BMJ Open

Incidence of adverse events in antipsychotic-naïve children and adolescents treated with antipsychotic drugs: a French multicentre naturalistic study protocol (ETAPE)

Marie-Line Menard,[1,2] Susanne Thümmler,[1,2] Marianna Giannitelli,[3,4] Bertrand Olliac,[5] Olivier Bonnot,[6] David Cohen,[3,7] Florence Askenazy,[1,2] ETAPE Study group

To cite: Menard M-L, Thümmler S, Giannitelli M, *et al*. Incidence of adverse events in antipsychotic-naïve children and adolescents treated with antipsychotic drugs: a French multicentre naturalistic study protocol (ETAPE). *BMJ Open* 2016;**6**: e011020. doi:10.1136/bmjopen-2015-011020

▸ Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2015-011020).

Received 6 January 2016
Revised 1 March 2016
Accepted 8 March 2016

For numbered affiliations see end of article.

Correspondence to
Dr Marie-Line MENARD; menard.ml@pediatrie-chulenval-nice.fr

ABSTRACT

Introduction: In France, over recent years, the prescription rate of antipsychotic (AP) remained stable in children and adolescents. Prescription of second-generation antipsychotics increased, whereas prescription of first-generation antipsychotics decreased. Off-label prescriptions are very frequent in this population. Adverse events (AEs) in youth treated with AP are common and may be severe. AEs have hitherto been poorly monitored in naturalistic studies independent from industry.

Method and analysis: We describe a French prospective multicentre study in an AP-naïve paediatric population named Etude de la Tolérance des AntiPsychotique chez l'Enfant (ETAPE). The study started in April 2013. So far, 200 patients have been included. The inclusion criteria are: male or female inpatients aged from 6 to 18 years, treated with an AP drug for less than 28 days, never been treated or having received AP for less than 3 months, discontinued at least 6 months prior to inclusion. These assessments of AE are performed at inclusion, as well as at 3, 6, 9 and 12 months after the introduction of the AP. The monitoring period will end in May 2016.

Ethics and dissemination: The study protocol was approved by the Ethics Committee 'Sud Méditerrané V' (number 12.082) and by the French National Agency for Medicines and Health Products Safety (number 2012-004546-15). All patients and their parents signed informed consent on enrolment in the study. We will submit the results of the study to relevant journals and offer national and international presentations. This study will enable better characterisation of the prescription of AP drugs. The results will further help to develop quality standards and recommendations for monitoring AE during the prescription of AP.

Trial registration number: NCT02007928.

BACKGROUND

The prescription of psychotropic drugs has increased in the paediatric population all over the world since about 15 years. This increase varies widely, depending on the country and compounds, ranging from 1.5 to 5 times in many European countries and the USA.[1–4] In the paediatric population, this increase is linked to a major expansion of the prescription of second-generation antipsychotics (SGAs). That is explained, in large part, by the lower occurrence of adverse events (AEs) than with first-generation antipsychotic (FGA) treatment.[5–8] In France, whereas SGA prescriptions are increasing and FGA prescriptions are decreasing over the period 2006–2013, antipsychotic (AP) dispensing rates are stable in persons aged 0–25 years.[1] In the USA, AP use increased from 2006 to 2010 for adolescents and young adults but not for children aged 12 years or younger.[2]

SGAs have been proven to be effective for treating several conditions in children and adolescents.[9] As of March 2010, aripiprazole, olanzapine, quetiapine and risperidone are Food and Drug Administration (FDA)-approved medications for bipolar mania in children and adolescents (age 10–17 years; except olanzapine, age 13–17 years) and for adolescent schizophrenia (age 13–17 years). In addition, aripiprazole and risperidone are also FDA-approved medications for behavioural disturbances (irritability and aggression) associated with autism and/or intellectual disabilities in children and adolescents (age 6–17 years).[10] However, naturalistic studies underline that SGAs are prescribed for many off-label indications in paediatric patients in several countries.[11–13] In France, only two SGAs have been granted market authorisation: (1) risperidone for severe behavioural disorders in mental retardation and for autistic syndromes from the age of 5 years, and for

schizophrenia and psychosis from the age of 18 years; and (2) aripiprazole for schizophrenia from the age of 15 years, and for moderate to severe manic episodes of bipolar I disorder in adolescents aged 13 years or older. Therefore, many prescriptions of AP are off-label and at discretion of the practitioner.[14 15]

