.9%) (p<0.001). This leads to significantly more patients being discharged with clozapine in Canada (23.8%) than in Belgium (11%) (p=0.007). In addition, a large majority of patients discharged on clozapine received it in combination with another antipsychotic (80% in Canada vs. 75.4% in Belgium (p=0.011). Significantly more patients received clozapine in combination with an LAI in Canada than in Belgium (60% vs. 36.8% of all patients on clozapine antipsychotic polypharmacy, respectively) (p=0.003). In both countries, paliperidone was the antipsychotic most frequently combined with clozapine.

3.3.2. Other psychotropic and anticholinergic prescribing patterns

Examining the prescriptions of hypno-sedative drugs on admission reveals that 22.1% of the Belgian patients and 1.6% of the Canadian patients had a low-dose antipsychotic for sleep disorders (p<0.001), 12.8% and 3.2%, respectively, had trazodone or a sedating antihistamine (p=0.022), and 45.5% and 22.2%, respectively, had a BZRA (p<0.001). This trend persisted at discharge (Table 2). Furthermore, in Belgium, the prevalence of patients on low-dose antipsychotics used for sleep disorders (22.1% vs. 29.3%, p<0.001), on BZRAs (45.5% vs. 54.3%, p<0.001) and on mood stabilisers (16.9% vs. 19.6%, p=0.008) increased significantly from admission to discharge. No significant change in the prevalence of psychotropic medications was observed after hospitalisation in Canada (Figure 2).

Finally, significantly more Canadian (22.2%) than Belgian patients (9.3%) had an anticholinergic on admission (p=0.004), but the prevalence of anticholinergics at discharge decreased significantly in Canada (9.5%) (p=0.027) while it increased slightly in Belgium (11.6%) (p=0.025), reversing the trend (Figure 2).

4. Discussion

Differences were identified in prescribing and deprescribing patterns in schizophrenia between the Belgian and Quebec sites, although the characteristics of the two populations were very similar.

Despite the fact that rather more patients were admitted involuntarily in the Canadian hospital, which potentially translates more severe symptoms, a hospitalisation in Canada increases the probability of having an antipsychotic deprescribed and significantly more patients had a switch from APP to monotherapy in this hospital. These findings may suggest that the willingness of clinicians to deprescribe would overcome the barrier of symptom severity. Indeed, patients with schizophrenia are often reluctant to take an antipsychotic, especially when they have a negative attitude toward medication[30] or lack insight[31]. Adherence to antipsychotics is challenging in schizophrenia, with up to 50% of schizophrenic patients being non-adherent[32], and is reduced by polypharmacy[14]. However, some clinicians believe that APP can speed up effect, increase adherence or further reduce psychotic symptoms[4,33], making them more reluctant to deprescribe, especially during the acute psychotic state[33]. The barrier to deprescribing thus appears to be more related to psychiatrists than patients, which is different from what is observed for benzodiazepines, where the barriers come from both sides[34]. However, the patient or family barrier to deprescribing cannot be excluded, and as it has never been specifically addressed in schizophrenia, further studies are needed. Nevertheless, this result may help convince clinicians that deprescribing is a possible option, even for the more severely affected patients. In addition, antipsychotic deprescribing was beneficial for patients, as it was correlated with a lower antipsychotic exposure, which reduces the risk of extrapyramidal symptoms[14]. Patients experiencing antipsychotic side effects were also more likely to have an antipsychotic deprescribed, indicating that prescribers have a good understanding of the increased risk of side effects when using APP. As one of the main causes of non-adherence is adverse effects[35], it would be preferable to progressively deprescribe to reach monotherapy with close monitoring rather than the patient abruptly stopping all medication. Indeed, deprescribing may improve patient adherence to their sole antipsychotic by reducing the side effect burden[14].

In Belgium, more patients were discharged on a first-generation antipsychotic, and the combination of a first-generation and an atypical antipsychotic was also more frequent among patients on APP. Augmentation with a first-generation antipsychotic reverses the benefit of the atypical antipsychotic in terms of motor adverse effects while exposing patients to the metabolic side effects of the second-generation drug. In addition, there are no significant differences in efficacy between these two classes [13,36-39]. The higher level of prescribing of anticholinergics in Belgium than in Canada and the increase in this measure after psychiatric hospitalisations suggests that there are more motor adverse effects in the Belgian population, presumably induced by the higher rate of first-generation prescribing. Besides, more patients were treated with an LAI antipsychotic in the Canadian hospital than in Belgium. LAI antipsychotics reduce the risk of treatment discontinuation, relapse and hospitalisation in comparison with oral antipsychotics [13,40-43], which is crucial in schizophrenia, because the higher the number of relapses, the worse the patient's psychopathological state will be over time [43]. A prescribing algorithm for LAI antipsychotic treatment in psychosis has been developed in Canada, with recommendations to propose it after a first episode, even to supposedly adherent patients[44]. No such algorithm is available in Belgium however, which could explain this difference. Surprisingly, having an LAI antipsychotic was associated with a lower odds of deprescribing, even though that the majority of patients with schizophrenia can be safely switched to monotherapy without symptoms worsening, especially when the combination involves an LAI antipsychotic [45].

