*Key Words: schizophrenia spectrum, psychotic disorders, observational study, first-episode psychosis, clinical outcomes, long-acting injectable antipsychotics*

# Three-Year Naturalistic Study On Early Use Of Long-Acting Injectable Antipsychotics In First Episode Psychosis

*By Sofia Medrano, Amal Abdel-Baki, Emmanuel Stip, Stéphane Potvin*

***ABSTRACT*** *~ Poor adherence to antipsychotics, which affects outcome, is frequent in first episode psychosis (FEP). Most randomized studies demonstrate no superiority of long-acting injectable antipsychotics (LAI-AP) over oral antipsychotics (OAP). However, participants in these studies represent a minority of patients who may benefit from LAI-AP. Mirror and naturalistic studies generally demonstrate efficacy of LAI-AP on more representative samples, but studies on FEP are scarce.* ***Aim****: To describe LAI-AP's utilization and impact on FEP outcome in a naturalistic setting.* ***Methods****: A 3-year longitudinal prospective and retrospective descriptive study of all consecutive admissions from two Early Intervention Services for psychosis (EIS) in Montréal, Canada, compared the characteristics and evolution of patients who received LAI-AP for at least 12 months to those who received OAP only.* ***Results****: From 375 FEP patients included, 26,7% received LAI-AP during their follow-up. They were more likely to have poor prognostic factors (male gender, lower premorbid functioning, homelessness, substance use disorder and schizophrenia spectrum diagnoses). Despite a more severe illness and lower functioning in the LAI-AP group, at admission and study endpoint, clinical and functional improvements were observed.* ***Conclusion****: Early prescription of LAI-AP seems beneficial in FEP with poor prognostic factors.* Psychopharmacology Bulletin. *2018;48(4):25–61.*

## Introduction

Despite high response rates in first episode psychosis (FEP), relapses are frequent – 40%–50% of patients relapse within 2 years[1] – mainly because of poor

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adherence to medication (more than 50% of patients during the first year),[2–4] and of comorbid substance use disorder (SUD)[5] in 30 to 70% of patients,[6,7] SUD being a culprit of poor adherence.[8]

Long-acting injectable antipsychotics (LAI-AP), by removing the need for daily intake of medication, represent a promising tool to overcome poor medication adherence in FEP, therefore improving the poor outcome associated with it. Indeed, in schizophrenia and FEP patients, LAI-AP have been shown to reduce the risk of relapse[9–12] and also of rehospitalization by about 20%–60%[13–15] in comparison to oral antipsychotics (OAP). However, other studies and meta-analyses report no superiority of LAI-AP over OAP.[16–19] These contradictions in terms of relapse rate or symptom reduction[2] probably stem from distinct methodologies including different measurement tools (e.g., definitions of relapse vary from one study to another, scales used), heterogeneous inclusion/exclusion criteria and unsimilar study designs, i.e., randomized controlled trials (RCTs) vs naturalistic studies.[20] Of note, RCTs tend to create a cohort bias by usually including stabilized patients with a less severe sickness, better cognitive capacities, and good adherence to medication or good engagement toward health professionals in order to improve homogeneity of their sample and maximize the probability of finding results.[9,18] Also, in many clinical trials, particularly RCTs, there is alteration of the therapeutic experience: more attention, financial compensation, free medication, more frequent visits with physician and appointment reminders.[9,18,20] Several studies exclude patients with poor adherence and SUD, creating a favorable bias toward OAP and a lower degree of external validity.[20] Hence, they do not reflect the reality of everyday clinical practice.[2,17]



Furthermore, there is an absence of data on the impact of LAI-AP on the outcome of young adults with FEP,[9,10] but also a lack of knowledge regarding the characteristics of individuals to whom are prescribed LAI-AP in everyday clinical practice.

In this context, we first sought to describe, in a naturalistic setting, the utilization of LAI-AP and the characteristics of FEP patients who are prescribed LAI-AP compared to those who are prescribed OAP. Secondly, we compared the symptomatic and functional outcome, and service use of FEP patients treated early in the course of their illness with LAI-AP versus those who received OAP.

## Method

### *Study Design and Subjects*

A prospective and retrospective longitudinal naturalistic 3-year study took place in two urban early intervention services (EIS) in the University of Montreal's network of early psychosis specialized intervention programs in Montréal, Québec, Canada.[21] Both programs offer services to all FEP patients in their respectively defined catchment areas. The EIS were *Programme PEP* of the *Institut Universitaire en Santé Mentale de Montréal*, covering a population of 340,000 inhabitants in the eastern part of the city, and *Clinique JAP* of the *CHUM*, located in the city center and covering a catchment area of 225,000 inhabitants. The 5-year programs provide specialized treatment based on early psychosis intervention guidelines, including an array of psychosocial treatments, case management and pharmacological treatment.[22]

The study was approved by the institutional ethics and scientific committees. Recruitment started in fall 2005 until April 30th 2012. Patients were approached when stable and apt to provide written informed consent. In order to avoid major biases and to better represent the whole population, file reviews of FEP patients who refused to participate or who had not been approached for different reasons, i.e., not able to provide consent, or lost to follow-up (LTF) early, were authorized by the ethics and scientific committees and the Hospital Direction. Indeed, the description of the entire cohort, including those who are more suspicious or reluctant to collaborate to care or research, is of primary importance since many of these FEP patients were good candidates for LAI-AP.



The inclusion criteria were age 18–30 and a primary diagnosis of untreated psychotic disorder or within 1 year of treatment initiation. Patients with FEP and a comorbid disorder (e.g., SUD or cluster B personality) were included. Patients with a primary intellectual disability were excluded. A subject was also excluded if he received an antipsychotic medication from another institution within a year of admission in our EIS and if we did not have the necessary information on his treatment and could not assess with precision his adherence to medication.

### *Group Categorization*

Eligible patients were classified in two study groups. The first consisted of patients who received LAI-AP medication for at least 12 months during their 36 months follow-up (f/u). This group might have received OAP medication during their f/u (both before, after or during

LAI-AP). The second group consisted of FEP patients who were only prescribed OAP or who were prescribed OAP and a trial of 3 months or less of LAI-AP (since their exposition to the LAI-AP was insufficient to consider its impact on outcome). Those who took LAI-AP for >3 months, but <12 months were excluded (as it was difficult to evaluate the impact of LAI-AP because of insufficient but still significant exposition to LAI-AP), making this group different from the one receiving only OAP.

### *Assessments*

Socio-demographics, symptoms and functional data were collected at admission and annually for three years. A research assistant trained in the administration of psychometric scales interviewed the patients and reviewed files for the collection of socio-demographic data, Positive and Negative Syndrome Scale) (PANSS),[23] Calgary Depression Scale for Schizophrenia (CDS),[24] Quality of Life Scale (QLS),[25] Drug Use Scale (DUS), Alcohol Use Scale (AUS),[26] and types of substances abused. Inspired from Childhood trauma questionnaire items (CTQ),[27] childhood trauma history was collected from file review or clinicians and patient interview (when possible) on the different types of trauma experienced before the age of eighteen: negligence, physical, psychological and sexual abuse, foster care, bullying, parents' separation/divorce, separation from caregiver and caregiver's death. If one of these types of trauma was present, history of childhood trauma was considered positive.



DSM-IV-TR[28] diagnoses of psychotic disorder, SUD and Cluster B personality traits or disorder were determined by the best-estimate consensus method[29] with all available data considered by 2 raters (one psychiatrist and either a psychiatry resident, a medical doctor or another psychiatrist). Although all Cluster B personality traits were noted, the most frequent presentation was borderline and antisocial personality traits not better explained by a DSM-IV axis I disorder.

The Social and Occupational Functioning Assessment Scale (SOFAS),[30] the Global Assessment of Functioning (GAF) Scale[31] and Clinical Global Impression-Severity sub-scale (CGI-S)[32] were administered by the research psychiatrists, as was the assessment of AUS, DUS and type of substance used. At admission, a retrospective assessment of the best in lifetime premorbid functioning was estimated with the GAF and SOFAS according to the information available in patients' files. If patient was transferred or LTF at the date of evaluation, we extrapolated the data up to 3 months prior to exit from study if data

was easily estimable (e.g., stable patient since many months/years in the same occupation and housing).

For LAI-AP medication, the following was recorded by file reviews: type of LAI-AP prescribed, reason for prescription, reason for cessation and type of cessation. Based on recommendations in the field,[33] medication compliance was assessed by multiple sources of information: patients' self-reports, patients' file reviews (including information from family reports), laboratory measures, and patients' case manager and psychiatrist reports. Based on these 5 sources of information, for OAP medication, adherence was recorded and defined as good (90%–100% adherence), and poor adherence (partial or none).

For both LAI-AP and OAP, information on the number of medication trials and community treatment order (CTO) was collected.