Importantly, many major AEs in children and adolescents treated with AP have been reported in the literature.[6 16–18 19] SGA compounds have distinct profiles of secondary effects[20 21] and at least some compounds (eg, olanzapine) have more AEs in young patients than in adults.[22] The most common AEs of SGAs are metabolic (weight gain, obesity, dyslipidemia, hyperglycaemia, diabetes, insulin resistance), cardiac,[10] neuromoto (somnolence/sedation, extrapyramidal syndrome, akathisia, dystonia, catatonia) and endocrine (hyperprolactinaemia).[23–26] Several authors expressed concerns about the consequences of SGAs after long-term exposure in this population.[20 27 28] Indeed, the paediatric population treated by AP is at high risk of AEs.[16 29] Yet, AEs are often poorly monitored. For example, among children, metabolic monitoring is carried out about two times less than in the adult population.[30]

The Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in children (CAMESA) published recommendations for monitoring children and adolescents treated with SGA drugs based on a meta-analysis of studies conducted between 1996 and 2010[31 32] The American Diabetes Association, American Psychiatric Association, North American Association for the Study of Obesity and the American Association of Clinical Endocrinologists subsequently issued a joint consensus that expanded the FDA screening recommendations to include a monitoring protocol for children and adolescents starting treatment with SGAs.[30] However, these recommendations are based on a limited amount of studies. In a recent experts' panel discussion on unmet needs, experts highlighted the need for more specific research given the numerous issues raised in paediatric psychopharmacology including: "the frequent off-label prescription of medications to children and adolescents based exclusively on data from randomized controlled studies involving adult patients; the frequent lack of age-specific dose, long-term efficacy and tolerability/safety data; […]; the current lack of biomarkers to predict treatment response and severe AEs; the effective dissemination of evidence-based treatments to the general public, to better inform patients and families of the benefits and risks of pharmacological interventions during development".[33]

In conclusion, the published data concerning AEs of the AP treatment in the paediatric population are currently insufficient, limiting the development of standardised recommendations, essential to improve the safe use of drugs in child psychiatry. Moreover, a better understanding of AEs of AP in paediatric patients is needed in order to improve the benefit—risk ratio. In addition, more secure prescriptions should help to reduce global healthcare costs of child psychiatry patients.

METHODS/DESIGN

Ethical consideration, funding and registration

ETAPE was funded and authorised by the French National Agency for Medicines and Health Products Safety (ANSM, number 2012-004546-15). The study protocol was approved by the Local Ethics Committee of the principal investigator (MLM) 'Sud Méditerrané V' (number 12.082). All patients and their parents signed informed consent on enrolment in the study. The ETAPE study has also been registered on ClinicalTrials.gov (number NCT02007928). It started in April 2013 (the Gantt diagram is shown in figure 1).

Objectives

The main objective of this study is the evaluation of the incidence of AE related to AP drugs in a French paediatric population with no history of treatment with AP drugs. Secondary objectives are the evaluation of risk factors associated with the occurrence of AEs, persistence of AEs at the end of the study, evaluation of risk factors associated with changing AP drug, evaluation of disorder' severity, social functioning, therapeutic alliance, quality of life, eating patterns and physical activity.

Trial design

ETAPE is a naturalistic prospective multicentre study.[34 35] Patients were recruited over a period of 25 months (from April 2013 to May 2015). A total of 200 patients have been enrolled in 10 University Departments of Child and Adolescent Psychiatry (Children's Hospitals of NICE CHU-Lenval, NICE; University Hospital Pitié Salpêtrière, Paris; Nantes University Hospital, Nantes; Lille University Hospital, Lille; Nancy University Hospital, Nancy; Esquirol Hospital, Limoges; Lyon University Hospitals (HCL Lyon, CH Vinatier, St Jean de Dieu); Toulouse University Hospital, Toulouse; Hospital Fondation Vallée, Gentilly; Poitiers University Hospital, Poitiers; Monaco Hospital) (figure 2). Both inpatients and outpatients have been included in the study. The follow-up for each patient is 12 months. Thus, the monitoring period will end in May 2016.

Patients have been included up to 28 days after the introduction of AP drug. Assessments are performed at inclusion and at 3, 6, 9 and 12 month follow-up (M3, M6, M9, M12). Results of laboratory assessment and ECG up to 90 days prior to and 28 days after initiation of AP treatment are considered for the inclusion visit. Follow-up visits are scheduled at 3, 6, 9 and 12 months after the introduction of AP drug (± 14 days). Follow-up and clinical assessments are specified in table 1. Given the naturalistic design, prescribing decisions will remain free and independent of the study. Practitioners will take all decisions about change or cessation of AP medication according to their usual clinical practice. Each centre will be responsible for the interpretation of all additional examinations performed during the study.

