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# Short communication: Prevalence of long-acting injectable antipsychotic use in Canadian early intervention services for psychosis

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A B S T R A C T

The use of long-acting injectable (LAI) antipsychotic drugs for psychotic disorders in Canada has been historically low compared to other jurisdictions despite advantages of LAIs in improving medication adherence and preventing relapse. In response, treatment recommendations were developed in 2013 by the Canadian Consortium for Early Intervention in Psychosis and other Canadian provincial expert groups. The impact of these guidelines needed to be assessed. To document practices in LAI use in early intervention services (EIS) for psychosis, Canadian EIS were surveyed in 2016 (n = 18) and 2020 (n = 12). Trends and descriptive information were examined using repeated cross-sectional survey data. Eight EIS responded to surveys at both time points allowing for longitudinal comparisons. Outcomes of interest included i) LAI use frequency, ii) timing of LAI starts, and iii) factors influencing LAI use. Cross-sectional analysis identified a significant increase in overall LAI usage (24.7% in 2016; 35.1% in 2020). Longitudinal analysis indicated that patients in the second program year saw the greatest increase in LAI use between 2016 and 2020 (25.6% vs. 36.1%), especially among patients under community treatment orders (65.5% vs. 81.5%). Results support increases in LAI use over time, accessibility, awareness, and increasing comfortability among Canadian clinicians.

## 1. Introduction

Long-acting injectable (LAI) antipsychotic medications have been used for the long-term treatment of psychotic symptoms since their development in the 1960s. Availability and prescribing patterns of LAIs vary by country, however they are most often indicated for use in the treatment of individuals with schizophrenia, schizoaffective disorder, and bipolar disorder. Their utility in service delivery (e.g., improved medication adherence, lower rates of treatment discontinuation, lower rates of relapse, reduced hospitalizations, lower overall healthcare cost burden, and lower mortality) has been demonstrated in meta-analyses of randomized control trials (Kishi et al., 2021; Kishimoto et al., 2021; Lian et al., 2022; Lin et al., 2021; Olagunju et al., 2019; Ostuzzi et al., 2021; Park et al., 2018; Uribe et al., 2020), mirror image studies (Bartoli et al., 2022a; Bioque et al., 2020; Fefeu et al., 2018; Mahlich et al., 2020; Miura et al., 2019; Ostuzzi et al., 2023; Pappa and Mason, 2020) and population-based registries (Brodeur et al., 2022a, 2022b; Taipale et al., 2018; Takács et al., 2019; Wu et al., 2016). Interestingly, levels of LAI use have varied both geographically (Agid et al., 2010) and over time, with a noted decrease in use when oral second-generation antipsychotics were introduced with purported better side-effect profiles when compared to the first-generation long-acting injectable antipsychotics

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(FG-LAIs) (Mond et al., 2003). The introduction of second generation long-acting injectable antipsychotics (SG-LAIs) have since renewed the role of LAIs in the treatment of psychotic disorders, with a community-based study from 2007 to 2014 reported rising rates of LAI prescribing, reportedly due primarily to increasing rates of SG-LAI prescriptions (Verdoux et al., 2016) and there is preliminary evidence for such an increase in the Province of Québec as well (Roy, 2020).