Clozapine is under-prescribed in Belgium compared with Canada, despite being the only antipsychotic registered for the treatment of refractory illness[13,14]. Although a similar proportion of patients were eligible for clozapine in the two countries, more than seven times more patients had clozapine introduced during their stay in the Canadian hospital. Blood monitoring is often put forward as the main

barrier to clozapine introduction, due to patients' reluctance to have blood tests. However, it has not restrained prescribing of clozapine in the Canadian site, even though blood monitoring is mandatory for clozapine to be dispensed by a pharmacist in Canada, which is not the case in Belgium. Furthermore, a large majority of patients on clozapine were being treated with a combination of clozapine and another antipsychotic in both countries, even though this is considered the last-option treatment after an insufficient response to clozapine (i.e. ultra-resistance). Few treatment options have high quality supporting evidence for patients who are ultra-resistant and the majority of the clinical guidelines do not support the use of clozapine antipsychotic polypharmacy [12]. In addition, in both countries, the majority of patients for whom clozapine was introduced for the first time were immediately prescribed clozapine antipsychotic polypharmacy without a prior trial of clozapine monotherapy.

Far more patients were treated with hypno-sedative drugs (e.g. BZRAs, low-dose trazodone) in the Belgian sites than in the Canadian hospital, both on admission and at discharge. BZRAs are often prescribed in a context of psychotic agitation or to induce sedation but their use should be temporary [14], especially as BZRAs augmentation in schizophrenia increases the risks of both suicidal and non-suicidal death, emergency visit, and rehospitalisations [46-49]. Moreover, a larger number of low-dose antipsychotics were prescribed in Belgium compared with Canada for treatment of sleep disorders. Off-label use of antipsychotics is increasing worldwide [50,51], even though the efficacy of adding a low-dose antipsychotic to an antipsychotic at a regular dose to improve sleep has never been studied in patients with schizophrenia. This can expose them to potentially serious adverse effects, such as a neuroleptic malignant syndrome [52]. The benefit-risk ratio for their use as hypno-sedatives is thus uncertain and their use is controversial [53,54]. Non-pharmacological approaches should be prioritised over pharmacological treatment in situations of sleep disorders in schizophrenia [55]. Interestingly, patients on a larger number of hypno-sedative drugs were less likely to have an antipsychotic deprescribed. As hypno-sedative drugs are often prescribed in situations of agitation, aggressiveness and/or anxiety, prescribing of these drugs may indicate a more complicated clinical context. However, although a higher daily dose of antipsychotics may be temporarily necessary during acute psychotic episodes, the options recommended by the current prescribing guidelines are to choose an antipsychotic with sedating properties or to add a short-term benzodiazepine but not to combine different antipsychotics, and this should not prevent antipsychotic deprescribing [14]. Particular attention should be paid to reducing the number of antipsychotics given to these patients.

Overall, Belgian patients are more exposed to non-evidence-based prescribing patterns of psychotropic drugs than patients in the Canadian hospital. Lower adherence to schizophrenia prescribing guidelines increases healthcare costs and reduces quality-adjusted life-years, in addition to exposing patients to greater risks of adverse effects [56]. As both countries have universal health coverage, medication costs are unlikely to play a major role in these differences. A number of hypotheses can be put forward. Firstly, algorithms aimed at deprescribing psychotropics, such as BZRAs or antipsychotics have been advertised in Canada, but not in Belgium [26]. Promotion of these may have increased awareness of the necessity of deprescribing in Canada, and made psychiatrists more cautious about using antipsychotic polypharmacy. In addition, these different patterns may be due to differences in culture and norms between the two countries, with an evidence-based-medicine practice more common in Canada than in Belgium. A last hypothesis is the presence of a clinical pharmacist in the Canadian team, who may have encouraged deprescribing of antipsychotics and prescribing of clozapine, as well as the rational use of hypno-sedative drugs. Indeed, it is proven that psychiatric clinical pharmacists improve quality of care when included in mental health teams [57], and their interventions in psychiatry are associated with cost avoidance, especially regarding the use of antipsychotics [58]. Such services should therefore be encouraged.

