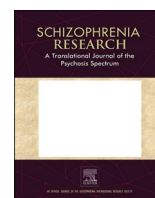


Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Letter to the Editor

Trends in the use of long-acting injectable antipsychotics in children and adolescents in France between 2014 and 2018^{*}

While the use of long-acting injectable antipsychotics (LAI) has not been approved in pediatric population by any national agency for health products safety, it off-label use has been recommended by the American Academy of Child and Adolescent Psychiatry (AACAP) in 2013 for adolescents with schizophrenia and poor medication adherence (McClellan et al., 2013). Anecdotal evidence (case reports/series, small open label clinical trials) supports the clinical usefulness of LAI in youths with non-psychotic disorders, such as bipolar disorder or behavioral problems in patients with neurodevelopmental disorders.

Based on a retrospective analysis of the Indiana Medicaid database, Modesitt et al. (2018) found a total of 1013 LAI atypical antipsychotic doses over 2 year (2012–2014) in pediatric patients. Paliperidone palmitate was billed most frequently, followed by risperidone microspheres, aripiprazole extended-release injection, and then olanzapine pamoate.

To determine whether a comparable trend also exist in European countries we used data from the French national health assurance agency (OPENMEDIC http://open-data-assurance-maladie.ameli.fr/medicaments/index.php#Open_Medic). We aimed at assessing the frequencies of LAI prescriptions in patients below 19-year-old during the year 2018, as well as the change observed over the last five years. Of note, in France access to mental health care system is completely free of charge. Professionals in private practice are less frequently involved in the care of patients with complex or resistant form of mental health issues, such as those requiring LAI antipsychotic.

Over the 4603 antipsychotic prescriptions reported among the subjects below 19-year-old, 3.6 % concern LAI (n = 167). By comparison, 6076 antidepressant prescriptions were reported in the same-age class, and 1758 psychostimulant prescriptions. Second-generation LAI antipsychotic represented 86 % of the total number of LAI prescriptions in pediatric patients. The most frequent LAI prescribed were paliperidone palmitate for monthly injection (n = 69), followed by aripiprazole extended-release injection (n = 52), risperidone long-acting injection (n = 42) and paliperidone palmitate for quarterly injection (n = 4). The profiles of prescribing physicians differed between LAI and oral antipsychotics, $\chi^2(2) = 61.84, p < .001$. Psychiatrists in public facility prescribed 76 % of LAI antipsychotic, psychiatrists in private practice 2 %, general practitioners 5 %, pediatricians in private practice 0 %, and other professionals 17 %. In comparison, psychiatrists in public facility prescribed 46 % of oral antipsychotic, psychiatrists in private practice 12 %, general practitioners 20 %, pediatricians in private practice 0.4 %, and other professionals 22 %.

As shown Fig. 1, a 22 % increase in the number of prescriptions of LAI in this class of age was observed from 2014 to 2018. The pace of

increase was faster the first two years (+10 % in 2015, +9 % in 2016, then +1 % in 2017 and +1 % in 2018). The proportions of LAI out of all antipsychotics prescribed in this class of age, oscillated between 3.5 % and 3.9 % without clear trend.

When considering the specific classes of LAI, a decrease in the total numbers of prescriptions of risperidone long-acting injection was observed since 2014, while the number of prescriptions of aripiprazole extended-release injection firmly increased since it becomes available in France in 2015. Other classes of LAI remained relatively stable. No prescription of olanzapine pamoate in youths below 19-year-old was found. The prescriptions of paliperidone palmitate for quarter injection were very marginal (only 4 prescriptions in 2017, none the other years).

The current study showed that the prescriptions of LAI antipsychotics to pediatric patients in France are not rare, in line with the trend observed in US by Modesitt et al. (2018). The trend of prescriptions were consistent with the international recommendations of using preferentially a second- rather than a first-generation antipsychotic (Findling et al., 2011) and of not prescribing olanzapine as a first therapeutic option (Cohen et al., 2012). The increase in aripiprazole extended-release injection and concomitant decrease in risperidone long-acting injection reflect changes in clinical practice also noted for oral antipsychotics (Hálfánarson et al., 2017). Indeed, aripiprazole is more and more used in France as a first option, considering the low rate of metabolic side effect and the fact that it received the approvals from the European agency for health products safety for bipolar disorder (since 13-year-old) and schizophrenic disorder (since 15-year-old) (Coustals et al., 2021).