### *Statistical Analyses*

Analyses were performed using IBM SPSS software version 20.[34] Sample representativeness was determined by comparing subjects LTF at 36 months to those still followed on independent variables (known to be associated with outcome) at baseline. To determine whether there were differences in outcome between the two treatment groups, the baseline, 12th month, 24th month and 36th month clinical and functional outcome measures were compared. Analysis of variance (ANOVA) were used for group comparisons for continuous variables. For discrete variables, Pearson chi-square were performed. Type I error was fixed at $p = 0{,}05$. The same outcome analyses were also run between the OAP group and a hypothetical LAI-AP group where only patients exposed to LAI-AP for >3 months but <6 months (instead of <12 months) would be excluded. These analysis were performed in order to ascertain whether the decision to exclude those with >3 months but <12 months LAI-AP would bias results. Since baseline characteristics and outcome results were very similar in terms of representativity of those still followed at 36 months, it was decided to present the data for the group with a significant LAI-AP exposition of 12 months or more.



## Results

Of the 416 eligible patients, 2 groups were created: the LAI-AP group and the OAP group. Of the latter, 10 patients had received OAP for most of the study and LAI-AP for 3 months or less. Those who took LAI-AP for >3 months, but <12 months were excluded ($n = 41$),

leaving a total of 375 patients for analyses. In the LAI-AP group, 24% of patients received LAI-AP only, i.e., they had no trial of OAP during f/u.

Among the 375 patients included (LAI-AP ($n = 100$), OAP ($n = 275$)), 62,9% accepted to participate, 13,3% refused and 23,7% had not been approached because of inability to consent or early loss to f/u (i.e., before being approached to participate in the research). Of the 375 patients, 34,4% ($n = 129$) were LTF at 36 months. Those who were still followed compared to those LTF (Supplemental Material Table S1) had previous work income in greater proportion, had a lower best premorbid GAF during adulthood, were more likely to have a schizophrenia spectrum diagnosis, to be single, to live with their parents at admission and throughout their adult life, and to be in the LAI-AP group (15% were LTF) than the OAP group (41,5% were LTF).

### *Baseline Characteristics*

The LAI-AP group were more likely to be males with lower education and a history of childhood trauma, homelessness and legal problems. Compared to the OAP group who was more likely to live on its own at baseline, the LAI-AP group lived in greater proportion with their parents. Their premorbid and baseline functioning was lower (e.g., best in lifetime GAF and SOFAS, baseline GAF, baseline employment and autonomous living arrangements) (Table 1). The level of illness severity (CGI-S) was higher in the LAI-AP group, but there was no difference in PANSS and CDS scores. The LAI-AP group was more likely to be diagnosed with schizophrenia spectrum disorders and to suffer from comorbid SUD (Table 1).



### *LAI-AP and OAP Treatment*

Medication utilization profile is described in Table 2 and Figures 1–2. Relapse due to non-adherence was the most frequent reason (56,4%) for LAI-AP prescription. Interestingly, 14,3% of patients preferred a LAI-AP to an OAP after physician's explanations of the advantages/disadvantages of this formulation (Figure 1).

Sixty-five percent of patients in the LAI-AP group had only one trial of LAI-AP. Second generation LAI-AP were mostly prescribed (76,4%). More than half (50,8%) of the LAI-AP group ceased medication because of a desire to see if medication was needed (Table 2).

Although 40,7% stopped the LAI-AP against psychiatrist's advice, 59,3% of those who ceased did so in context of a collaborative treatment plan with their treatment team (insert Figure 2). Moreover, 16,3% ($n = 61$) of the whole cohort ($n = 375$) have been the object of a CTO, of which 82% ($n = 50$) were prescribed LAI-AP, 18% ($n = 11$) an OAP and

TABLE 1

**Baseline Sociodemographic Characteristics, Symptomatic And Functional Outcome, And Service Use Of Young Adults With A First-Episode Psychosis (Fep) And Treated With A Long-Acting Injectable Antipsychotic (Lai-Ap) For At Least 12 Months During 3-Year Follow-Up Compared To Those Treated With An Oral Antipsychotic Medication (Oap)**

| | BASELINE | | | 12 MONTHS | | | 24 MONTHS | | | 36 MONTHS | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | LAI-AP N = 100 | OAP N = 275 | P-VALUE | LAI-AP N = 97 | OAP N = 210 | P-VALUE | LAI-AP N = 92 | OAP N = 188 | P-VALUE | LAI-AP N = 85 | OAP N = 161 | P-VALUE |
| Baseline sociodemographics | | | | | | | | | | | | |
| Age, mean (s.d) | 22,9 (3,4) | 23,4 (3,6) | 0,170 | – | – | – | – | – | – | – | – | – |
| Male, n (%) | 84 (84,0) | 203 (73,8) | 0,040 | – | – | – | – | – | – | – | – | – |
| Diagnosis*, n (%) | | | <0,001 | – | – | – | – | – | – | – | – | – |
| - Schizophrenia spectrum | 86 (86,0) | 144 (52,4) | | – | – | – | – | – | – | – | – | – |
| - Affective psychosis | 10 (10,0) | 89 (32,4) | | – | – | – | – | – | – | – | – | – |
| - Psychosis NOS/delusional disorder/reactive psychosis | 4 (4,0) | 42 (15,3) | | – | – | – | – | – | – | – | – | – |
| Cluster B personality disorders, n (%) | 30 (30,0) | 74 (27,0) | 0,603 | – | – | – | – | – | – | – | – | – |
| Immigration status, n (%) | | | 0,445 | – | – | – | – | – | – | – | – | – |
| - Non-immigrant | 50 (50,0) | 153 (55,6) | | – | – | – | – | – | – | – | – | – |
| - FGI[a] | 30 (30,0) | 65 (23,6) | | – | – | – | – | – | – | – | – | – |
| - SGI[b] | 20 (20,0) | 57 (20,7) | | – | – | – | – | – | – | – | – | – |

(*Continued*)

**TABLE 1 (*Continued*)**

| | BASELINE | | | 12 MONTHS | | | 24 MONTHS | | | 36 MONTHS | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | LAI-AP N = 100 | OAP N = 275 | P-VALUE | LAI-AP N = 97 | OAP N = 210 | P-VALUE | LAI-AP N = 92 | OAP N = 188 | P-VALUE | LAI-AP N = 85 | OAP N = 161 | P-VALUE |
| Last completed diploma, n (%) | | | <0,001 | – | – | – | – | – | – | – | – | – |
| - No diploma | 57 (57,0) | 89 (33,1) | | – | – | – | – | – | – | – | – | – |
| - High school, completed | 30 (30,0) | 98 (36,4) | | – | – | – | – | – | – | – | – | – |
| - Post high school diploma | 13 (13,0) | 82 (30,5) | | – | – | – | – | – | – | – | – | – |
| Years of education, n (%) | | | <0,001 | – | – | – | – | – | – | – | – | – |
| - Less than 11 years | 71 (71,0) | 135 (50,2) | | – | – | – | – | – | – | – | – | – |
| - More than 11 years | 29 (29,0) | 134 (49,8) | | – | – | – | – | – | – | – | – | – |
| Employment best in lifetime, n (%) | | | 0,051 | – | – | – | – | – | – | – | – | – |
| - Full time/Part time/Stay-at-home parent/Rehabilitation | 91 (91,0) | 225 (82,7) | | – | – | – | – | – | – | – | – | – |
| - None | 9 (9,0) | 47 (17,3) | | – | – | – | – | – | – | – | – | – |
| Income**, best in lifetime, n (%) | | | 0,021 | – | – | – | – | – | – | – | – | – |
| - Independent income | 90 (90,0) | 214 (79,9) | | – | – | – | – | – | – | – | – | – |
| - Government income security/ Dependent of family | 10 (10,0) | 54 (20,1) | | – | – | – | – | – | – | – | – | – |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Living arrangements best in lifetime***, n (%) | | | 0,830 | – | – | – | – | – | – | – | – | – |
| - Living independently | 66 (66,7) | 182 (66,9) | | – | – | – | – | – | – | – | – | – |
| - Living with parents | 33 (33,3) | 89 (32,7) | | – | – | – | – | – | – | – | – | – |
| - Homelessness | 0 (0) | 1 (0,4) | | – | – | – | – | – | – | – | – | – |
| History of childhood trauma, n (%) | 40 (62,5) | 52 (43,7) | 0,020 | – | – | – | – | – | – | – | – | – |
| Homelessness history, n (%) | 33 (33,0) | 29 (10,8) | <0,001 | – | – | – | – | – | – | – | – | – |
| History of legal problems before admission, n (%) | 36 (36,0) | 57 (21,5) | 0,007 | – | – | – | – | – | – | – | – | – |
| Symptomatology | | | | | | | | | | | | |
| PANSS[c], mean (s.d) | 79,6 (11,8) | 77,1 (15,6) | 0,358 | 59,1 (17,3) | 54,5 (14,6) | 0,120 | 55,2 (14,6) | 48,5 (13,1) | 0,013 | 54,3 (2,5) | 45,6 (12,1) | 0,002 |
| - Positive symptoms | 20,1 (5,2) | 19,6 (6,1) | 0,673 | 13,0 (5,2) | 12,1 (4,9) | 0,353 | 12,0 (4,3) | 10,0 (3,6) | 0,011 | 11,4 (4,6) | 9,4 (3,4) | 0,015 |
| - Negative symptoms | 23,2 (4,7) | 21,8 (5,9) | 0,201 | 17,5 (5,8) | 15,7 (4,8) | 0,063 | 16,5 (5,0) | 14,0 (4,9) | 0,010 | 16,2 (4,7) | 13,0 (4,6) | 0,001 |
| - General symptoms | 36,4 (5,9) | 35,6 (7,0) | 0,562 | 28,6 (7,2) | 26,7 (6,2) | 0,128 | 26,8 (6,3) | 24,5 (5,9) | 0,058 | 26,7 (6,8) | 23,1 (5,3) | 0,004 |
| CDS[d], mean (s.d) | 6,0 (3,5) | 6,4 (3,8) | 0,544 | 3,3 (3,0) | 3,0 (2,5) | 0,618 | 3,3 (3,6) | 2,3 (2,6) | 0,086 | 2,9 (3,1) | 1,6 (2,4) | 0,029 |
| CGI[e], mean (s.d) | 5,0 (0,7) | 4,8 (1,0) | 0,022 | 3,7 (1,3) | 2,8 (1,2) | <0,001 | 3,4 (1,1) | 2,7 (1,3) | <0,001 | 3,6 (1,1) | 2,9 (1,2) | <0,001 |