The results of this study should be interpreted within their limitations. Explanatory variables were extracted from medical records. Some information was not always available if not systematically reported, such as adverse effects or the history and number of previous antipsychotic trials. However,

certain variables were dichotomised in the analysis to increase accuracy. Furthermore, the data from the Canadian population come from a single hospital in Québec, and generalisability to the whole situation in Canada cannot be assumed. In a previous study in the province of Ontario, Canada, inpatients with psychotic disorders received fewer LAI antipsychotics than in the Québec hospital, and also less APP, but a similar proportion of first-generation antipsychotics[59]. Moreover, in a national Canadian comparison, the proportion of LAI new starts was much higher in Québec than in other Canadian provinces[60]. Thus, since the treatment on admission reflects prescribing patterns in the outpatient setting, and is therefore not hospital-specific, it is more likely to reflect prescribing patterns in Québec more closely than those in other provinces.

5. Conclusion

Antipsychotic deprescribing is already performed in identifiable patients, settings or situations. Patients hospitalised in the Canadian hospital were more likely to be deprescribed than those hospitalised in Belgium. Belgian patients were also more exposed to low-value psychotropic prescribing than Canadian patients. Strategies and interventions should be developed and implemented to improve psychotropic prescribing and encourage antipsychotic deprescribing to achieve antipsychotic monotherapy. More complex deprescribing strategies should target patients who are less likely to be deprescribed.

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Table 1. Characteristics of included patients with schizophrenia or schizoaffective disorder hospitalised in the Belgian and Canadian hospitals

Characteristics	**Canadian patients (N=63)[†] N, (%)**	**Belgian patients (N=516)[†] n, (%)**	**p-value**
Sociodemographic characteristics			
Male	39 (61.9)	286 (55.4)	0.349
Female	24 (38.1)	230 (44.6)	
Age (y), mean (SD)	40 (12)	40 (12)	/
Single	39 (61.9)	420 (81.4)	0.269
Living situation			0.339
Residential facility	8 (12.7)	105 (20.3)	
Homeless	5 (7.9)	48 (9.3)	
Living alone or with relatives	50 (79.4)	363 (70.4)	
Legal guardian	5 (7.9)	217 (42.3)	**<0.001**
Unemployed	55 (87.3)	489 (94.8)	0.051
Medical characteristics			
Tobacco smoking	30 (47.6)	348 (67.6)	**0.009**
Alcohol use disorder	20 (31.8)	118 (22.9)	0.12
Substance use disorder	26 (41.3)	183 (35.6)	0.406
History of violent or aggressive behaviour	24 (38.1)	224 (43.6)	0.422
Intellectual disability	2 (3.2)	49 (9.5)	0.103
Prior suicide attempt	14 (22.2)	135 (26.6)	0.869
Illness duration (y), median (IQR)	9 (4-17)	12 (6-20)	0.085
Age of onset (y), median (IQR)	27 (21-32)	24 (19-30)	**0.017**
Hospitalisation characteristics			
Involuntary admission	51 (81)	104 (20.2)	**<0.001**
Length of hospital stay (d), median (IQR)	28 (15.5-55.5)	27 (13-52)	0.427
Antipsychotic adverse effect(s)	21 (33.3)	238 (46.2)	0.06
Primary diagnosis			**0.003**
Schizophrenia	37 (58.7)	398 (77.1)	
Schizoaffective disorder	26 (41.3)	118 (22.9)	

[†]Data were extracted from one hospital in Montréal, Canada and from 6 Belgian hospitals.

Table 2. Antipsychotic prescribing patterns in Belgium and Canada, before and after psychiatric hospitalisations

