

Use of long acting antipsychotics and relationship to newly diagnosed bipolar disorder: a pragmatic longitudinal study based on a Canadian health registry

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Abstract

Background: There is limited data from large naturalistic studies to inform prescribing of long-acting injectable medication (LAIs). Guidance is particularly rare in the case of primary mood disorders.

Methods: This study describes prescribing trends of LAIs in 3879 patients in Quebec, Canada, over a period of 4 years. Health register data from the Quebec provincial health plan were reviewed.

Results: In this specific registry, 32% of patients who received LAIs drugs for schizophrenia had a confirmed diagnosis of bipolar disorder and 17% had a diagnosis of major depressive disorder. Non-schizophrenia syndromes were preferentially prescribed risperidone long-acting antipsychotic, whereas patients with schizophrenia were prescribed an excess of haloperidol decanoate. Patients with non-schizophrenia disorders prescribed long-acting antipsychotics were more frequently treated in primary care compared with patients with schizophrenia.

Conclusion: Data from a large number of patients treated naturalistically in Quebec with long-acting antipsychotics suggests that these compounds, prescribed to treat symptoms of schizophrenia and schizoaffective disorders, were maintained when mood symptoms emerged, even in cases when the diagnosis changed to bipolar disorder. This pragmatic study supports the need to explore this intervention as potential treatment for affective disorders.

Keywords: Antipsychotics, bipolar disorder, mood stabilisers, schizophrenia

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Introduction

Lehmann and Saucier pioneered the use of neuroleptics in North America approximately 65 years ago. In the 1950s, chlorpromazine was prescribed not only for schizophrenia or paranoid psychosis but also for mood disorders including manic episodes, recurrent mania and major depression.¹ Subsequently, prescribers' choice became more selective in treating the most severe psychotic pathologies, particularly because of the neurological side effects of first-generation antipsychotics.

In the mid-1990s, with the introduction of second-generation antipsychotics, the spectrum of action of neuroleptics became broader. In the last two decades, the availability of new molecules with better neurological tolerability and marketed new indications has favoured the expansion of the use of antipsychotics. These newer molecules with comparable effectiveness to first-generation antipsychotics, have, however, been associated with metabolic and vascular side effects requiring a risk–benefit analysis for each individual patient.²

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Mood disorders are often recurrent conditions with tremendous implications for the quality of life of affected individuals.^{3,4} Long term mood stabilisation is the essential aim of the treatment of mood disorders, which relies firmly on pharmacotherapy and psychotherapy.^{5,6} In bipolar disorder, the use of atypical antipsychotics is one of the treatment strategies used in monotherapy and as an adjunctive treatment, both in case of manic episodes and in prophylaxis.⁷ The use of long-acting antipsychotics in bipolar disorder is limited largely to risperidone formulations and aripiprazole, with uncertainty about their superiority over oral equivalents in prophylaxis, due mostly to lack of direct comparisons in controlled studies.^{8–10} In major depressive disorders, atypical antipsychotics can be used as an adjunct to mainstream first-line antidepressant treatment with no specific indication for injectable formulation.¹¹

In Canada, up to 50% of the 1–2% individuals diagnosed with bipolar or schizoaffective disorders, are prescribed long-acting antipsychotics.^{12,13} This approach is open to controversy, with concerns about the superiority of long-acting compounds in prophylaxis compared with their oral equivalent, the side effect profile of typical and atypical antipsychotics,^{14–17} and limitations in dopaminergic D2 blockade mechanisms to control mood symptoms.^{18,19}

The strongest evidence for prescribing long-acting injectable (LAI) antipsychotics is related to its effectiveness in cases of non-adherence to treatment, known to negatively impinge on outcome.²⁰ Guidelines regarding the use of long-acting antipsychotics in bipolar disorders tend to either promote the use of LAIs as maintenance monotherapy/adjunctive therapy with lithium or divalproex (e.g. Canadian Network for Mood and Anxiety Treatments),²¹ or more conservatively recommend their use when favoured by patients or in case of a recurrent pattern of illness driven by nonadherence (e.g. The American Psychiatric Association).²²

In this study, we present data from a naturalistic study conducted at population level from Quebec, Canada. The aim of the work was to explore prescribing patterns of long acting antipsychotics once patients initially treated for schizophrenia or schizoaffective disorder/other psychotic conditions received a subsequent diagnosis of bipolar disorder or major depressive disorder.