Inclusion criteria

The study was proposed to AP-naive children and adolescents with a practitioner's prescription of AP. Participants

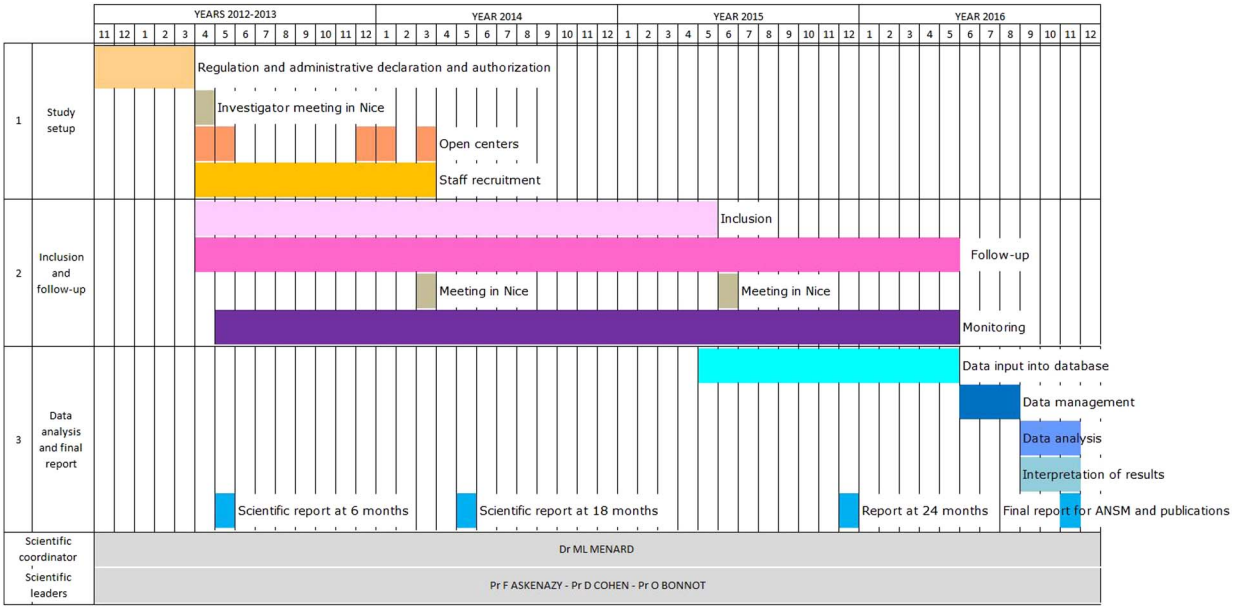

Figure 1 Gantt diagram of the ETAPE study. ANSM, French National Agency for Medicines and Health Products Safety; ETAPE, Etude de la Tolérance des AntiPsychotique chez l'Enfant.

accessed the study either by direct access at the study sites or by referral by a general practitioner or specialists prescribing the medication. Inclusion criteria were as follows:

- Male or female aged from 6 to 18 years
- Treated by AP drug for less than 28 days
- Never having received AP treatment before, or having received AP for less than 3 months and discontinued 6 months prior to the study
- Informed consent of parents or guardian
- Informed consent of child aged 12 years and older
- Consent of child aged under 12 years
- Affiliation to French social security

Exclusion criteria

Since our goal was to conduct a naturalistic study of all types of prescriptions of AP, we did not retain frequently used exclusion criteria such as off-label prescription, patients with severe condition (eg, suicidal behaviour; hospitalisation; comorbid organic condition) and patients with intellectual disability. Therefore, the only exclusion

Figure 2 Inclusion per centre. Legend of figure 2: Less than 6 inclusions per centre (Fondation Vallée, Gentilly; Nancy University Hospital; Poitiers University Hospital; Monaco Hospital) N=12 (6%).