Appreciating that the use of LAIs for psychotic disorders in Canada had been historically low (~6%) compared to regions in Europe, Australia and China (25%–36%) (Barnes et al., 2009; Jablensky et al., 2000; Weiden, 2013; Williams et al., 2006; Xiang et al., 2008), members of the Canadian Consortium for Early Intervention in Psychosis (CCEIP), a national not-for-profit organization of early intervention services clinicians and researchers, published Canadian treatment recommendations in 2013 (Malla et al., 2013; Manchanda et al., 2013) as well as Canadian provincial expert groups (Stip et al., 2011). These recommendations were not only informed by the quantitative literature on the potential benefits of LAIs over oral antipsychotics at this phase of illness, but additionally by qualitative studies including physician and patient perspectives on LAI use (Iyer et al., 2013a, 2013b; Manchanda et al., 2013). In particular, the first recommendation stated that "the existence and potential use of LAIs for antipsychotic therapy should be discussed with patients and families at all phases of illness, including the 'critical period' of the first two-to five-years" (Malla et al., 2013). This recommendation promoting greater use of LAIs during the early phase of psychosis illness aimed to prevent relapses and hospitalizations in vulnerable patients (Kane et al., 2020), prolong periods of remission (Abdel-Baki et al., 2020) and facilitate engagement in psychosocial interventions and rehabilitation in early psychosis patients otherwise unlikely to engage in these aspects of treatment. A group of experts has recommended systematically offering LAIs in the first few weeks of initiating treatment for a first psychotic episode (Stip et al., 2011, 2019).

LAIs can ensure continuous pharmacological treatment in the context of phase appropriate integrated care, which could allow for the goal of sustained remission, and be vital for improving functional outcomes. The current rate of LAI use in early phase psychosis in Canada remains unknown, especially with the more recent availability of SG-LAIs, and in the context of evidence-based care through early intervention services (EIS) for psychosis. Compared to other psychosis treatment models, EIS aim to provide treatment to patients as soon as possible after their first episode of psychosis and typically involve a more comprehensive approach to treatment that includes addressing the individual's social and occupational needs, in addition to symptom reduction (Nolin et al., 2016). The aim of this investigation was to evaluate the evolution of LAI use over time in Canadian EIS for psychosis at two time points (2016 and 2020) with data elements designed within the framework of the 2013 Canadian recommendations (Malla et al., 2013). We hypothesised that the rates of LAI use would be higher than the previously reported rate of 6% (Williams et al., 2006) and increasing over time in Canada for this discrete population of individuals experiencing psychosis using an in-depth survey approach of EIS programs to explore this hypothesis.

## 2. Methods

### 2.1. Instrument

A CCEIP expert working group developed an in-depth online survey of LAI use in Canadian EIS. The questionnaire was pilot tested for content validity by four authors (PGT, MAR, AB, AM) with a range of clinical and research expertise. The EIS that were contacted to participate in the survey were identified by multiple mechanisms including existing membership in CCEIP, health region/provincial health websites and regional early psychosis networks (e.g., Early Psychosis Intervention Ontario Network, EPION).

The initial survey distributed in 2016 (see supplement 1) consisted of 47 questions in five domains: program characteristics, number of patients in EIS, administration, treatment specifics, and factors influencing LAI use. The follow-up survey distributed in the last six months of 2020 (see supplement 2) included the same five domains but was reduced to 36 questions to encourage a higher completion rate. Note that distribution of the follow-up survey coincided with the onset of COVID-19 related restrictions across Canada, delaying the distribution of the follow-up survey that year and likely impacting the overall response rate. For both surveys, contacts were made with participating sites when indicated for completion of missing data or data clarification. This research was conducted exclusively with secondary use of anonymized data collected from existing EIS databases, and as such did not fall within the scope of Research Ethics Board review. This research was conducted according to the Declaration of Helsinki.

### 2.2. Data analysis/outcomes measured

Investigated variables included EIS program length, population density served, number of active patients, total LAI use, LAI use by program year, LAI use associated with CTO/extended leave, FGA-vs SGA-LAI use, medication switch events, administration protocols, LAI formulations used, starting and maintenance doses, timing of LAI starts, barriers to LAI use, hospitalization, and relapse frequency. Variables of interest were also analyzed for gender related differences.

Descriptive statistics were used to describe patient demographic data and aggregate data on frequency of LAI use, and timing of LAI starts during the EIS program at both survey time points. ANOVAs were used to examine cross-sectional data trends across time points, and Fisher's exact test was used for examining longitudinal trends. Statistical analyses were performed where appropriate using SPSS 22.0 (IBM corporation) and were conducted only for valid comparisons with a sample size of five sites, or greater. Respondents also had the option to provide free-text responses for several questions. Where applicable, free-text responses are reported directly as a list of all responses.