(*Continued*)

**TABLE 1 (*Continued*)**

| | BASELINE | | | 12 MONTHS | | | 24 MONTHS | | | 36 MONTHS | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | LAI-AP N = 100 | OAP N = 275 | P-VALUE | LAI-AP N = 97 | OAP N = 210 | P-VALUE | LAI-AP N = 92 | OAP N = 188 | P-VALUE | LAI-AP N = 85 | OAP N = 161 | P-VALUE |
| Substance use disorder, n (%) | 63 (63,0) | 131 (47,6) | 0,008 | 59 (60,2) | 63 (30,4) | <0,001 | 51 (56,0) | 51 (27,6) | <0,001 | 44 (52,4) | 42 (26,6) | <0,001 |
| - alcohol | 18 (18,0) | 52 (18,9) | 0,882 | 21 (21,4) | 28 (13,5) | 0,095 | 17 (18,7) | 26 (14,1) | 0,378 | 15 (17,9) | 23 (14,6) | 0,578 |
| - cannabis | 57 (57,0) | 111 (40,4) | 0,005 | 49 (50,0) | 52 (25,1) | <0,001 | 43 (47,3) | 37 (20,0) | <0,001 | 38 (45,2) | 32 (20,3) | <0,001 |
| - cocaine | 6 (6,0) | 20 (7,3) | 0,820 | 9 (9,2) | 10 (4,8) | 0,202 | 9 (9,9) | 8 (4,3) | 0,107 | 4 (4,8) | 7 (4,4) | 1,000 |
| - amphetamines | 19 (19,0) | 31 (11,3) | 0,059 | 16 (16,3) | 11 (5,3) | 0,004 | 15 (16,5) | 8 (4,3) | 0,001 | 14 (16,7) | 10 (6,3) | 0,013 |
| - others | 3 (3,0) | 6 (2,2) | 0,705 | 2 (2,0) | 3 (1,4) | 0,658 | 2 (2,2) | 2 (1,1) | 0,601 | 0 (0) | 3 (1,9) | 0,553 |
| GAF[f] best in lifetime, mean (s.d.) | 58,4 (10,6) | 62,8 (11,0) | <0,001 | – | – | – | – | – | – | – | – | – |
| GAF, mean (s.d.) | 28,3 (8,5) | 30,6 (10,2) | 0,041 | 45,4 (12,4) | 53,0 (13,3) | <0,001 | 47,6 (11,8) | 53,2 (13,9) | 0,001 | 46,7 (11,5) | 53,6 (13,2) | <0,001 |
| SOFAS[g], best in lifetime, mean (s.d.) | 59,6 (9,1) | 62,7 (11,3) | 0,013 | – | – | – | – | – | – | – | – | – |
| SOFAS, mean (s.d) | 32,1 (10,9) | 34,3 (13,2) | 0,130 | 48,5 (11,9) | 54,5 (12,9) | <0,001 | 51,0 (11,1) | 55,2 (13,6) | 0,011 | 51,1 (10,6) | 56,5 (11,8) | 0,001 |
| QLS[h], mean (s.d) | 45,1 (19,7) | 51,7 (22,4) | 0,102 | 60,5 (27,6) | 73,9 (27,2) | 0,011 | 65,5 (22,5) | 82,2 (25,5) | 0,001 | 64,2 (20,1) | 82,6 (23,8) | <0,001 |

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|---|---|---|---|---|---|---|---|---|---|---|
| Marital status, n (%) | | | 0,730 | | 0,290 | | | 0,246 | | 0,286 |
| - Single | 84 (84,0) | 229 (83,3) | | 85 (85,9) | 170 (82,1) | 78 (85,7) | 142 (78,0) | | 75 (86,2) | 124 (77,5) | |
| - Boyfriend/Girlfriend | 9 (9,0) | 31 (11,3) | | 7 (7,1) | 26 (12,6) | 9 (9,9) | 26 (14,3) | | 8 (9,2) | 22 (13,8) | |
| - Separated/Divorced | 3 (3,0) | 4 (1,5) | | 3 (3,0) | 2 (1,0) | 2 (2,2) | 2 (1,1) | | 2 (2,3) | 3 (1,9) | |
| - Married/Common-law partner | 4 (4,0) | 11 (4,0) | | 4 (4,0) | 9 (4,3) | 2 (2,2) | 12 (6,6) | | 2 (2,3) | 11 (6,9) | |
| Studying, n (%) | | | 0,132 | | 0,249 | | | 0,090 | | 0,028 |
| - Full-time/Part-time | 12 (12,0) | 58 (21,2) | | 18 (18,2) | 55 (26,5) | 17 (18,7) | 63 (29,1) | | 9 (10,3) | 39 (24,4) | |
| - None | 88 (88,0) | 216 (78,8) | | 81 (81,8) | 152 (73,4) | 74 (81,3) | 129 (70,9) | | 78 (89,7) | 121 (75,6) | |
| Employment****, n (%) | | | 0,009 | | 0,072 | | | 0,036 | | 0,013 |
| - Full time/Part time/Work rehabilitation | 18 (18,0) | 86 (31,5) | | 27 (27,3) | 79 (38,2) | 27 (29,7) | 78 (42,9) | | 23 (26,4) | 69 (43,1) | |
| - None | 82 (82,0) | 187 (68,5) | | 72 (72,7) | 128 (61,8) | 64 (70,3) | 104 (57,1) | | 64 (73,6) | 91 (56,9) | |
| Employment and/or studying, n (%) | | | 0,002 | | 0,007 | | | 0,003 | | 0,000 |
| - Full time/Part time | 29 (29,0) | 129 (47,1) | | 40 (40,4) | 118 (57,0) | 39 (42,9) | 113 (62,1) | | 31 (35,6) | 96 (60,0) | |
| - None | 71 (71,0) | 145 (52,9) | | 59 (59,6) | 89 (43,0) | 52 (57,1) | 69 (37,9) | | 56 (64,4) | 64 (40,0) | |
| Income, n (%) | | | <0,001 | | 0,015 | | | 0,001 | | 0,021 |
| - Independent outcome | 49 (49,0) | 190 (70,9) | | 26 (26,3) | 82 (40,6) | 24 (26,4) | 83 (46,9) | | 26 (29,9) | 72 (45,3) | |
| - Government income security/ Dependent of family | 51 (51,0) | 78 (29,1) | | 73 (73,7) | 120 (59,4) | 67 (73,6) | 94 (53,1) | | 61 (70,1) | 87 (54,7) | |

(*Continued*)

**TABLE 1 (*Continued*)**

| | BASELINE | | | 12 MONTHS | | | 24 MONTHS | | | 36 MONTHS | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | LAI-AP N = 100 | OAP N = 275 | P-VALUE | LAI-AP N = 97 | OAP N = 210 | P-VALUE | LAI-AP N = 92 | OAP N = 188 | P-VALUE | LAI-AP N = 85 | OAP N = 161 | P-VALUE |
| Living arrangements****, n (%) | | | 0,045 | | | 0,035 | | | 0,011 | | | 0,001 |
| - Living independently | 44 (44,0) | 151 (54,9) | | 34 (34,3) | 89 (42,8) | | 27 (29,7) | 87 (47,8) | | 28 (32,2) | 71 (44,4) | |
| - Living with parents | 42 (42,0) | 107 (38,9) | | 35 (35,4) | 86 (41,3) | | 38 (41,8) | 67 (36,8) | | 25 (28,7) | 63 (39,4) | |
| -Supervised living, hospital, family | 6 (6,0) | 5 (1,8) | | 27 (27,3) | 30 (14,4) | | 24 (26,4) | 24 (13,2) | | 32 (36,8) | 24 (15,0) | |
| - Homelessness/other | 8 (8,0) | 12 (4,4) | | 3 (3,0) | 3 (1,4) | | 2 (2,2) | 4 (2,2) | | 2 (2,3) | 2 (1,2) | |
| History of legal problems during follow-up, n (%) | – | – | – | – | – | – | – | – | – | 21 (21,0) | 25 (10,0) | 0,008 |
| Homelessness during follow-up, n (%) | – | – | – | – | – | – | – | – | – | 23 (23,0) | 20 (7,8) | <0,001 |
| Service use during 3-year follow-up | | | | | | | | | | | | |
| Community treatment order at some point during follow-up*****, n (%) | – | – | – | – | – | – | – | – | – | 50 (50,0) | 11 (4,0) | <0,001 |

[a]FGI: First generation immigrant. [b]SGI: Second generation immigrant. [c]PANSS: Positive and negative syndrome scale. [d]CDS: Calgary depression scale. [e]CGI: Clinical global impression - severity subscale. [f]GAF: General assessment of functioning. [g]SOFAS: Social and occupational functioning assessment scale. [h]QLS: Quality of Life scale. *Diagnosis has been revised at 3 years will all the information available. **Work/Bank loan/Employment insurance benefits/Scholarship. ***Living arrangements were rated according to scales adapted from Ciompi,1980: "Independent" regrouped all patients living on their own alone, with their partner and/or their children; "With parents" regrouped all patients living with any family members; "Supervised" regrouped patients living in supported housing (supervised apartment, group home, foster home, hospital). ****"Full- or part-time work" included competitive work, work rehabilitation programs, sheltered work, and stay-at-home parents taking care of their own children full time. *****Community treatment orders duration varied from 1 to 3 years.