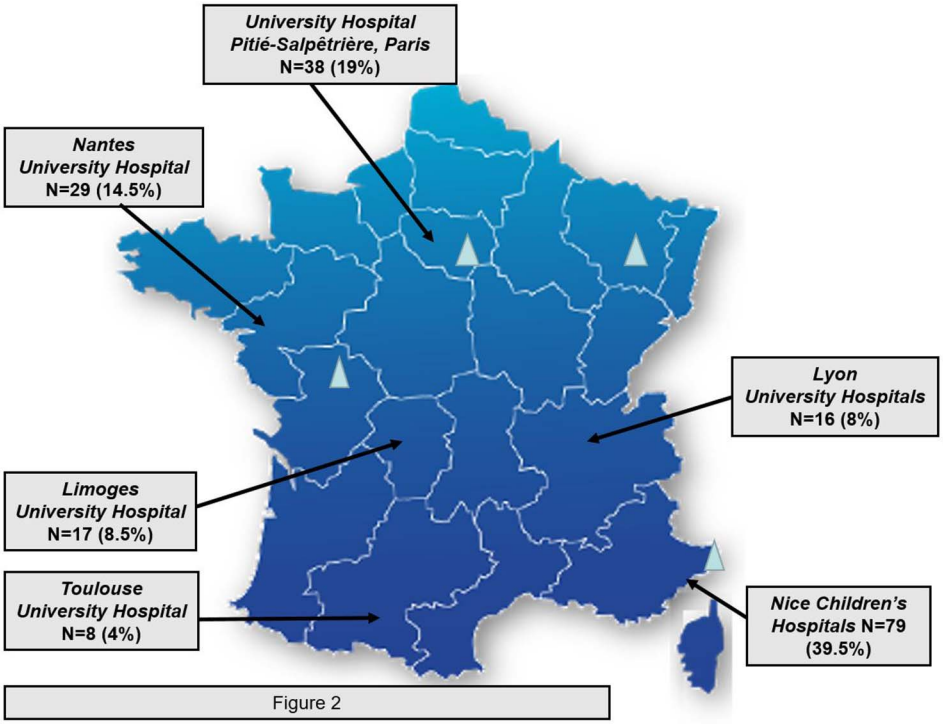

Table 1 ETAPE study procedure and evaluation criteria

	Selection	Inclusion	M3	M6	M9	M12
Inclusion criteria	×					
Informed consent	×					
Somatic parameters weight, height, BMI, waist circumference, blood pressure, temperature	–	×	×	×	×	×
Tanner stage	–	×	–	×	–	×
AIMS[36]						
SAS[37 38]	–	×	×	×	×	×
BARS[39]						
BFCRS[40]						
Laboratory assessment						
Full blood count, liver enzymes, creatine phosphokinase, glycaemia, cholesterol (total, HDL, LDL), triglycerides, hsCRP,	–	×	×	×	×	×
Prolactin, insulin, HbA1c, HOMA	–	×	×	×	–	×
Vitamin D	–	×	×	–	–	×
Thyroid hormones	–	×	–	–	–	×
ECG, QTc interval	–	×	–	×	–	×
Semistructured interview	–	×	–	–	–	×
K-SADS[41]						
MINI/MINI-kid[42]						
Clinician questionnaires	–	×	×	×	×	×
CGI-S[43 44]						
CGAS[45 46]	–	×	–	×	–	×
PAERS[47]	–	×	×	×	×	×
Patient Questionnaires						
QEWP[48]	–	×	×	×	×	×
HAQ[49 50]	–	–	×	×	×	×
SDS[51]	–	×	×	×	×	×
Dennison[52]	–	×	×	×	×	×

AIMS, abnormal involuntary movement scale; BARS, barnes akathisia rating scale; BFCRS, bush francis catatonia rating scale; BMI, body mass index; CGAS: clinical global assessment scale; CGI-S, clinical global impression scale; ECG, electrocardiogram; HAQ, helping alliance questionnaire; HDL, high-density lipoprotein; hs-CRP, high sensitivity C-reactive protein; HbA1c, glycated haemoglobin; HOMA, insulin resistance; K-SADS, SAS, simpson and angus scale; LDL, low-density lipoprotein; MINI, mini international neuropsychiatric interview; PAERS, pediatric adverse event rating scale; QEWP, questionnaire of eating and weight patterns; schedule for affective disorders and schizophrenia for school age children; SDS, sheehan disability scale.

criterion was refusal or withdrawal of consent by the patient or his/her parents.

Measures

Quantitative and qualitative measures are assessed during the study (summary in table 1): clinical parameters (eg, body weight), laboratory assessment (eg, blood cholesterol), ECG (eg, QTc interval), semistructured interviews to assess main diagnosis at inclusion and after 12 month follow-up (Kiddie-SADS,[41] and/or MINI/MINI-Kid[42]), several clinical heteroassessments with a specific rating scale (eg, the Modified Bush-Francis Catatonia Rating Scale, BFCRS[40 53]), and several self-report questionnaires (eg, Pediatric Adverse Event Rating Scale, PAERS[47]).

Data collection process

Each investigator of the different study centres (child psychiatrist, clinical psychologist, physician, paediatrician, cardiologist) is responsible for collecting and entering data on the paper CRF at the time of the visit. Data control for quality and regulation requirement is realised in each every five inclusions centre by the monitoring clinical research assistant. Results will be entered by the clinical research assistants of the NICE study centre in the database. Double-check in order to avoid missing data or filling errors will be carried out before freezing of the database. Data extraction and analysis of the database (Open Clinica V.3.1.3 Community Edition) will be performed by the Department of Clinical Research and Innovation (DRCI) at NICE University Hospital (data and metadata) after freezing.