The data provided no clue about the socio-demographic and clinical features of the patients who received these medications. This would be useful to know more precisely the patient age and if such prescriptions were limited to patients with resistant treatment-refractory schizophrenic disorders (following the AACAP guideline) or also to patients with a less severe form of psychiatric disorder. Considering the large amount of evidence stressing the importance of securing medical adherence and preventing relapse at the very early phases of bipolar and psychotic disorders (Benarous et al., 2016; Fusar-Poli et al., 2014), the clinical usefulness of prescribing LAI earlier in the natural course of these disorders (i.e., after a first acute manic or psychotic episode) is open to discussion.

The increasing number of prescriptions of LAI observed in youths here highlights the urge of collecting more scientific evidence to guide these prescriptions (Benarous et al., 2022). Apart from clinical trials to determine the effectiveness and tolerance of LAI, pharmacological

^{*} Funding source: none.

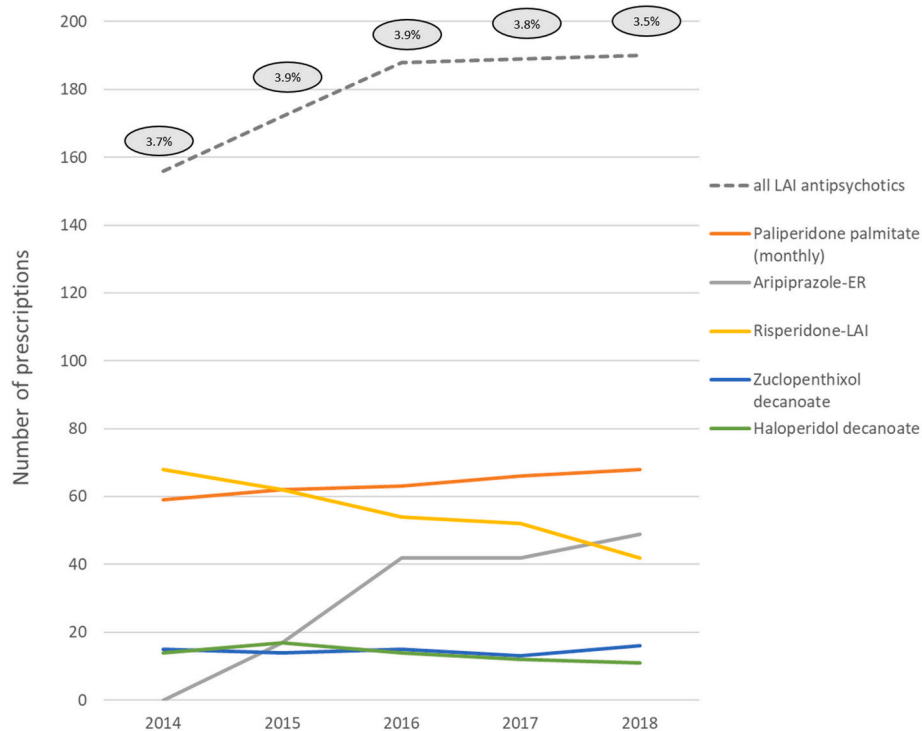


Fig. 1. Trend in the prescriptions of long-lasting injectable antipsychotics among subjects below 19-year-old in the OPEN MEDIC database.

Note: The proportion of LAI antipsychotics over the total number of antipsychotics prescribed for year in youths below 19-year-old are presented in the grey circles.

studies could help determining their pharmacokinetic profiles according to age and optimal doses.

Prescription of LAI in children and adolescent should not remained hidden, but put in light of a clinical debate encouraging a more rational and scientific-based approach of such prescriptions.

CRedit authorship contribution statement

Study concept and design: XB, OB, DC

Acquisition of data: XB, GC, HL

Interpretation of data: XB, GC, HL, SGR, JMG, MS

Drafting the manuscript: XB, HL, SGR, JMG, MS

Critical revision of the manuscript for important intellectual content: XB, OB, DC

Final draft: All authors.

Acknowledgements

No.