TABLE 2

**LAI-AP and OAP Utilization Profile**

| | |
|---|---|
| Delay between admission and first prescription of LAI-AP (months) (mean (s.d.)/median) | 6,0 (7,1)/3,2 |
| Total exposure to LAI-AP (months) (mean (s.d.)) | 25,4 (7,6) |
| Duration of first trial of LAI-AP (months) (mean (s.d.)) | 22,8 (10,0) |
| Duration of first trial of OAP[a] (for OAP group, n = 275) (months) (mean (s.d.)) | 15,2 (14,9) |
| Proportion of good adherence (>90% of adherence) to first trial of OAP group (%) | 57,2 |
| Type of LAI-AP prescribed during 3-year follow-up, all trials combined (%) | – |
| - Long-acting risperidone | 44,3 |
| - Monthly paliperidone palmitate | 32,1 |
| - Long-acting zuclopenthixol | 12,1 |
| - Long-acting haloperidone | 7,9 |
| - Long-acting flupenthixol | 2,1 |
| - Long-acting aripiprazole | 0,0 |
| - Fluphenazine decanoate | 0,7 |
| - Pipothiazine palmitate | 0,7 |
| Number of trials of LAI-AP for the LAI-AP group (n = 100) during 3-year follow-up (%) | – |
| - 1 trial | 65,0 |
| - 2 trials | 30,0 |
| - 3 trials | 5,0 |
| - 4 trials | 0 |
| Number of trials of OAP for the OAP group (n = 275) during 3-year follow-up (%) | – |
| - 1 trial | 70,5 |
| - 2 trials | 23,6 |
| - 3 trials | 5,1 |
| - 4 trials | 0,7 |
| Reasons for LAI-AP cessation (%) | – |
| - Desire to see if medication is needed | 50,8 |
| - Desire to stop LAI-AP but accepts OAP | 28,8 |
| - Adverse effects | 10,2 |
| - No efficacy/switch to clozapine | 10,2 |
| Proportion of LAI-AP group receiving LAI-AP and OAP concomitantly (%) | 13,0 |

[a]Including lost to follow-up (23,6% at 12 months, 31,6% at 24 months and 41,5% at 36 months.

none were prescribed clozapine. Fifty percent of the LAI-AP group ($n$ = 50) were the object of a CTO.

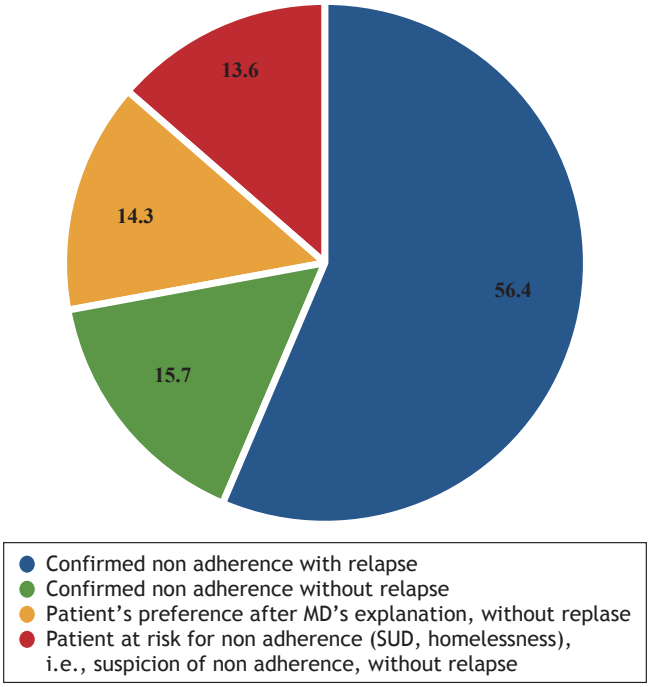
### *Outcome*

#### Symptomatology

Although symptom severity improved in equal proportions (PANSS, CGI) throughout the 3-year f/u for both groups, at 36 months, the

FIGURE 1

Reasons Justifying The Prescription of LAI-AP (%)






LAI-AP group had more psychotic (PANSS) and depressive (CDS) symptoms, and were considered more severely ill (CGI-S) (Table 1; Supplementary Table S2).

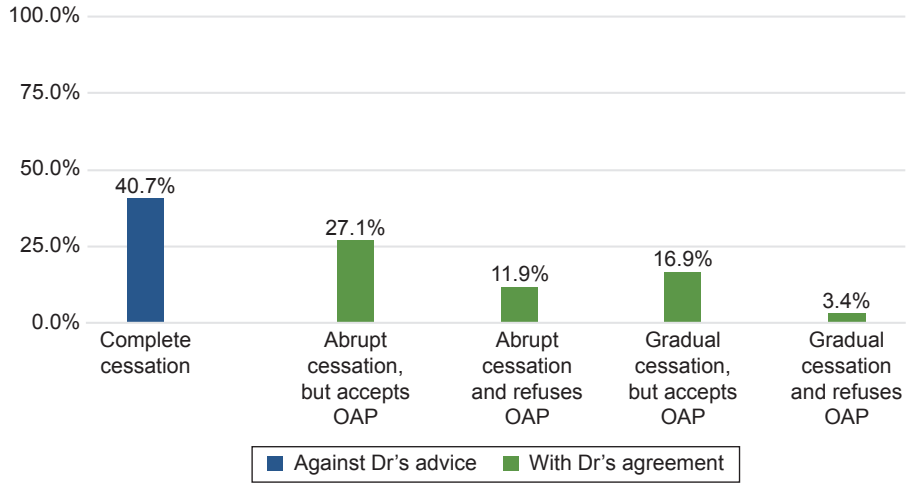
SUD rate decreased in both groups during the study, but the proportion of patients with SUD was larger in the LAI-AP group at study endpoint (Table 1; Supplemental Table S2). Patients prescribed LAI-AP misused cannabis and amphetamines in a greater proportion (Table 1).

## Functioning

Both groups show a marked improvement of similar amplitude in functioning (GAF, SOFAS, rate of homelessness) and quality of life (QLS) at the end of the study (Table 1; supplemental Table S2). However, GAF, SOFAS and QLS scores remain significantly lower for the LAI-AP group at 36 months. The LAI-AP group was less likely to be studying or working at the end of the study. At the end of the study, a greater proportion of the OAP group lived independently or with their families compared to the LAI-AP group (83,8% vs 60,9%), while the LAI-AP group was more likely to be living in a supervised setting than the OAP group (36,8% vs 15,0%). A greater proportion of the LAI-AP group experienced homelessness during f/u as well as legal problems.

FIGURE 2

Type of Cessation of LAI-AP (%)




## Discussion



Our study highlights the improvement in symptomatic and functional outcomes, and of quality of life over the 36 months f/u for both treatment groups. It is nonetheless difficult to conclude on LAI-AP's impact since both groups are very dissimilar at baseline. According to our results, in real life setting, clinicians are indeed more likely to prescribe LAI-AP to FEP patients with poor prognostic factors associated with poor adherence and, consequently, relapse: history of childhood trauma, homelessness, and legal problems, male gender, low level of education, poor premorbid functioning, unemployment, higher illness severity, as well as schizophrenia spectrum diagnosis and comorbid SUD.