Statistical analysis

Statistical analysis will be conducted by DRCI at NICE University Hospital using SAS Enterprise Guide V.5.1 (Copyright (c) 1999–2006 by SAS Institute Inc, Cary, North Carolina, USA). A descriptive analysis of all the parameters collected at baseline and during follow-up will be performed. For continuous variables (age, weight, body mass index, etc), indicators such as the mean, SD and range values will be calculated. Categorical data will be presented by means of frequency (n, %).

Changes in the parameters and in the distribution of categorical variables from baseline to follow-up points will be tested with univariate analysis using appropriate

testing according to the type of variable and distribution with a level of significance for the p value fixed at <0.05.

In addition, multivariate analysis will be carried out. An intention-to-treat approach will be used; this means that patients who will be lost to follow-up will be censored at the time of the last visit they attended and included in the analysis. Survival analysis techniques will be performed using Cox analysis for binary outcomes and generalised models for continuous variables. Missing data will also be handled by using the Last Observation Carried Forward method.

OUTCOMES

The implementation of this national study should help in raising awareness and educating all French practitioners (child psychiatrists, psychiatrists, paediatricians, general physicians) about AEs of AP in young people. The study will also enable better characterisation of the prescription of AP drugs in children and adolescents and evaluate the incidence of AEs related to AP drugs in a French population with no history of taking AP drugs.

The secondary objectives of the ETAPE study are the assessment of risk factors associated with the occurrence of AEs (eg, age at onset of treatment, pubertal status at baseline, age at onset of disorder for which the prescription of an SGA drug was indicated, type of AP treatment, concomitant treatment, Diagnostic and Statistical Manual Fourth Edition (DSM-IV) diagnosis). In addition, these items will help to identify risk factors associated with change of AP treatment. The course of disorder' severity, social functioning, therapeutic alliance, quality of life, eating patterns and physical activity during follow-up will also be analysed.

The results will serve to:

- Help practitioners for prescription decisions
- Reinforce monitoring of AEs related to AP drugs
- Develop recommendations for AP prescription and follow-up by adding original data from a naturalistic study
- Improve the safety of AP drugs in child and adolescent psychiatry

The results will further help to develop quality standards and monitoring methods for the prescription of AP in order to improve the benefit/risk ratio.

DISCUSSION

The results of this study are very important as AEs of antipsychotic treatment are sometimes overlooked in current practice in child psychiatry. In addition, few studies target the antipsychotic-naive paediatric population.

The ETAPE study proposes a methodology enabling an exhaustive search for AE. Early identification and better understanding of AE will help to improve mental healthcare of the paediatric population, and also reduce the costs of the treatment of AE.

Limitations of the study: The paediatric psychiatric population is very difficult to follow up reliably. There is a high risk of loss to follow-up, which is estimated to be at least 20%. The size of the sample could be limited by these factors. The clinical scales used to assess neuromuscular AEs are validated in the adult population, which might be a limitation for analyses in young patients. Secondary analyses may be limited by the number of patients in each subgroup.

Author affiliations
[1]University Department of Child and Adolescent Psychiatry, Children's Hospitals of NICE CHU-Lenval, NICE, France
[2]CoBTek, EA7276, University of NICE Sophia Antipolis, Nice, France
[3]Department of Child and Adolescent Psychiatry, GH Pitié-Salpêtrière, APHP, Paris, France
[4]GRC-PSYDEV, Université Pierre et Marie Curie, Hôpital Piété-Salpêtrière, AP-HP, Paris, France
[5]Department of Child and Adolescent Psychiatry, Esquirol Hospital, Limoges, France
[6]Department of Child and Adolescent Psychiatry, Nantes University Hospital, Nantes, France
[7]CNRS UMR 7222 Institut des Systèmes Intelligents et Robotiques, Université Pierre et Marie Curie, Paris, France