	Admission			**Discharge**		
	Canada (N=63)	**Belgium (N=516)**	**p-value**	**Canada (N=63)**	**Belgium (N=516)[1]**	**p-value**
APP	31 (49.2%)	247 (47.9%)	0.894	30 (47.6%)	305 (59.1%)	0.081
PDD/DDD	1.7 (IQR 1-2.6)	1.5 (IQR 1-2.3)	0.653	1.8 (IQR 1.1-2.4)	1.8 (IQR 1.1-2.5)	0.662
APP alternative definition	30 (47.6%)	183 (35.5%)	0.072	29 (46%)	227 (44%)	0.789
Number of antipsychotics per patient			0.861			0.062
2 antipsychotics	23 (36.5%)	182 (35.3%)		23 (36.5%)	216 (41.9%)	
3 antipsychotics	7 (11.1%)	57 (11%)		7 (11.1%)	76 (14.7%)	
4 antipsychotics	1 (1.6%)	7 (1.4%)		0	11 (2.1%)	
5 antipsychotics	0	1 (0.2%)		0	2 (0.4%)	
Type of antipsychotics			0.322			**0.002**
Only FGA	7 (11.1%)	41 (7.9%)		8 (12.7%)	45 (8.7%)	
Only SGA	43 (68.3%)	326 (63.2%)		46 (73%)	280 (54.4%)	
FGA+SGA	13 (20.6%)	149 (28.9%)		9 (14.3%)	190 (36.9%)	
At least one FGA	20 (31.7%)	190 (36.8%)	0.489	17 (27%)	235 (45.6%)	**0.005**
At least one SGA	56 (88.9%)	475 (92%)	0.342	55 (87.3%)	470 (91.3%)	0.351
Route of administration			**<0.001**			**<0.001**
Only LAI	18 (28.6%)	98 (19%)		22 (34.9%)	87 (16.9%)	
Only per os	20 (31.7%)	319 (61.8%)		14 (22.2%)	281 (54.6%)	
Per os + LAI	25 (39.7%)	99 (19.2%)		27 (42.9%)	147 (28.5%)	
At least one LAI	43 (68.3%)	197 (38.3%)	**<0.001**	49 (77.8%)	234 (45.4%)	**<0.001**
At least one per os	45 (71.5%)	418 (81%)	0.094	41 (65.1%)	428 (83.1%)	**0.002**

[1]515 patients for type and route of antipsychotics at discharge in the Belgian cohort as one patient discharged without any antipsychotic.

Fisher test for dichotomic variables and Chi² test for categorial variables with more than 2 categories. Mann-Whitney for quantitative with a non-normal distribution, t-test for quantitative with a normal distribution.

Abbreviations: APP, Antipsychotic polypharmacy; PDD, Prescribed daily dose; DDD, Defined daily dose; FGA, First generation antipsychotic; SGA, Second generation antipsychotics, LAI, Long-acting injectable antipsychotics

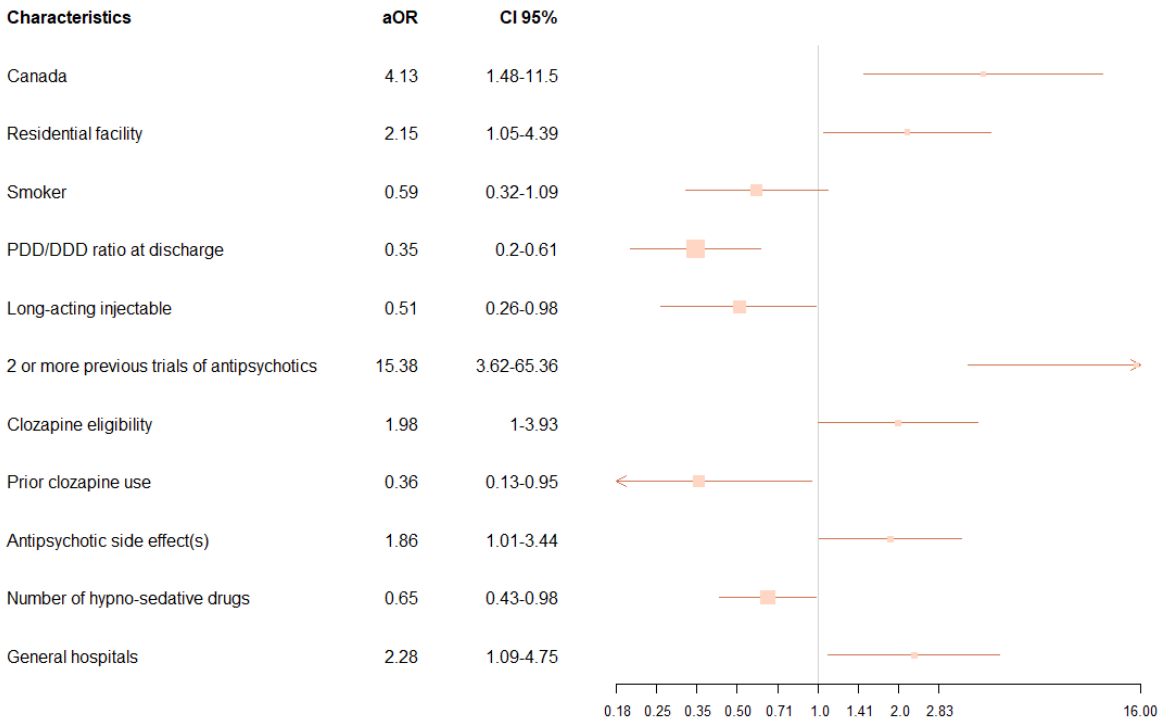

Figure 1. Factors associated with antipsychotic deprescribing at discharge from psychiatric hospitalisations in the multivariable model.

aOR, adjusted odds ratio; PDD/DDD, Prescribed Daily Dose on Defined Daily Dose.