Even if there is great improvement at the end of the study compared to baseline, the final outcome levels for the LAI-AP group are poorer than those of the OAP group. Since individuals with poorer prognostic factors seem more likely to be prescribed LAI-AP,[6,35,36] this group was possibly more severely ill than the other. It is then important to keep in mind a realistic prognosis; a patient having a low premorbid level of functioning can't be expected to reach much higher levels of functioning than premorbidly despite intensive treatment and therapies.[37–39]

### *Baseline Characteristics*

The differences between the two groups on baseline socio-demographics and clinical characteristics were not noted in two observational studies on FEP[12,40] (Supplemental Table S3). This could be explained by the

exclusion of patients with SUD in both studies, hence excluding patients who have factors of poor prognosis and possibly poorer adherence to medication, while in the present study 51,7% have a SUD at baseline. Our results corroborate previous ones[6,35,36] suggesting that patients with poor prognostic factors are more likely to be prescribed LAI-AP. Therefore, the evidence suggests that clinicians tend to prescribe LAI-AP to patients with factors of poor adherence to antipsychotics or at risk thereof (severe psychopathology, SUD and legal antecedents).[41–43]

### *Reasons for Prescription and Cessation of LAI-AP*

The vast majority (70,5%) of the OAP group had only one trial of antipsychotics, suggesting good satisfaction (efficacy/tolerance) (Table 2). High non adherence rate in both groups to first trial of oral antipsychotics (LAI-AP group = 73,7%; OAP group = 34,2%; total sample = 42,8%) confirms previous studies.[44]

Similarly to the present study, previous research report that poor adherence with or without relapse is the main reason that motivates prescription of LAI-AP both in FEP[45] or later in psychotic illness evolution,[46–48] and about 15% of FEP patients were prescribed LAI-AP because they preferred this formulation.[45] This contrasts with many psychiatrists' belief that patients perceive injectable medication as unacceptable.[49,50]



As the present study, previous investigations report that patient's desire to stop medication is a major reason to cease LAI-AP in chronic psychosis.[46,51] More than a third of them[46] and half of FEP patients[52] do so against medical advice.

Finally, in this study (spanning from 2005 to 2012), long-acting injectable risperidone was the LAI-AP most frequently used because it was the only 2nd generation LAI-AP available in Canada from 2005[53] until July 2010, when paliperidone palmitate became available.[54] Long-acting aripiprazole became available only in March 2014[55] (a year before study's end).

### *Symptoms and Functioning*

The LAI-AP group show symptomatic and functional improvement, as described in many studies,[11,40,56–58] as well as a reduction in SUD rate. However, at study endpoint, symptom severity is higher and functioning is lower in the LAI-AP group compared to OAP group, which is in contrast with observational studies[12,40] or RCTs and their meta-analysis.[11,17,58,59] Indeed, these studies demonstrated that patients taking LAI-AP have a better outcome than the OAP group[11,40] or that

there were no differences between groups.[12,17,58,59] These differences might result from the high prevalence of poor prognostic factors in the LAI-AP group versus the OAP group in the present study, which is not the case in previously mentioned trials.[11,12,40,58,59] Indeed, previous studies had similar groups at baseline,[11,12,40,58,59] a consequence of selection bias induced by the exclusion of patients with a SUD,[11,12,40,58] or severe psychopathology (e.g., resistance to antipsychotics, high suicidal risk, involuntary hospitalization).[40,58,59]

### *Strengths and Limitations*

A strength of the present study is its naturalistic design in a "real life" setting assuring representativeness of the whole FEP population since no patient was excluded. Indeed, in the Quebec province (Canada), the public and universal healthcare system is sectorized for mental health services delivery, thus all individuals living in a specific catchment area are treated in a designated hospital. Additionally, we had access, by file review, to data on all FEP patients even those who refused to participate (13,3%) or who could not be recruited (23,7%). Among these patients, 25,2% were on LAI-AP, a similar proportion to the whole sample. Furthermore, compared to the present naturalistic study, in the three RCTs on recent-onset psychosis,[11,58,59] patients who are susceptible to benefit from LAI-AP are under-represented or even excluded (e.g., unstable patients, those with poor adherence, SUD, aggressivity, suicide risk, AP-resistant symptoms, involuntary hospitalization, etc). More than half of the patients included in this study would have been excluded from recruitment if the selection criteria of many other studies had been applied, e.g., 51,7% of the present study participants had comorbid SUD. Of the latter, 12,4% refused to participate and 22,2% could not be recruited. Since 63% of them were prescribed LAI-AP, this indicates that an important proportion of FEP patients likely to benefit from LAI-AP are not included in most previous studies. Nevertheless, contrary to what could have been anticipated, the rate of refusal or impossibility of recruitment are alike between patients with and without a SUD. Other characteristics render our sample representative of the whole FEP population, such as a broad definition of psychosis (e.g. affective psychosis, delusional disorder), and inclusion of patients being the object of a CTO (16,3%).

Compared to other studies,[11,40,58] a larger sample size, and a significant proportion of them taking LAI-AP, conferred greater statistical power. Many dimensions of recovery were considered, since different dimensions of outcome may have different evolution.[60]

More than a third of the cohort is LTF, the majority (88,4%) being in the OAP group. Hence, those with poor prognostic factors and on LAI-AP or CTO are more likely to remain in the study (Table 1). Therefore, the sample is possibly biased towards an over-estimation of the benefits of OAP. The lower rate of relapse per person for the OAP group may be influenced by a higher proportion of LTF in this group, since a shorter period of f/u does not allow to observe many relapses. On the other hand, the rate of LTF of the present study is similar to the ones of previous observational[61,62] and randomized[11,59] FEP studies, including two RCTs who also find a higher rate of LTF for their OAP groups compared to their LAI-AP groups.[11,59]

Another limit is that the introduction or change of medication does not occur simultaneously to the appointed time in which outcome measures were taken (baseline, 12, 24, 36 months). However, most participants in the LAI-AP group were receiving LAI-AP at the time measurements were taken (72,2%–89,4%).



About a third of FEP patients of the EIS where the study was conducted were prescribed LAI-AP, though in this study the proportion of FEP on LAI-AP is 26,7% since the 41 patients who received LAI-AP for a too short period (4–11 months) were excluded from analysis. At study's end, 51,2% ($n$ = 21) of these 41 patients were still on LAI-AP, so a longer study duration might capture LAI-AP's effect on those with later initiation of LAI-AP in their evolution, since exposition would have been sufficient to evaluate its impact. Those patients might have a specific profile, since they were prescribed LAI-AP later in the first three years of f/u.

Although several sources of information were used to estimate adherence, there was no objective measure for medication adherence (e.g., pill counts) therefore possibly overestimating adherence. However, sample's total rate of adherence to first trial of OAP was similar to the one reported previously.[44]

Like all naturalistic studies, since there is no random allocation of treatment, it seems obvious that treatment selection bias explains the worse outcome of patients prescribed LAI-AP because they had risk factors of poor prognosis and poor adherence. Nevertheless, this study design provides a higher external validity with a more representative sample[2,20] that allows the description of the population that receives LAI-AP and its evolution. A mirror-image study[63,64] could have been a better design to estimate the impact of LAI-AP for each outcome dimension and determine if LAI-AP contribute to modify the outcome trajectory positively. However, real-time measurements are complex in terms of evaluation timing and patient recruitment for interviews.

## Conclusion

In FEP patients, LAI-AP are prescribed mainly to patients presenting risk factors of poor adherence and poor outcome. Nevertheless, FEP patients receiving LAI-AP improve on a symptomatic, functional and quality of life level as the OAP group, but to a lesser extent. These results suggest that FEP patients may benefit from early prescription of LAI-AP in the course of their illness, as recommended by different guidelines.[65–71] ✤

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## Conflict of Interest

AAB has received speaker honoraries for continuing medical education talks from Janssen Canada, and received an unrestricted research grant from Janssen Canada, Otsuka Pharmaceuticals (for student grant) and Bristol-Myers Squibb. SP is holder of a grant from Otsuka Pharmaceuticals. ES is on the advisory board of Janssen Canada, Lundbeck and Otsuka Canada, and has given lectures with Janssen in France and Belgium, and with Otsuka and Lundbeck Canada. SM declares no conflict of interest.

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SP is holder of the Eli Lilly Canada Chair in Schizophrenia Research.

## Supplemental Materials

**TABLE S1**

**Baseline Sociodemographic, Symptomatic And Functional Characteristics Of Sample (N = 375) Of Young Adults With First Episode Psychosis (Fep) According To Follow-Up Status At 3 Years (Representativity Analyses Of Residual Sample)**