Methods

The study is based on the Quebec provincial health plan – a public health care program that provides all residents of Quebec with free health care access. The Regie de l'Assurance Maladie du Quebec (RAMQ) medical service database contains encrypted patient identifier information pertaining to physician service claims related to treatment and medication reimbursement for all health care concerns. Data related to long-acting antipsychotic reimbursement claims by physicians within the Quebec provincial health plan, as well as patients' demographic information, were extracted from the RAMQ database from 1 January 2008 to 31 March 2012 (index period). The RAMQ medical services database contains information from physicians' claims for services provided within and outside the hospital. The RAMQ pharmaceutical services database includes information from pharmacists' claims for dispensed medications reimbursed by the program, but not for medications received in a hospital. The RAMQ database also includes information on the insured person, such as age and sex, and information on the physicians, such as the period of graduation. Patients were selected if they (1) were prescribed a long-acting antipsychotic for the first time up to 12 months prior to the index period; (2) were at least 20 years old; and (3) had continuous enrolment in the database for at least 1 year prior to, and after, the index data. Diagnoses were established according to the International Classification of Diseases version 9 (ICD-9). At that time, the Quebec administration still used the ICD-9. Descriptive statistics, and non-parametric statistical tests (chi-square test unless stated otherwise and Fisher's exact test) were utilised to determine rates of patients with and without schizophrenia and to compare information pertaining the use of long-acting antipsychotics.

Similarly to previous articles published from the Regie de l'Assurance Maladie du Quebec (RAMQ) dataset,^{9,23} this study did not require an ethical board institutional approval. This is because the review board of the Ministry of Health and Social Services (Quebec) delivered the dataset and gave global approval to investigate and publish the data, having validated the anonymity and the security of the encrypted information. The consent of patients is embedded into the RAMQ. The review board is linked to the Ministry of Health and is in charge of issuing the ethical approval related to each question as requested by the researchers' team.

Results

A total of 3879 patients were treated with LAI antipsychotics over the 4 years duration of the study. Therapy was initiated for the treatment of schizophrenia ($n=1964$) or schizoaffective disorder/delusional disorder ($n=1915$). To our knowledge, patients did not start treatment for an initial diagnosis of bipolar disorder. Table 1 shows that, over the 4 years, a similar number of patients in both groups were confirmed bipolar cases (339 *versus* 319 respectively, $p=0.888$), and over 300 patients in each group developed a major depressive episode ($p=0.284$). Long-acting antipsychotics prescribed during the 4 years included typical (haloperidol decanoate, fluphenazine decanoate, zuclopenthixol LAI and flupentixol decanoate) and atypical (risperidone and paliperidone LAIs) compounds. Aripiprazole long-acting formulation was not available between 2008 and 2012 in Canada. Haloperidol decanoate was the most frequently prescribed long-acting antipsychotic medication in the case of initial diagnosis of schizophrenia ($p=0.001$), whereas long-acting risperidone was the most commonly prescribed in the non-schizophrenic group ($p<0.001$). In both groups, although the diagnosis changed, the long-acting medication of choice did not. Users of long-acting antipsychotics with confirmed diagnosis of schizophrenia were significantly more likely to be prescribed these medications by psychiatrists ($p<0.001$), whereas general practitioners prescribed more frequently for non-schizophrenia cases ($p<0.001$). Inpatient and outpatient psychiatric departments were the most frequent locations for long-acting prescribing in patients with schizophrenia ($p<0.001$).