Collaborators ETAPE Study group: Boublil Michel, MD (CAMPS de Grasse, Grasse, France); Castaings Agnès, PhD (University Department of Child and Adolescent Psychiatry, Children's Hospitals of NICE CHU-Lenval, NICE, France); Chambry Jean, MD (Fondation Vallée, Gentilly, France); Charvet Dorothée, MD (Unité de Soins pour Adolescents Ulysse, Saint Jean de Dieu Hospital, Lyon, France); Cseterky Mona, MD (Princess Grace Hospital Centre, Monaco); Fontas Eric, MD (Department of Clinical Research and Innovation, NICE University Hospital, NICE, France); Fourneret Pierre, MD, PhD (Hôpital Femme Mère Enfant, Fondation Hospices Civils de Lyon, Lyon, France); Gicquel Ludovic, MD, PhD (Henri Laborit Hospital, Poitiers, France); Kabuth Bernard, MD, PhD (Department of Child and Adolescent Psychiatry, Brabois Vandoeuvre-les-Nancy Hospital, France); Leroy Bernard, MD (Pôle Parents-Femme-Enfant, Cannes Hospital, France); Maria Fanny (University Department of Child and Adolescent Psychiatry, Children's Hospitals of NICE CHU-Lenval, NICE, France); Moceri Pamela, MD (Children's Hospitals of NICE CHU-Lenval, NICE, France); Raynaud Jean-Philippe, MD, PhD (University Department of Child and Adolescent Psychiatry, Toulouse University Hospital, Toulouse, France); Roche Jean-François, MD (Department of Child and Adolescent Psychiatry, Esquirol Hospital, Limoges, France); Rochet Thierry, MD (Hospital Center Le Vinatier, Bron, France).

Contributors M-LM, FA, OB and DC form the scientific committee of the study and contributed to the conceptualisation of the ETAPE study and the design of this protocol. M-LM is responsible for all aspects of the study including preparation of grant application, securing funding, data analysis, interpretation and preparation of the final manuscript for publication. M-LM, ST, FA and DC have been involved in drafting the first version of the MS. All authors have been involved in revising it critically for important intellectual content, and approved the final version.

Funding This study is funded by the French National Agency for Medicines and Health Products Safety (ANSM, number 2012-004546-15).

Competing interests During the past 2 years, DC reported past consultation for the receipt of honoraria from Otsuka, Shire, Lundbeck and IntegraGen. OB reported past consultation for the receipt of honoraria from Otsuka, Shire, Orphan Europe and Actelion.

Patient consent Obtained.

Ethics approval The study was sponsored by the Ethic Committee 'Sud Méditerrané V' (number 12.082) and by the French National Agency for Medicines and Health Products Safety—ANSM (number 2012-004546-15).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The study protocol was approved by the Ethics Committee 'Sud Méditerrané V' (number 12.082) and by the French National

Agency for Medicines and Health Products Safety (number 2012-004546-15). All patients and their parents signed informed consent on enrolment in the study. We will submit the results of the study to relevant journals and offer national and international presentations. This study will enable better characterisation of the prescription of AP drugs. The results will further help to develop quality standards and recommendations for monitoring AEs during the prescription of AP.