| | LTF[a] AT 3 YEARS (N = 129) | STILL FOLLOWED AT 3 YEARS (N = 246) | P-VALUE |
|---|---|---|---|
| Sociodemographics | | | |
| Age, mean (s.d) | 23,3 (3,5) | 23,3 (3,6) | 0,849 |
| Male, n (%) | 94 (72,9) | 193 (78,5) | 0,249 |
| Diagnosis*, n (%)[b] | | | <0,001 |
| - Schizophrenia spectrum | 58 (45,0) | 172 (69,9) | |
| - Affective psychosis | 43 (33,3) | 56 (22,8) | |
| - Psychosis NOS/delusional disorder/ reactive psychosis | 28 (21,7) | 18 (7,3) | |
| Cluster B personality disorders, n (%) | 43 (33,3) | 61 (24,9) | 0,090 |
| Immigration status, n (%) | | | 0,469 |
| - Non-immigrant | 72 (55,8) | 131 (53,3) | |
| - FGI[c] | 35 (27,1) | 60 (24,4) | |
| - SGI[d] | 22 (17,1) | 55 (22,4) | |
| Last completed diploma, n (%) | | | 0,276 |
| - No diploma | 48 (37,8) | 98 (40,5) | |
| - High school, completed | 40 (31,5) | 88 (36,4) | |
| - Post high school diploma | 39 (30,7) | 56 (23,1) | |
| Years of education, n (%) | | | 0,912 |
| - Less than 11 years | 70 (55,1) | 136 (56,2) | |
| - More than 11 years | 57 (44,9) | 106 (43,8) | |
| Employment best in lifetime, n (%) | | | 0,068 |
| - Full time/Part time/Stay-at-home parent/Rehabilitation | 101 (80,2) | 215 (87,4) | |
| - None | 25 (19,8) | 31 (12,6) | |
| Income**, best in lifetime, n (%) | | | 0,008 |
| - Independent income | 92 (74,8) | 212 (86,5) | |
| - Government income security/ Dependent of family | 31 (25,2) | 33 (13,5) | |
| Living arrangements best in lifetime, n (%) | | | 0,005 |
| - Living independently | 98 (77,8) | 150 (61,2) | |
| - Living with parents | 28 (22,2) | 94 (38,4) | |
| - Homelessness | 0 (0) | 1 (0,4) | |
| History of childhood trauma, n (%) | 28 (50,9) | 64 (50,0) | 1,000 |
| Homelessness history, n (%) | 16 (12,8) | 46 (18,9) | 0,145 |
| History of legal problems before admission, n (%) | 35 (29,2) | 58 (23,7) | 0,306 |
| Symptomatology | | | |
| PANSS[e], mean (s.d) | 76,9 (13,9) | 78,0 (15,3) | 0,649 |
| - Positive symptoms | 20,0 (5,1) | 19,6 (6,2) | 0,660 |
| - Negative symptoms | 21,7 (5,2) | 22,3 (5,9) | 0,516 |
| - General symptoms | 35,2 (6,8) | 36,1 (6,8) | 0,403 |

(*Continued*)

**TABLE S1 (*Continued*)**

| | LTF[a] AT 3 YEARS (N = 129) | STILL FOLLOWED AT 3 YEARS (N = 246) | P-VALUE |
|---|---|---|---|
| CDS[f], mean (s.d) | 6,1 (3,9) | 6,4 (3,6) | 0,635 |
| CGI-S[g], mean (s.d) | 4,8 (1,0) | 4,8 (0,9) | 0,638 |
| Substance use disorder, n (%) | 67 (51,9) | 127 (51,6) | 1,000 |
| - alcohol | 23 (17,8) | 47 (19,1) | 0,889 |
| - cannabis | 58 (45,0) | 110 (44,7) | 1,000 |
| - cocaine | 11 (8,5) | 15 (6,1) | 0,397 |
| - amphetamines | 16 (12,4) | 34 (13,8) | 0,751 |
| - others | 3 (2,3) | 6 (2,4) | 1,000 |
| Functioning | | | |
| GAF[h] best in lifetime, mean (s.d.) | 63,2 (10,3) | 60,8 (11,4) | 0,046 |
| GAF, mean (s.d.) | 29,3 (9,2) | 30,4 (10,1) | 0,337 |
| SOFAS[i], best in lifetime, mean (s.d.) | 62,7 (11,0) | 61,4 (10,7) | 0,252 |
| SOFAS, mean (s.d) | 33,3 (13,2) | 33,9 (12,4) | 0,629 |
| QLS[j], mean (s.d) | 50,1 (21,2) | 50,1 (22,4) | 0,990 |
| Marital status, n (%) | | | 0,040 |
| - Single | 101 (78,3) | 212 (86,2) | |
| - Boyfriend/Girlfriend | 19 (14,7) | 21 (8,5) | |
| - Separated/Divorced | 5 (3,9) | 2 (0,8) | |
| - Married/Common-law partner | 4 (3,1) | 11 (4,5) | |
| Studying, n (%) | | | 0,075 |
| - Full-time/Part-time | 29 (22,6) | 41 (16,7) | |
| - None | 99 (77,3) | 205 (83,3) | |
| Employment***, n (%) | | | 0,115 |
| - Full time/Part time/Work rehabilitation | 42 (33,1) | 62 (25,2) | |
| - None | 85 (66,9) | 184 (74,8) | |
| Income**, n (%) | | | 0,489 |
| - Independent income | 83 (67,5) | 156 (63,7) | |
| - Government income security/ Dependent of family | 40 (32,5) | 89 (36,3) | |
| Living arrangements****, n (%) | | | 0,001 |
| - Living independently | 85 (65,9) | 110 (44,7) | |
| - Living with parents | 37 (28,7) | 112 (45,5) | |
| - Supervised living, hospital, family | 1 (0,8) | 10 (4,1) | |
| - Homelessness/other | 6 (4,7) | 14 (5,7) | |
| Service use | | | |
| Community treatment order, n (%) | 9 (7,0) | 52 (21,1) | <0,001 |

[a]LTF: Lost to follow-up. [b]Diagnosis has been revised at 3 years with all the information available. [c]FGI: First generation immigrant. [d]SGI: Second generation immigrant. [e]PANSS: Positive and negative syndrome scale. [f]CDS: Calgary depression scale. [g]CGI: Clinical global impression - severity subscale. [h]GAF: General assessment of functioning. [i]SOFAS: Social and occupational functioning assessment scale. [j]QLS: Quality of Life scale. *Diagnosis has been revised at 3 years will all the information available. **Work/Bank loan/Employment insurance benefits/Scholarship. ***"Full- or part-time work" included competitive work, work rehabilitation programs or sheltered work, and stay-at-home parents taking care of their own children full time. ****Living arrangements were rated according to scales adapted from Ciompi,1980: "Independent" regrouped all patients living on their own alone, with their partner and/ or their children; "With parents" regrouped all patients living with any family members; "Supervised" regrouped patients living in supported housing (supervised apartment, group home, foster home, hospital).

TABLE S2

## Improvement Between Admission And 36 Months (Mean Or %) For Both Study Groups

| VARIABLES | EVOLUTION | CHANGE AT 36 MONTHS COMPARED TO BASELINE LAI-AP GROUP | OAP GROUP | P-VALUE |
|---|---|---|---|---|
| PANSS-T[a] (mean) | Less total sx | −26,9 | −31,7 | 0,998 |
| PANSS-P[b] (mean) | Less positive sx | −8,1 | −9,7 | 0,671 |
| PANSS-N[c] (mean) | Less negative sx | −8,1 | −9,0 | 0,142 |
| PANSS-G[d] (mean) | Less general sx | −10,7 | −13,0 | 0,790 |
| CDS[e] (mean) | Less symptoms | −3,1 | −5,0 | 0,022 |
| CGI[f] (mean) | Lower illness severity | −1,4 | −1,9 | 0,429 |
| SUD[g] (%) | Prevalence reduction | −25,0 | −47,8 | 0,009 |
| SUD-cannabis (%) | Prevalence reduction | −31,4 | −47,3 | 0,094 |
| GAF[h] (mean) | Improvement | 18,0 | 22,5 | 0,089 |
| SOFAS[i] (mean) | Improvement | 18,6 | 21,8 | 0,221 |
| QLS[j] (mean) | Improvement | 20,6 | 30,6 | 0,536 |
| Studying and/or employment (%) | Improvement | 8,0 | 16,2 | <0,001 |
| Homelessness (%) | Prevalence reduction | −6,9 | −2,5 | 0,533 |

[a]PANSS-T: Positive and negative syndrome scale - total symptoms. [b]PANSS-P: Positive and negative syndrome scale - positive symptoms subscale. [c]PANSS-N: Positive and negative syndrome scale - negative symptoms subscale. [d]PANSS-G: Positive and negative syndrome scale - general symptoms subscale. [e]CDS: Calgary depression scale. [f]CGI: Clinical global impression. [g]SUD: Substance use disorder. [h]GAF: General assessment of functioning scale. [i]SOFAS: Social and occupational functioning assessment scale. [j]QLS: Quality of life scale.

TABLE S3

## Summary Of The Literature Review Of Observational Studies On First Episode Psychosis (Fep) And Randomized Controlled Trials (Rct) On Recent-Onset Psychosis Studying The Impact Of Lai-Ap On Symptomatic And Functional Outcomes, Relapse And Service Use

| AUTHOR/YEAR | METHOD/DURATION | POPULATION | SYMPTOMS | FUNCTIONING | RELAPSE/SERVICE USE | OTHER |
|---|---|---|---|---|---|---|
| Observational Studies on FEP[1] | | | | | | |
| Emsley et al., 2008 (South Africa)[56] | 2-year, single site, prospective, 1 arm, open label, descriptive study, performed between Feb 2004–Dec 2006.<br>Assessment of rate, predictors and correlation of remission[2] in FEP patients under RLAI[a].<br>Inclusion: 16–45 years, in-outpatient, dx[b] ⩽1 year of scz[c]/schizophreniform/ sczaff[d], ⩽2 hospitalization for psychosis, ⩽12 weeks lifetime exposition to AP[e]. Exclusion: tx[f] with mood stabilizers or AD[g] at baseline, SUD[h] in the month preceding the study, anterior use of LAI-AP[i], mental retardation, acute suicide risk. | n = 50: RLAI remission (n = 32; 64%) vs RLAI non remission (n = 18)<br>32 males; mean age = 23 years; mean DUP[j] = 129 days; 54% AP naive.<br>At baseline, remission group has more women (53,1% vs 5,6%). No difference in race/ethnicity, mean age, dx, anterior exposition to AP, DUP, total PANSS[k] and sub-scales, CGI-S[l], SF-12[m], CDS[n]<br>n = 36 (72%) completed study. | ↓ total PANSS and sub-scales remission group >non remission group<br>↓ CGI-S remission group >non remission group no difference in CDS between groups<br>92% have a clinical response[3] | ↑ SOFAS remission group >non remission group no difference in SF-12 between groups | Remission at 2 years achieved by 64% (97% maintained this status throughout study)<br>Median time to remission = 301 days | |