## 3. Results

### 3.1. Program characteristics, patient demographics, and LAI usage data

Detailed EIS program characteristics, patient demographics and LAI use frequency data are presented in Table 1. The specific LAI formulations used at each time point (reported as total patient numbers) are detailed in Supplement 3. Long-acting injectable antipsychotic starting doses (mg) and maintenance doses (mg) are detailed in Supplement 4. In 2016, of fourteen programs responding with detailed information, there was a significant difference ($p < 0.001$) between use of FG-LAIs and SG-LAIs with almost exclusive use of SG (97.5%; range 86–100% of the population on LAI medication) versus FG (2.5%; range 0–15%). In 11 programs responding in 2020, the ratio of FG-LAIs and SG-LAIs use remained largely unchanged, with SG-LAIs accounting for 96.8% all LAI medication prescribed across EIS clinics (range 84.2–100%), versus 3.3% for FG-LAIs (range 0–15.8%). Furthermore, the proportion of patients started on aripiprazole vs. paliperidone was similar at both time points (2016: 41.2% and 49.0% respectively; 2020: 49.7% and 47.4%).

In 2016, a relatively small number of patients were reported to have been switched from an LAI back to an oral formulation in the last year (41 patients from a cohort of 458 (9.0%); 13 sites reporting). The number of reported LAI switch events in the past year nearly doubled among the 2020 cohort (96 patients from a current cohort of 596 (16.9%); ten sites reporting).

### 3.2. LAI administration protocols

In 2016, of the 14 sites who responded with information regarding LAI administration protocols, 64.3% reported that they performed injections on-site, and 69.2% said that the EIS clinical nurse was also the

**Table 1**
Summary data comparisons for full complement of surveys from 2016 (N = 18 EIS programs) and 2020 (N = 12 EIS programs).

| Variable | | 2016 | 2020 | Significance |
|---|---|---|---|---|
| Sample size (N of patients) | | 2574 | 2284 | – |
| Gender | Men (% mean ± SD) | 67.3 ± 14.8 | 70.0 ± 9.6 | ns |
| | Women (% mean ± SD) | 31.8 ± 12.7 | 29.6 ± 9.7 | ns |
| | Transgender (% mean ± SD) | 0.9 ± 2.5 | 0.4 ± 0.6 | ns |
| Total LAI Use (all years in program) | | 24.7 ± 11.9 | 35.1 ± 9.5 | $p < 0.05$ |
| Proportion of LAI using patients, by gender | Men (% mean ± SD) | 29.7 ± 12.2 *N = 15* | 39.3 ± 9.0 | ns |
| | Women (% mean ± SD) | 20.1 ± 10.7 *N = 15* | 25.1 ± 11.8 | ns |
| | Transgender (% mean ± SD) | 33.3 ± 47.1 *N = 15* | 20.8 ± 33.2 | ns |
| LAI use associated with CTO/extended leave | | 17.9 ± 15.1 *N = 13* | 22.3 ± 22.4 | ns |
| LAI use on CTO/ extended leave, by gender | Men (% mean ± SD) | 84.3 ± 15.6 | 89.2 ± 7.5 | ns |
| | Women (% mean ± SD) | 15.7 ± 15.6 | 10.8 ± 7.5 | ns |
| | Transgender (% mean ± SD) | – | – | – |
| EIS Program Length (years) | <2-years | 1 | 0 | – |
| | 2-years | 4 | 1 | – |
| | 3-years | 7 | 6 | – |
| | 4-years | 1 | 0 | – |
| | 5-years | 4 | 5 | – |
| | no fixed length | 1 | 0 | – |
| LAI Use in Year-1 (% mean ± SD) | | 34.0 ± 22.6 *N = 15* | 35.8 ± 15.2 | ns |
| LAI Use in Year-2 (% mean ± SD) | | 37.2 ± 25.3 *N = 13* | 38.2 ± 10.4 | ns |
| LAI Use in Year-3 (% mean ± SD) | | 28.4 ± 14.5 *N = 11* | 32.7 ± 17.2 *N = 11* | ns |