References

- Benarous, X., Consoli, A., Milhiet, V., Cohen, D., 2016. Early interventions for youths at high risk for bipolar disorder: a developmental approach. *Eur. Child Adolesc. Psychiatry* 25 (3), 217–233.
- Benarous, X., Cottin, G., Lahaye, H., de la Rivière, S.G., Guilé, J.M., Speranza, M., Bonnot, O., Cohen, D., 2022. Efficacy, tolerability, and acceptance of long-lasting antipsychotics in children and adolescents: a systematic review. *J. Child Adolesc. Psychopharmacol.* 32 (6), 312–327.
- Cohen, D., Bonnot, O., Bodeau, N., Consoli, A., Laurent, C., 2012. Adverse effects of second-generation antipsychotics in children and adolescents: a bayesian meta-analysis. *J. Clin. Psychopharmacol.* 32 (3), 309–316.
- Coustals, N., Ménard, M.-L., Cohen, D., 2021. Aripiprazole in children and adolescents. *J. Child Adolesc. Psychopharmacol.* 31 (1), 4–32.
- Findling, R.D., Jensen, P.S., Rapoport, J.L., AACAP Committee on Quality Issues, 2011. AACAP Practice Parameter for the Use of Atypical Antipsychotic Medications in Children and Adolescents. American Academy of Child and Adolescent Psychiatry (AACAP), Washington, DC.
- Fusar-Poli, P., Yung, A.R., McGorry, P., van Os, J., 2014. Lessons learned from the psychosis high-risk state: towards a general staging model of prodromal intervention. *Psychol. Med.* 44, 17–24.

- Hálfánarson, Ó., Zoëga, H., Aagaard, L., Bernardo, M., Brandt, L., Fusté, A.C., Furu, K., Garuolienė, K., Hoffmann, F., Huybrechts, K.F., Kalverdijk, L.J., Kawakami, K., Kieler, H., Kinoshita, T., Litchfield, M., López, S.C., Machado-Alba, J.E., Machado-Duque, M.E., Mahesri, M., Nishtala, P.S., Pearson, S.A., Reutfors, J., Saastamoinen, L. K., Sato, I., Schuiling-Veninga, C.C.M., Shyu, Y.C., Skurtveit, S., Verdoux, H., Wang, L.J., Yahni, C.Z., Bachmann, C.J., 2017. International trends in antipsychotic use: a study in 16 countries, 2005–2014. *Eur. Neuropsychopharmacol.* 27 (10), 1064–1076.
- McClellan, J., Stock, S., Issues, A.C.o.Q., 2013. AACAP practice parameter for the assessment and treatment of children and adolescents with schizophrenia. *J. Am. Acad. Child Adolesc. Psychiatry* 52 (9), 976–990.
- Modesitt, T., Kubascik, E., Ott, C., 2018. Extent of use of long-acting injectable antipsychotics in children and adolescents within Indiana medicaid. *Ment. Health Clin.* 8 (5), 202–207.

Xavier Benarous^{a,b,*}, Héléne Lahaye^{a,b}, Guillaume Cottin^{a,b}, Sébastien Garny de la Rivière^{a,b}, Jean-Marc Guilé^{a,b,c}, Mario Speranza^d, Olivier Bonnot^e, David Cohen^{f,g}

^a Department of Child and Adolescent Psychopathology, Amiens University Hospital, Amiens, France

^b INSERM Unit U1105 Research Group for Analysis of the Multimodal Cerebral Function, University of Picardy Jules Verne (UPJV), Amiens, France

^c Department of Psychiatry, McGill University, Montreal, Canada

^d Department of Child and Adolescent Psychiatry, Versailles University Hospital, Versailles, France

^e Department of Child and Adolescent Psychiatry, Nantes University Hospital, Nantes, France

^f Department of Child and Adolescent Psychiatry, Pitié-Salpêtrière Hospital, Paris, France

^g CNRS UMR 7222, Institute for Intelligent Systems and Robotics, Sorbonne University, Paris, France

* Corresponding author at: Department of Child and Adolescent Psychopathology, Amiens University Hospital, 1 Rue du Professeur Christian Cabrol, 80054 Amiens, France.

E-mail address: Benarous.xavier@chu-amiens.fr (X. Benarous).