REFERENCES

1. Verdoux H, Pambrun E, Cortaredona S, *et al*. Antipsychotic prescribing in youths: a French community-based study from 2006 to 2013. *Eur Child Adolesc Psychiatry* 2015;24:1181–91.
2. Olfson M, King M, Schoenbaum M. Treatment of young people with antipsychotic medications in the United States. *JAMA Psychiatry* 2015;72:867–74.
3. Acquaviva E, Peyre H, Falissard B, *et al* Panorama de la prescription et de la consommation des psychotropes chez l'enfant et l'adolescent en France. *Neuropsychiatr Enf Adolesc* 2012;60:77–85.
4. Harrison JN, Cluxton-Keller F, Gross D. Antipsychotic medication prescribing trends in children and adolescents. *J Pediatr Health Care* 2012;26:139–45.
5. Ben Amor L. Antipsychotics in pediatric and adolescent patients: a review of comparative safety data. *J Affect Disord* 2012;138:S22–30.
6. Vitiello B, Correll C, Zwieten-Boot B, *et al*. Antipsychotics in children and adolescents: increasing use, evidence for efficacy and safety concerns. *Eur Neuropsychopharmocol* 2009;19:629–35.
7. Kalverdijk LJ, Tobi H, Van den Berg PB, *et al*. Use of antipsychotic drugs among Dutch youths between 1997 and 2005. *Psychiatr Serv* 2008;59:554–60.
8. Zito JM, Safer DJ, de Jong-van den Berg LT, *et al*. A three-country comparison of psychotropic medication prevalence in youth. *Child Adolesc Psychiatry Ment Health* 2008;2:26.
9. Aparasu RR, Bhatara V. Patterns and determinants of antipsychotic prescribing in children and adolescents, 2003-2004. *Curr Med Res Opin* 2007;23:49–56.
10. Jensen PS, Buitelaar J, Pandina GJ, *et al*. Management of psychiatric disorders in children and adolescents with atypical antipsychotics: a systematic review of published clinical trials. *Eur Child Adolesc Psychiatry* 2007;16:104–20.
11. McKinney C, Renk K. Atypical antipsychotic medications in the management of disruptive behaviors in children: safety guidelines and recommendations. *Clin Psychol Rev* 2011;31:465–71.
12. Doey T, Handelman K, Seabrook JA, *et al*. Survey of atypical antipsychotic prescribing by Canadian child psychiatrists and developmental pediatricians for patients aged under 18 years. *Can J Psychiatry* 2007;52:363–8.
13. Cooper WO, Arbogast PG, Ding H, *et al*. Trends in prescribing of antipsychotic medications for US children. *Ambul Pediatr* 2006;6:79–83.
14. Auby P. Nouveaux enjeux de la recherche clinique en psychopharmacologie chez l'enfant et l'adolescent. *Neuropsychiatr Enfance Adolesc* 2012;60:62–8.
15. Cohen D. Les antipsychotiques atypiques chez l'adolescent : quels enjeux pour l'avenir ? *Encéphale* 2011;37:15–17.
16. Arango C, Giraldez M, Merchan-Naranjo J, *et al*. Second-generation antipsychotic use in children and adolescents: a six-month prospective cohort study in drug-naïve patients. *JAACAP* 2014;53:1179–90.
17. Merchán-Naranjo J, Tapia C, Bailón C, *et al*. Secondary effects of antipsychotic treatment in naïve or quasi naïve children and adolescents: design of a follow-up protocol and baseline results. *Rev Psiquiatr Salud Ment* 2012;5:217–28.
18. San L, Arranz B, Perez V, *et al*. One-year, randomized, open trial comparing olanzapine, quetiapine, risperidone and ziprasidone effectiveness in antipsychotic-naïve patients with a first-episode psychosis. *Psychiatry Res* 2012;200:693–701.
19. Correll CU. Monitoring and management of antipsychotic-related metabolic and endocrine adverse events in pediatric patients. *Int Rev Psychiatry* 2008;20:195–201.
20. Cohen D, Bonnot O, Bodeau N, *et al*. Adverse effects of second-generation antipsychotics in children and adolescents: a Bayesian metaanalysis. *J Clin Psychopharmacol* 2012;32:309–16.
21. Fraguas D, Correll CU, Merchán-Naranjo J, *et al*. Efficacy and safety of second-generation antipsychotics in children and adolescents with psychotic and bipolar spectrum disorders: comprehensive review of prospective head-to-head and placebo-controlled comparisons. *Eur Neuropsychopharmacol* 2011;21:621–45.
22. Woods SW, Martin A, Spector SG, *et al*. Effects of development on olanzapine associated adverse events. *J Am Acad Child AdolescPsychiatry* 2002;41:1439–46.
23. Keinänen J, Mantere O, Kieseppä T, *et al*. Early insulin resistance predicts weight gain and waist circumference increase in first-episode psychosis—a one year follow-up study. *Schizophr Res* 2015;169:458–63.
24. Druyts E, Eapen S, Wu P, *et al*. The risk of elevated prolactin levels in pediatric patients exposed to antipsychotics for the treatment of schizophrenia and schizophrenia spectrum disorders: protocol for a systematic review and meta-analysis. *Syst Rev* 2014;3:116.
25. Pina-Camacho L, Díaz-Caneja C, Saiz PA, *et al*. Pharmacogenetic study of second-generation antipsychotic long-term treatment metabolic side effects (the SLiM Study): rationale, objectives, design and sample description. *Rev Psiquiatr Salud Ment* 2014;7:166–78.
26. Raffin M, Giannitelli M, Consoli A, *et al*. Management of adverse effects of second-generation antipsychotics in youth. *Current Treatment Options in Psychiatry* 2014;1:84–105.
27. Rani FA, Byrne PJ, Murray ML, *et al*. Paediatric atypical antipsychotic monitoring safety (PAMS) study. Pilot study in children and adolescents in secondary and tertiary care settings. *Drug Saf* 2009; 32:325–33.
28. Bonnot O, Inaoui R, Raffin-Viad M, *et al*. Children and adolescents with severe mental illness need vitamin D supplementation regardless of disease or treatment. *J Child Adolesc Psychopharmacol* 2011;21:1–5.
29. Nielsen RE, Laursen MF, Vernal DL, *et al*. Risk of diabetes in children and adolescents exposed to antipsychotics: a Nationwide 12-year case-control study. *J Am Acad Child Adolesc Psychiatry* 2014;53:971–9.
30. Morrato EH, Nicol GE, Maahs D, *et al*. Metabolic screening in children receiving antipsychotic drug treatment. *Arch Pediatr Adolesc Med* 2010;164:344–51.
31. Pringsheim T, Panagiotopoulos C, Davidson J, *et al*. Des recommandations probantes pour surveiller l'innocuité des antipsychotiques de deuxième génération chez les enfants et les adolescents. *Paediatr Child Health* 2012;17:12B–21B.
32. Ho J, Pangiotopoulos C, McCrindle B, *et al*. Management recommendations for metabolic complications associated with second generation antipsychotic use in children and youth. *J Can Acad Child Adolesc Psychiatry* 2011;20:3.
33. Persico AM, Arango C, Buitelaar JK, *et al*. Unmet needs in paediatric psychopharmacology: present scenario and future perspectives. *European Neuro Psycho Pharmacology* 2015;25:1513–31.
34. Menard ML, Thümmler S, Auby P, *et al*. Preliminary and ongoing French multicenter prospective naturalistic study of adverse events of antipsychotic treatment in naive children and adolescents. *Child Adolesc Psychiatry Ment Health* 2014;8:18.
35. Menard ML, Askenazy F. Evaluation de l'incidence des événements indésirables sous antipsychotique en population pédiatrique naïve (Étude ETAPE: étude de la tolérance des antipsychotiques chez l'enfant). *Neuropsychiatrie de l'Enfance et de l'Adolescence* 2013;61:131–2.
36. Guy W. *ECDEU. Assessment manuel for psychopharmacology: revised (DHEW publication number ADM 76-338)*. Rockville, MD: US Department of Health, Education and Welfare, Public Health Service, Alcohol, Drug Abuse and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs, 1976a:534–7.
37. Lejoyeux M, Gorwood P, Stalla-Bourdillon A, *et al*. Traduction et utilisation de l'échelle de Simpson et Angus de symptômes extra-pyramidaux. *Encéphale* 1993;19:17–21.
38. Simpson GM, Angus JWS. A rating scale for extra-pyramidal side effects. *Acta Psychiatr Scand* 1970;212:11–19.
39. Barnes TRE. A rating scale for drug-induced akathisia. *Br J Psychol* 1989;154:672–6.
40. Bush G, Fink M, Petrides G, *et al*. Catatonia.I. Rating scale and standardized examination. *Acta Psychiatr Scand* 1996;93:129–36.
41. Kaufman J, Birmaher B, Brent D, *et al*. Schedule for affective disorders and schizophrenia for school age children. Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 1997; 36:980–8.