**Note.** *Not all sites provided data for every question. Data based on partial samples are indicated by the inclusion of the number of responding EIS programs (N = # of EIS programs).*

patient's case manager, administered the injections. Of the 14 sites, eleven reported that EIS nurses were responsible for administering LAI injections, four sites used a psychiatric nurse outside of the EIS program, three sites used community nurses (e.g., emergency room/community health centre nurse/nurse practitioners), and one site referred patients to their general practitioner.

In 2020, all 12 sites provided detailed information about LAI injection administration: 10 (83.3%) reported that injections were typically administered on-site, one clinic provided injections at home or a nurse's office, and one clinic administered injections at a nearby hospital. Six clinics reported that EIS nurses were responsible for administering injections to patients. Two clinics identified psychiatric nurses outside of the EIS program as the staff person responsible for administering injections. Four clinics reported that both EIS nurses and outside psychiatric nurses shared the responsibility of administering injections to patients. The patient's case manager/EIS clinical nurse who administered patient's LAI injection was the same person at eight clinics.

### 3.3. Hospitalization and relapse frequency

Delays in commencement of LAI use were examined by assessing hospitalizations and relapses prior to start of LAI treatment. In 2016, on average, patients experienced at least one hospitalization after admission to the EIS (1.4 ± 0.5) and one relapse (1.6 ± 0.7) prior to starting an LAI (n = 14). It was noted by one respondent in 2016 that their associated inpatient unit would not start LAIs on inpatients. It was found that 13.7% (13.7 ± 20.0) of patients were started on LAIs prior to being referred to an EIS. This could suggest that in 2016, over half the patients on LAIs were started in the EIS services surveyed prior to entering the EIS as the overall survey rate of LAI use was 25.5%. However, only half of the clinics (n = 9) responding to the survey answered this question and a large variability was observed (0–60% of patients).

Similarly, in 2020, patients had at least one hospitalization (1.1 ± 0.7) and one relapse (1.0 ± 0) prior to starting an LAI (n = 11). Information related to use of LAIs prior to EIS referral was not collected in 2020. However, EIS were asked to provide estimates for the number of LAI using patients who were still using an LAI following discharge from the EIS. At six-months following discharge, on average 88.7% ( ± 15.0) of patients were still using an LAI (n = 9 clinics); at one-year after discharge, 71.3% ( ± 15.5) were still using an LAI (n = 8), and at two-years after discharge, 59.3% ( ± 22.6) of patients were still using an LAI (n = 7).

### 3.4. Barriers to LAI use

When EIS clinics were asked to identify the primary barriers that prevented greater use of LAIs among their patient population, several themes emerged. This question included a free-text field. In 2016, of the 14 clinics that provided detailed information with respect to barriers, patient choice was the most cited factor influencing the rate of LAI use (n = 12 clinics), adherence issues (n = 6), cost (n = 3), lack of response (n = 1), tolerability (n = 1) and physician experience (n = 1).

Of the nine EIS clinics that provided detailed information about barriers in 2020, patient choice (n = 3) and cost (n = 3), convenience (n = 2), adherence issues (n = 1), lack of response (n = 1), and COVID-19 (n = 1) were the most identified factors influencing the rate of LAI use. Two clinics responded no identifiable barriers to LAI usage.

### 3.5. Longitudinal comparisons between 2016 and 2020

Eight programs responded to both the 2016 and the 2020 surveys allowing for comparisons in trends over time. Of the programs that responded at both time points, one was a two-year program, four were three-year programs and three programs followed patients for five-years. See Table 2 for detailed longitudinal comparisons of LAI use.