Discussion

The purpose of this paper was to ascertain current trends in prescribing long-acting antipsychotics by reviewing the Quebec provincial health plan's RAMQ database over a 4-year period. The focus of the work was to ascertain the number of patients prescribed long-acting antipsychotics particularly in the context of a mood disorder diagnosis. It is notable that, within the Quebec provincial health plan, diagnoses changed from the time of the first clinical assessment. This could be related to more clinical information becoming available over time, and possibly to the cumulative effect of clinical impressions in different settings at different stages of illness. The analyses showed that, overall, there was no significant difference in the prescription of long-acting antipsychotics for patients with schizophrenia *versus*

non-schizophrenia, whilst the diagnosis changed to mood disorders during the course of time. Whilst haloperidol decanoate was more frequently prescribed in case of an initial diagnosis of schizophrenia, clinicians were more inclined to prescribe risperidone long-acting medication, a second-generation antipsychotic, in case of non-schizophrenia illness. The groups of patients with schizophrenia and schizoaffective disorder/delusional disorder contained a comparable number of patients whose primary diagnosis became later on, in the course of the 4 years, bipolar disorder. Furthermore, over 300 patients in each group developed symptoms of major depression in the same time period. Non-schizophrenia cases were more commonly treated by general practitioners rather than in specialised inpatient and outpatient psychiatric services. This could be related to severity of illness and/or operational arrangements in Quebec health services. Overall, 32% of patients who received long-acting antipsychotic medication and an initial diagnosis of schizophrenia had a final alternative diagnosis of bipolar disorder and 17% a co-diagnosis of major depressive disorder. Although the diagnosis changed, prescribing choices did not. There is no specific outcome data comparing the schizophrenia and non-schizophrenia groups available from this study. However, a naturalistic follow up for the whole group, recently published, suggests that the use of long-acting medication from the time of entry in the database to endpoint, resulted in approximately 50% reduction in hospital re-admission, a reduction in duration of episodes and CAD\$29,876 cost reduction per patient per year irrespective of diagnosis.²³ Taking into account the newly diagnosed mood disorder diagnoses that occurred within the same time period, this information indirectly supports the notion that long-acting antipsychotic medications may be effective in prophylaxis not just for schizophrenia but also for mood disorders, and could be included more confidently in treatment guidelines. Risperidone LAI was the second-generation antipsychotic most widely prescribed overall in this study and more frequently prescribed in cases of non-schizophrenic illness. This is not surprising as this injectable is the most investigated in controlled studies and in bipolar illness.²⁴ There is only one randomised controlled study investigating aripiprazole long-acting preparation in bipolar disorder and no controlled studies are available for paliperidone palmitate (one observational study and one case series) and olanzapine pamoate (case report).²⁵ Aripiprazole long-acting formulation was, however, not available in Canada at the time of the study and risperidone

Table 1. Treatment characteristics for patients diagnosed with schizophrenia and non-schizophrenia disorders at study entry and subsequent confirmed cases of mood disorders. The index drug was defined as the first LAI-AP prescribed between 1 January 2008 and 31 March 2012.

Initial diagnosis	Schizophrenia diagnosis (n=1964)	Schizoaffective/delusional disorder (n=1915)	p value
Confirmed cases of mood disorders, n (%)			
Bipolar disorder	639 (32.5)	619 (32.3)	0.888
Major depressive disorder	339 (17.3)	306 (16.0)	0.284
Long acting injectable antipsychotics, n (%)			
Haloperidol decanoate	200 (10.2)	137 (7.2)	0.001
Fluphenazine decanoate	346 (17.6)	310 (16.2)	0.235
Zuclopenthixol long-acting injection	351 (17.9)	349 (18.2)	0.775
Flupentixol decanoate	109 (5.5)	84 (4.4)	0.096
Risperidone long acting	760 (38.7)	851 (44.4)	<0.001
Paliperidone long acting	198 (10.1)	184 (9.6)	0.621
Speciality of the principal prescriber, n (%)			
Psychiatry	1629 (82.9)	1476 (77.1)	<0.001
General practice	327 (16.6)	418 (21.8)	<0.001
Atypical LAI-AP	8.4 (10.4)	8.6 (10.1)	0.668
Typical LAI-AP	5.1 (7.1)	4.3 (6.8)	0.001
Characteristics of the prescriber of the index drug, n (%)			
By speciality:			
Psychiatry	1579 (80.4)	1463 (76.4)	0.002
General practice	374 (19.0)	426 (22.2)	0.014
Location of dispensation			
Inpatient	216 (11.0)	140 (7.3)	<0.001
Emergency department	37 (1.9)	42 (2.2)	0.495
Psychiatric department	612 (31.2)	618 (32.3)	0.457
Outpatient	695 (35.4)	576 (30.6)	<0.001
Private clinic	125 (6.4)	124 (6.5)	0.888
Other	8 (0.4)	32 (1.7)	<0.001
Not available	271 (13.8)	383 (20.0)	<0.001
LAI-AP, long-acting injectable antipsychotics.			