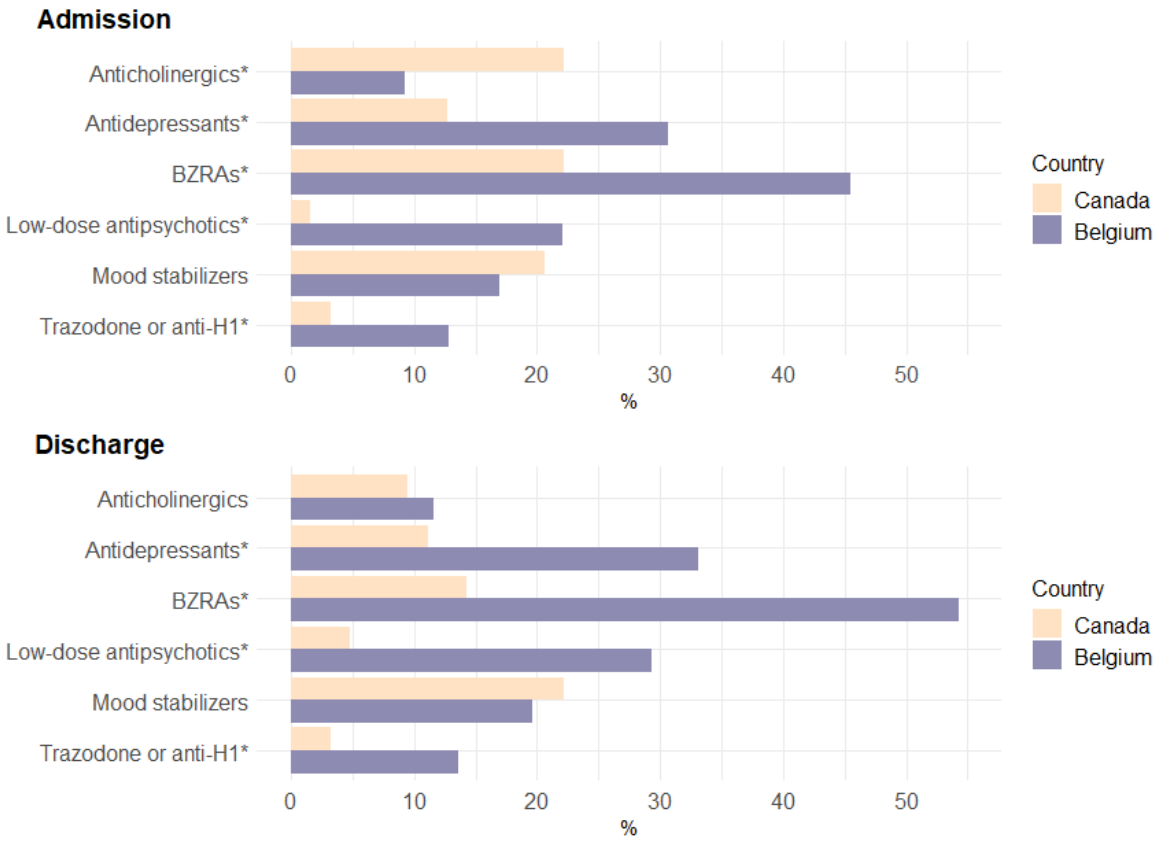

Figure 2. A. Psychotropic prescribing patterns in schizophrenia on admission of psychiatric hospitalisations in Belgium (N=516) and Canada (N=63).

B. Psychotropic prescribing patterns in schizophrenia at discharge from psychiatric hospitalisations in Belgium (N=516) and Canada (N=63).

At hospital admission, anticholinergics (p=0.004), antidepressants (p=0.003), benzodiazepines (p<0.001), low-dose antipsychotics for sleep disorders (p<0.001), and low-dose trazodone or sedating antihistamine (p=0.022) were significantly more prescribed in Belgium than in Canada. At discharge, antidepressants (p<0.001), benzodiazepines (p<0.001), low-dose antipsychotics for sleep disorders (p<0.001), and low-dose trazodone or sedating antihistamines (p=0.014) were significantly more prescribed in Belgium than in Canada. BZRAs, Benzodiazepine receptor agonists; anti-H1, Sedating antihistamines. *Statistically significant difference.