## 4. Discussion

It is optimistic that the overall use reported here (24.7% of 2574 patients in 2016, and 35.1% of 2284 patients in 2020) in sample of Canadian EIS programs (including rural, urban, hospital, and community-based clinics) increased over the study period and is higher

**Table 2**
Prevalence of long-acting injectable (LAI) antipsychotic use in Canada: longitudinal trends in LAI usage for eight Canadian early intervention service clinics with repeat data.

| Cohort | % Use (on LAI/ total) 2016 | % Use (on LAI/ total) 2020 | Significance |
|---|---|---|---|
| Sample size (N of patients) | 1193 | 1260 | |
| Total LAI use of all programs (2–5 years) | 28.9 (345/ 1193) | 34.1 (429/ 1260) | $p = 0.007$ |
| Use in Year-1 | 37.2 (107/288) | 33.6 (159/473) | ns |
| Use in Year-2 | 25.6 (52/203) | 36.1 (131/363) | $p = 0.01$ |
| Use in Year-3 | 29.4 (47/160) | 27.6 (73/265) | ns |
| LAIs use among patients on CTO/extended leave | 65.5 (36/55) | 81.5 (88/108) | $p = 0.03$ |

Fisher's exact test; ns = non-significant.

than the 6% that was reported in a 2006 mixed sample of early and chronic phase patients (Williams et al., 2006). Notably, the Canadian rates of LAI use reported here are on par with previously reported rates throughout Europe, Australia, and China (Barnes et al., 2009; Jablensky et al., 2000; Williams et al., 2006; Xiang et al., 2008). This is in line with the evidence showing benefits of LAI treatment for both early and later phases of psychotic illness. It is also important to note these survey results show that LAIs are currently being used early in the course of illness (28.8% of those in first year of an EIS program when surveyed on 2016; 31.6% in 2020) with a majority being initiated without the coercive/-legal context (e.g., community treatment orders), and increasingly as part of routine clinical care. The administration of LAIs in EIS for psychosis has evolved in that over two-thirds of the programs (78.6% in 2016; 83.3% in 2020) identified that the individual's case-manager/nurse gave the injection, and that majority of programs did not follow the more traditional injection clinic model that clinicians were familiar with in the chronic schizophrenia population prior to the 1990s, where patients would be referred to a separate injection clinic rather than having their LAI administered by their treating clinician or team. This patient centered approach can allow for better continuity of care and engagement with the EIS program.

A majority of early phase patients in this study were on SG-LAIs at maintenance doses not unexpected for this cohort and within product monographs for each formulation. Paliperidone palmitate and aripiprazole monohydrate were the most prescribed LAI at both time points (2016: 49.0% and 41.2%; 2020 47.4% and 49.7%). Recent prospective data suggests that both paliperidone (1-month) and aripiprazole do not significantly differ in terms of effectiveness (i.e., hospitalization rates and Brief Psychiatric Rating Scale scores) and acceptability (i.e., discontinuation rates) (Bartoli et al., 2022b). In general, the side effect profile for SG-LAIs is thought to be more favorable than FG-LAIs, the EIS programs in Canada were monitoring for potential side effects on a regular basis with standardized rating scales (Barnes, 2003; Chouinard and Margolese, 2005; Guy, 1976; Haro et al., 2003; Hastings, n.d.). This early recognition and management of potential side effects has been shown to improve adherence as, for example, parkinsonian side effects may increase discontinuation of medications (Robinson et al., 2002).