(*Continued*)

**TABLE S3 (*Continued*)**

| AUTHOR/YEAR | METHOD/DURATION | POPULATION | SYMPTOMS | FUNCTIONING | RELAPSE/SERVICE USE | OTHER |
|---|---|---|---|---|---|---|
| Hargarter et al., 2016 (Germany)[45,57] | 1-year multicentre, retrospective, non interventional exploratory descriptive study based on file review; period when study was held is unknown.<br>Evaluate impact of PP[o] on hospitalization and clinical outcome, and description of patterns of use; evaluation period from documentation of the first PP injection (baseline) to the first 12 months of continuous tx (endpoint).<br>Inclusion: 18–29 years at time of first PP injection, dx scz ⩽1 year before the first PP injection, regular continuous injections with not more than one missed injection within the 12-month documentation period (365 ± 31 days).<br>Exclusion: anterior tx with LAI-AP other than PP, tx with other LAI-AP during 12 months of PP | n = 84;<br>Mean age = 24,1;<br>Male = 69,0%;<br>Mean age at FEP suggestive of scz = 23,8;<br>Mean time between FEP suggestive of scz and first PP injection = 5,5 months;<br>Mean age at first AP tx = 23,9<br>Mean time between first AP treatment and first PP injection = 4,8 months. | PANSS: 79% have a clinical response<br>↓ total PANSS score (mean 31,6 points) from baseline to endpoint<br>↓ CGI 91% were deemed to have a clinically[7] relevant improvement in illness severity at last PP injection. | ↑ PSP[p] from baseline to endpoint<br>↑ GAF[q] from baseline to endpoint 65% were deemed to have a clinically[8] relevant improvement functioning at last PP injection | At PP initiation, 36 (42,9%) patients were in hospital.<br>Overall, 81 (96,4%) had no new hospitalization during the 12-month documentation period. Three (3,6%) patients had one new hospitalization for management of an episode/relapse. | Main reasons for initiating PP: relapse prevention (56%), partial/non-adherence to previous medication (20,2%), convenience (15,5%). |

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| Emsley et al., 2008 (South Africa)[40] | 2-year same site post-hoc comparison of effects of 2 groups extracted each from 2 separate studies:[6]<br>RLAI (Emsley et al., 2008):<br>2-year, single site, prospective, 1 arm, open label, descriptive study performed between Feb 2004–Dec 2006.<br>OAP[r] (Schooler et al., 2005):<br>2-year multisite, RCT, double-blind study performed between Nov 1996–January 2000, compares efficacy of oral risperidone to oral haloperidol. Inclusion: 16–45 y.o., dx ⩽1 year scz/schizophreniform/ sczaff; ⩽2 hospitalization for psychosis, ⩽12 weeks lifetime exposition to AP. Exclusion: tx with mood stabilizers or AD at baseline, SUD in the month preceding the study, anterior use of LAI-AP, mental retardation, acute suicide risk. | RLAI group: n = 50 (32 males); mean age = 25,4 OAP group: n = 47 (27 males); mean age = 25,9<br>At baseline: no difference between groups in age, gender, dx, proportion of AP naive and total PANSS scores.<br>Higher positive PANSS score and more caucasiens in OAP group. | Higher ↓ PANSS total score for RLAI group (44%) vs OAP group (28,8%) | – | Lower relapse[4] rate at 2 years for RLAI group (9,3%) vs OAP group (42,1%) among responders to medication. Lower proportion for all-cause discontinuation for RLAI vs OAP group (20% vs 48,9% at 1 year; 26% vs 70% at 2 years).<br>Higher remission rate at 2 years for RLAI group (64%) vs OAP group (40,4%). |

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**TABLE S3 (*Continued*)**

| AUTHOR/YEAR | METHOD/DURATION | POPULATION | SYMPTOMS | FUNCTIONING | RELAPSE/SERVICE USE | OTHER |
|---|---|---|---|---|---|---|
| Tiihonen et al., 2006 (Finland)[13] | 6-year prospective cohort study using national central registers and performed between January 1st 1995–Dec 31st 2001. Measures association between prescribed AP (perphenazine depot and diverse OAP) and rehospitalization after first admission for scz or sczaff Inclusion: dx scz or sczaff, patients hospitalized for the first time for scz/ sczaff, 15–45 y.o. at index hospitalization. Mean duration off /u[s] = 3,6 years. | 2230 consecutive adults hospitalization (1383 men) (many but not all had first episode psychosis at first hospitalization). Mean age = 30,7 | – | – | Clozapine, perphenazine depot and oral olanzapine are associated with lower risk of rehospitalization. Perphenazine depot had the lowest relative risk (0,32; IC 0,13–0,47). Rehospitalization incidence for perphenazine depot = 0,28. Rehospitalization incidence for oral perphenazine = 0,47. Rehospitalization incidence for OAP = 0,52. | Initial use of clozapine, perphenazine depot and oral olanzapine is associated to lower rate of discontinuation for any reason compared to other OAP. No difference in mortality rate between drugs. |
| Tiihonen et al., 2011 (Finland)[14] | 7-year prospective cohort study using national central registers and performed between 2000 – 2007. Measures risk of rehospitalization between LAI-AP (haloperidol, risperidone, perphenazine zuclopenthixol) and diverse OAP or oral equivalent. Inclusion: dx scz, patients hospitalized for the first time for scz, 16–65 y.o. atindex hospitalization. | 2588 consecutive first hospitalization for scz (62% male). Mean age = 37,8. | – | – | Risk of rehospitalization for pooled LAI-AP = 1/3 of risk for OAP (adjusted HR = 0,36; IC 0,17–0,75). Rehospitalization incidence for LAI-AP = 0,12. Rehospitalization incidence for OAP = 0,18. | LAI-AP have 59% lower risk of dis-continuation vs OAP. |

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| Tiihonen et al., 2017 (Sweden)[15] | Mean duration of f/u = 2 years.<br>7-year prospective cohort study using nationwide databases and performed between 2006 – 2013. Measures risk of rehospitalization and treatment failure (psychiatric rehospitalization, suicide attempt, discontinuation or switch of medication, death) between LAI-AP (fluphenazine, flupentixol, haloperidol, perphenazine, zuclopenthixol, risperidone, paliperidone, olanzapine) and diverse OAP (including clozapine) or oral equivalent.<br>Inclusion: dx scz, 16–64 y.o. in 2006., drug prescribed in outpatient care only.<br>Mean duration of f/u = 5,7 years. | 29 823 = prevalent cohort (57% male); 4603 = incident cohort (58,7% male).<br>SUD = 8,3% (prevalent); 7,5% (incident).<br>Mean age = 44,9 (prevalent); 36,5 (incident).<br>9–12 years of education = 47,3% (prevalent); 44.6% (incident). | – | – | 43.7% were rehospitalized (prevalent cohort)<br>Lower risk of rehospitalization with LAI-AP vs equivalent OAP (HR, 0.78 prevalent cohort; HR, 0.68 incident cohort). | Oral olanzapine = most frequently used drug, and zuclopenthixol = most frequently used LAI-AP.<br>71.7% experienced treatment failure (prevalent cohort).<br>Clozapine (HR, 0.58) and all LAI-AP (HRs 0.65–0.80) associated with the lowest rates of treatment failure compared with oral olanzapine. |

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**TABLE S3 (*Continued*)**

| AUTHOR/YEAR | METHOD/DURATION | POPULATION | SYMPTOMS | FUNCTIONING | RELAPSE/SERVICE USE | OTHER |
|---|---|---|---|---|---|---|
| Toll et al., 2015 (Spain)[12] | 6-month, single site, prospective and retrospective, 2 arms descriptive study performed between 2008–2014. Comparison of outcome for LAI-AP vs OAP in a FEP[t] clinic. Inclusion: age 18–35, dx scz/ schizophreniform/brief psychotic disorder/ psychosis NOS/ affectivepsychosis, <1 year of symptoms' evolution, IQ >80, absence of abuse/ dependance except to cannabis or tobacco. | 108 consecutive FEP patients: 11 LAI-AP (25% PP, 25% zuclopenthixol, 50% RLAI); mean age = 22,18 177 OAP; mean age = 24,92 No difference between groups in age, gender, substance use, dx, DUP[u]. | No difference between groups in total PANSS and sub-scales scores, or CDS. During f/u: no difference between groups in use of cannabis, tobacco, alcohol, cocaine, heroin, amphetamines. | No difference in GAF between groups. | Greater reduction of rehospitalization and emergency visits for LAI- AP vs OAP. | – |

RCT Studies on Recent-onset Psychosis[1]