42. Sheehan DV, Lecrubier Y, Harnett Sheehan K, *et al*. The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. *Eur Psychiatry* 1997;12:232–41.
43. Kadouri A, Corruble E, Falissard B. The improved Clinical Global Impression Scale (iCGI): development and validation in depression. *BMC Psychiatry* 2007;7:7.
44. Guy W. ECDEU. Assessment manuel for psychopharmacology. Revised 1976.
45. Endicott J, Spitzer RL, Fleiss JL. The global assessment scale: a procedure for measuring overall severity of psychiatric disturbance. *Arch Gen Psychiatry* 1976;33:766–71.
46. Dugas M, Halfon O, Cousin R. Double-blind study of mianserin, imipramine and placebo in childhood depression. *Poster presented at the annual meeting of the American Academy of Child and Adolescent Psychiatry;* New York, 11-15 October 1989.
47. March J, Karayal O, Chrisman A. CAPTN: the Pediatric Adverse Event Rating Scale. In: Novins DK, DeYoung, eds. *The Scientific Proceedings of the 2007 Annual Meeting of the American Academy of Child and Adolescent Psychiatry*; 23-28 october 2007; Boston, 2007:241.
48. Johnson WG, Grieve FG, Adams CD, *et al*. Measuring binge eating in adolescents: adolescent and parent versions of the Questionnaire of Eating and Weight Patterns. *Int J Eat Disord* 1999;26:301–14.
49. Kermarrec S, Kabuth B, Bursztejn C, *et al*. French adaptation and validation of the Helping Alliance Questionnaires for child, parents and therapist. *Can J Psychiatry* 2003;51:913–22.
50. Luborsky L. Helping alliances in psychotherapy: the groundwork for a study of their relationship to its outcome. In: Claghorn JL, ed. *Successful psychotherapy*. New York: Brunner/Mazel, 1976:92–116.
51. Leon AC, Shear MK, Portera L, *et al*. Assessing impairment in patients with panic disorder: the Sheehan Disability Scale. *Soc Psychiatry Psychiatr Epidemiol* 1992;27:78–82.
52. Dennison BA, Straus JH, Mellits DE, *et al*. Childhood physical fitness test: predictor of adult physical activity levels? *Pediatrics* 1988;82:324–30.
53. Cohen D, Nicolas JD, Flament MF, *et al*. Clinical relevance of chronic catatonia schizophrenia in children and adolescents: evidence from a prospective naturalistic study. *Schizophr Res* 2005;76:301–8.