Given the potential benefits to outcomes, it may be questioned why the use of LAIs in early phase psychosis is not even higher in Canada than our current results indicate. Barriers may include lack of awareness, knowledge, experience, and attitudes of LAIs by clinicians [e.g. (Iyer et al., 2013a, 2013b),]; cost, convenience, regional differences in ease of access to SG-LAIs including variations across Canada in provincial formularies; and direct costs and staffing for administrators and policy makers (Parellada and Bioque, 2016). An additional novel barrier identified in 2020 was the COVID-19 pandemic. While the transition of services to a remote delivery model may have imposed challenges to many EIS clinics; overall Canadian LAI prescribing trends were found to have remained markedly stable throughout the pandemic (McKee et al., 2021). Identifying and addressing these barriers to care, as well as inclusion of LAI formulations in early phase psychosis treatment algorithms has been an active focus of care in the last years which may have allowed the increased LAI use reported here.

### 4.1. Limitations

The results of the present study should be considered in view of the following limitations. Repeated cross-sectional data may be susceptible to a non-response bias. Notably, a minority (22%) of Canadian EIS programs responded to the survey (n = 22 EIS programs), and not all participating sites were able to provide data for every section of the survey. A major contributor to non-responsiveness was reportedly due to programs not having the required database infrastructure to easily complete the surveys which indicates an area for improvement to allow further research on this topic.

While hospitalization and relapse data prior to LAI treatment was briefly discussed, post-LAI treatment hospitalization data was not collected and was outside the scope of this study. The impact of higher rates of LAIs on hospitalization and relapse outcomes would be an important topic for future research.

## 5. Conclusions

The use of LAIs in early phase psychosis has increased in Canada between 2016 and 2020 and is on par with rates reported in other countries with similar demographics and levels of healthcare access. Results indicate that LAIs are being used earlier in the course of illness and with a patient-centered approach, allowing for better continuity of care and engagement with EIS programs. The majority of LAI using early phase patients in the study were on SG-LAIs at recommended maintenance doses. Barriers to wider adoption of LAIs still remain. Identified barriers included lack of awareness, knowledge, experience, and attitudes of clinicians, cost and convenience, regional differences in access, as well as staffing and policy considerations. Future research focused on identifying and addressing the identified barriers may help to increase the use of LAIs early in the course of illness and improve outcomes for patients. Further research is also needed to assess the impact of higher rates of LAIs on hospitalization and relapse outcomes.

## CRediT authorship contribution statement

**Kyle A. McKee:** Validation, Formal analysis, Data curation, Writing – original draft, Visualization. **Candice E. Crocker:** Methodology, Conceptualization, Writing – original draft, Writing – review & editing, Formal analysis, Data curation, Supervision. **Katerina Dikaios:** Validation, Writing – original draft, Writing – review & editing. **Nicola Otter:** Writing – review & editing. **Andrea Bardell:** Writing – review & editing. **Marc-André Roy:** Validation, Writing – review & editing. **Amal Abdel-Baki:** Validation, Writing – review & editing. **Lena Palaniyappan:** Writing – review & editing. **Ashok Malla:** Validation, Writing – review & editing. **Philip G. Tibbo:** Conceptualization, Methodology, Validation, Writing – original draft, Supervision.

## Declaration of competing interest

Authors P.G.T and M.A.R have received honoraria for speaking and has sat on advisory boards for Janssen Inc., Abbvie, and Otsuka Lundbeck alliance, outside the submitted work. Author L.P. reports personal fees for serving as chief editor from the Canadian Medical Association Journals, speaker/consultant fee from Janssen Canada and Otsuka Canada, SPMM Course Limited, UK, Canadian Psychiatric Association; book royalties from Oxford University Press; investigator-initiated educational grants from Janssen Canada, Sunovion and Otsuka Canada outside the submitted work. L.P. acknowledges research support from the Monique H. Bourgeois Chair in Developmental Disorders and Graham Boeckh Foundation (Douglas Research Centre, McGill University) and salary award from the Fonds de recherche du Quebec-Sante (FRQS). Author A.B. has received speaker fees and sat on advisory boards for Janssen Inc., HLS Therapeutics, Otsuka, Lundeck, and Abbvie. The remaining authors declare no potential competing financial interests with respect to the research, authorship, and/or publication of this article.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

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