microspheres/paliperidone palmitate were the only atypical long-acting compounds available. The evidence is more scattered for the superiority of typical injectable antipsychotics in comparison with oral equivalents in bipolar disorders. Evidence is difficult to gather in affective disorders,²⁶ and is often based on case series, retrospective studies and small randomised controlled trials. The most investigated compound, flupentixol long-acting, showed no clear superiority when compared with lithium or placebo.²⁷ It is of interest that haloperidol decanoate was prescribed more frequently in case of an initial diagnosis of schizophrenia.

As in patients with schizophrenia, adherence to treatment is, however, a major issue in the bipolar population.^{18,28} Up to 60% of patients do not take their medication regularly, and non-compliance is one of the negative prognostic factors most associated with relapse, thus contributing to a significant risk of re-hospitalisation, substance use disorders and suicide, and deterioration in long-term functioning.^{29–33} Increasing adherence to treatment therefore appears to be a priority therapeutic objective, hence the interest in long-acting antipsychotics.

Limitations

Limitations of this study include the fact that data presented in the registry may not accurately reflect population health trends. It might therefore demonstrate trends in practice-based medicine rather than evidence-based medicine. It was surprising that the diagnosis changed for so many patients from a formal diagnosis of schizophrenia or non-schizophrenic disorder into a mood disorder, even taking into account that diagnoses can be unstable over time.^{34,35}

Elucidation of the reasons for changes in diagnosis within the Quebec health services is highly recommended. This is also essential to effectively personalise treatment based on the best evidence-based options for a given diagnosis at any given time. On the other hand, the persistence of treatment despite diagnostic changes, suggests the possibility that the treatment (i.e. long acting antipsychotics) contributed to stabilise the clinical presentation. The major limitation of the study is that the time frame does not cover the last 8 years. The study time window was the most recent we could obtain permission for to retrospectively analyse the data from the local Quebec government. Details such as the number of hospitalisations, use/reduction in concurrent medications, adverse effects [weight

gain, cardiovascular impacts, diabetes, etc.] if recorded could have provided useful information and allow evaluation of positive and negative predictors in response to treatment with LAIs and clinical diagnosis as shown in recently published work.^{36,37} Nevertheless, information regarding prescription patterns can be informative in its own right,³⁸ and a useful stepped approach towards developing a comprehensive and inclusive registry regulated by governmental agencies.³⁹ Another advantage of this type of studies is that it minimises recruitment difficulties.⁴⁰ Other limitations include the possibility of selection bias, in that more severe patients could have dropped out or moved out of Quebec. Furthermore, we did not have measures of severity, which could have helped to better understand medication choice. We are also not able to comment as to whether the patients received additional treatment as any compound other than LAI antipsychotics were not monitored within the registry.

Conclusion

Future analyses of the Quebec registry should include information regarding demographic and clinical variables in patients with mood disorders maintained on LAIs to be able to ascertain predictors of treatment response and/or diagnostic changes possibly in comparison with oral medications. The data presented here supports collaborative work with governmental agencies to improve our understanding of mental disorders and their treatment. Data from a large number of patients treated naturalistically in Quebec with long-acting medication suggest that injectable antipsychotics prescribed to treat symptoms of schizophrenia and schizoaffective disorders were maintained when mood symptoms emerged, even in cases when the diagnosis changed to bipolar disorder. Although direct evidence of outcome is not available for the patients who developed mood symptoms, an extrapolation of data published from this cohort, indicates an overall improved prophylaxis from time of entry to endpoint. In the absence of controlled studies, large cohorts such as this one may provide information regarding current prescribing trends and guide decision making. Nevertheless, to generalise findings from this cohort, further research is necessary to directly compare the superiority of injectable antipsychotics to oral equivalents in the prophylaxis of mood disorders for atypical and typical long-acting antipsychotics in different health systems.

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