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| Malla et al., 2013 (Canada)[58] | 2-year multisite, exploratory, 2 arms, open label RCT, recruitment between 2004–2006.<br>Explore comparative efficacy, safety and tolerability of RLAI relative to OAP 2nd generation.<br>Inclusion: dx scz/sczaff/ schizophreniform <3 years, age 18–30, AP naive or under OAP 2nd gen., total PANSS 60–120, stable after stabilization phase.<br>Exclusion: mood stabilizers or AD, SUD, use of LAI-AP in the 3 months before study, AP resistance, suicide/violence risk at admission, drug use in the 30 days before study, anterior use of clozapine.<br>2 phases: stabilization (18 weeks) and maintenance (86 weeks). | RLAI: n = 42; mean age = 22,5 OAP: n = 35; mean age = 23 Mean time between dx and study = 9 months.<br>No difference between groups on baseline sociodemographic characteristics<br>n = 31 (40,3%) completed study. | Between baseline and end of study, no difference in CGI-S and positive or negative PANSS score, except for greater reduction of total PANSS score for RLAI. | – | No difference in time to relapse[4] between groups.<br>Higher number of relapse for RLAI (n = 11) vs OAP (n = 5). | No difference in attitudes towards medication. |

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**TABLE S3 (*Continued*)**

| AUTHOR/YEAR | METHOD/DURATION | POPULATION | SYMPTOMS | FUNCTIONING | RELAPSE/SERVICE USE | OTHER |
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| Subotnik et al., 2015 (USA)[11] | 1-year, single site, 2 arms RCT, recruitment between March 16, 2005–Sept 27, 2012.<br>Compare clinical efficacy of RLAI to RPOu<br>Inclusion: age 18–45, outpatient, FEP ⩽2 years, dx scz/sczaff/schizophreniform<br>Exclusion: substance abuse/dependance in the last 6 months, mental retardation<br>Mean duration of f/u = 10,2 months (no difference between groups).<br>Randomization of medication and psychosocial treatment (CR[v] ou HBT[w]). Run-in phase and stabilisation with RPO.<br>An intent-to-treat analysis was performed between October 4, 2012, and November 12, 2014. | n = 83 (RLAI = 40 RPO = 43)<br>No difference in sociodemographic characteristics between groups (age, gender, race/ethnicity, dx, time before dx, education, marital status, BPRS[x] (at baseline and at randomization)<br>mean age = 21,5; males = 78%; singles = 96%; caucasians = 49%, scz = 55% | Higher ↓ BPRS in terms of hallucinations and unusual thought content for RLAI vs RPO and this is attribuable to better adherence. Those with the best adherence have a BPRS <4. | – | 16/83 (19%) relapse:[5] RLAI = 2/40 (5%) vs RPO = 14/43 (33%) 86% of relapses in the first 6 months (relative risk reduction RLAI vs RPO = 84,7%) (effect not attributable to adherence).<br>Number of hospitalization: RLAI = 2/40 (5%) vs RPO = 8/43 (18,6%).<br>Time without exacerbation/relapse is associated to adherence. Adherence predicts need for hospitalization. | Higher rate of discontinuation for RPO under HBT.<br>Better adherence for RLAI vs RPO (95% excellent vs 33%).<br>Adherence during the first 6 months is highly correlated to adherence in the last 6 months. |

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| Schreiner et al., 2015 (Multinational)[59] | 2-year, multisite, prospective, open label, rater blinded, 2 arms RCT, unknown years of study. Assessment of efficacy of PP vs OAP.<br>Inclusion phase of 2 weeks: patients with acute episode of scz and a PANSS 70–120<br>who might benefit from switch to PP, age 18–65, dx scz since 1–5 years, history of ⩾2 relapses requiring hospitalization in the last 24 months.<br>Inclusion phase 2-year: score ⩽4 in at least 4 PANSS items (P1, P2, P3, P6, P7, G8) and CGI-S ⩽4<br>Exclusion: AP naive, resistance to AP, clozapine in the last 3 months, psychotherapy program started in the 2 months before study, involuntary hospitalization.<br>OAP dispensed at each visit, pill count, reminder to take pills. | Phase 2-year: n PP = 352; n OAP = 363<br>No difference in sociodemographic and clinical characteristics between groups.<br>Mean age = 32,6; mean age at dx = 30,1;<br>mean time between dx and study = 3 years for PP and 2,9 years for OAP; mean time between first treatment and start of study = 4 years for PP and 3,8 years for OAP. | No differences between groups for PANSS and CGI-S.<br>No mention if presence of SUD. | No differences between groups in PSP, SF-36[y] and EQ-5D[z]. | Time to relapse[4] longer for PP. 14,8% of PP relapse vs 20,9% for OAP (p = 0,032)<br>Relative risk reduction of relapse for PP = 29,4% | – |

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**TABLE S3 (*Continued*)**

| AUTHOR/YEAR | METHOD/DURATION | POPULATION | SYMPTOMS | FUNCTIONING | RELAPSE/SERVICE USE | OTHER |
|---|---|---|---|---|---|---|
| Kishi et al., 2016[17] | Systematic review and meta-analysis of the 3 RCTs above. | Only adults (no adolescent and no geriatric population).<br>Mean age = 30,7 62,7% male. | Pooled LAI-AP: no difference between LAI-AP and OAP in improvement of total PANSS score and its sub-scales. | – | Pooled LAI-AP are not superior to OAP in terms of relapse reduction (RR[aa] = 0,67; 95% CI[bb] = 0,24–1,83, P = 0,43; N = 3, N = 875), but significant heterogeneity ($I^2$ = 76%) [Malla 2013: RR=1,83; 95%CI = 0,70–4,77; N = 77] showing no superiority, whether Subotnik and Schreiner show superiority of LAI-AP vs OAP [Schreiner 2015: [RR = 0,71; 95%CI = 0,51–0,97; NNTcc = −17; n = 715] [Subotnik 2015: RR = 0,15; 95%CI = 0,04–0,63; NNT = −4; n = 83] | Pooled LAI-AP have higher rate of discontinuation secondary to non adherence or inefficacy.<br>The statistical power of the outcome in each study was 50,8% (Malla 2013), 69,4% (Schreiner 2015), and 95,3% (Subotnik 2015). |

[1]Only significant results are reported.
[2]Remission definition according to criteria by Andreasen et al., 2005: patient should keep for at least 6 months a score ≤3 on all the following key PANSS items: P1: Delusions, P2: Conceptual disorganization, P3: Hallucinatory behavior, N1: Blunted affect, N4: Passive/apathetic social withdrawal, N6: Lack of spontaneity, G5: Mannerisms and posturing, G9: Unusual thought content.
[3]Clinical response: lowering of 20% or more of PANSS score.
[4]Relapse definition according to criteria by Csernansky et al., 2002: Any one of the following: psychiatric hospitalization; an increase in the level of psychiatric care (e.g., from clinic visits to day treatment) and an increase of 25% from baseline in the total PANSS score or an increase of 10 points if the baseline score was 40 or less (total possible scores range from 30 to 210); deliberate self-injury; suicidal or homicidal ideation that was clinically significant in the investigator's judgment; violent behavior resulting in clinically significant injury to another person or property damage; or substantial clinical deterioration, defined as a change score of 6 ("much worse") or 7 ("very much worse") on the CGI.
[5]Exacerbation and/or relapse was identified based on increases in the BPRS items unusual thought content, hallucinations, or conceptual disorganization using computer scoring algorithms.
[6]Participants in the 2 groups come from the same site. No patients participate in both studies. Protocols are similar between studies in terms of selection criteria and instruments of evaluation.
[7] ⩾20% decrease in PANSS or BPRS total score; or CGI–S decrease of at least 2 points; or CGI–C improved, much improved, or very much improved; and with no PANSS, BPRS, CGI–S or CGI–C score indicating disease worsening.
[8]PSP total score increase ⩾7 points; or GAF total score increase ⩾20 points; or SOFAS total score increase ⩾30% from baseline; and with no PSP, GAF, or SOFAS score indicating worsening of the disease.
[a]RLAI: risperidone long-acting injection. [b]dx: diagnosis. [c]scz: schizophrenia. [d]sczaff: schizoaffective disorder. [e]AP: antipsychotics. [f]tx: treatment. [g]AD: antidepressants. [h]SUD: Substance use disorder. [i]LAI-AP: Long-acting injectable antipsychotic. [j]DUP: Duration of untreated psychosis. [k]PANSS: Positive and negative syndrome scale. [l]CGI-S: Clinical general impression - severity sub scale. [m]SF-12: 12 items Short form survey. [n]CDS: Calgary depression scale. [o]PP: Paliperidone palmitate. [p]PSP: Personal and social performance scale. [q]GAF: General assessment of functioning scale. [r]OAP: Oral antipsychotic. [s]f/u: follow-up. [t]FEP: First episode psychosis. [u]RPO: Risperidone per os. [v]CR: Cognitive remediation. [w]HBT: Healthy-behaviours training. [x]BPRS: Brief psychiatric rating scale. [y]SF-36: 36 items Short form survey. [z]EQ-5D: EuroQol (quality of life) 5 dimensions questionnaire. [aa]RR: risk ratio. [bb]CI: confidence interval. [cc]NNT: number needed to treat.

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