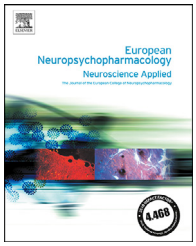
European Neuropsychopharmacology (2019) 29, 1397–1407

www.elsevier.com/locate/euroneuro



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

Marie-Line Menard[a,b,*], Susanne Thümmler[a,b], Marianna Giannitelli[c,d], Coralie Cruzel[e], Olivier Bonnot[f], David Cohen[c,d], Florence Askenazy[a,b], on behalf of the ETAPE Study Group[1]

[a] *University Department of Child and Adolescent Psychiatry, Children's Hospitals of Nice CHU-Lenval, 57 avenue de la Californie, 06200 Nice, France*
[b] *CoBTek, EA7276, University of Côte d'Azur, Nice, France*
[c] *Department of Child and Adolescent Psychiatry, GH Pitié-Salpêtrière, APHP, Paris, France*
[d] *CNRS UMR 7222 Institut des Systèmes Intelligents et Robotiques, Pierre & Marie Curie University, Paris, France*
[e] *Department of Clinical Research and Innovation (DRCI), Nice University Hospital, Nice, France*
[f] *Department of Child and Adolescent Psychiatry, University Hospital, Nantes, France*

Received 7 June 2019; received in revised form 10 October 2019; accepted 15 October 2019

KEYWORDS
Antipsychotics;
Adverse events;
Pediatric population;
Child and adolescent psychiatry;
Psychotropics

Abstract
The main objective of ETAPE study was to determine the incidence of adverse events (AEs) potentially related to antipsychotic (AP) during a 12-months observational study of naturalistic treatment. ETAPE is a naturalistic prospective multicenter study conducted between April 2013 and May 2016. 200 patients were included. The mean age was 12 ± 3 years, with 73.6% being males. Patients presented a significant clinical improvement over time. At baseline, 92% of patients received a second generation AP, 74% AP monotherapy and 79.5% off-label AP

* Corresponding author.
E-mail address: menard.ml@pediatrie-chulenval-nice.fr (M.-L. Menard).

[1] We are very grateful to all patients, their families as well as health professionals implicated in ETAPE study group. ETAPE study group are listed at the end of the Article.

https://doi.org/10.1016/j.euroneuro.2019.10.006

prescriptions. Clinical diagnoses were heterogeneous including psychosis, anxiety, mood and neurodevelopmental disorders. The overall AE incidence rate was 11.52 AEs per person-years. Among AEs potentially attributable to AP, 15.4% were neuromotor, 14.8% gastroenterological, 12.2% metabolic and 11.8% general symptoms. Weight and body mass index increased significantly. More than half of AE appeared during the first 3 months, but onset of AE was noted all over follow-up. The presence of AEs was stable over time. ETAPE study highlights a high incidence rate of AE in children treated with AP. A careful and continuous clinical and biological monitoring is required to adapt treatment decisions based on benefice-risk-analysis. Moreover, additional research is warranted, also in regard of high proportion of off-label prescriptions.

1. Introduction

Over the last twenty years, prescribing of antipsychotic (AP) drugs has increased dramatically in children and adolescents in Europe, Asia and the United States (Kalverdijl et al., 2017; Olfson et al., 2015; Santoch et al., 2017).

This increase is linked to major expansion of the prescription of second generation antipsychotics (SGA) (Halfdanarson et al., 2017). SGA are considered safe by clinicians (Caccia, 2013) given the substantially decreased risk of extrapyramidal side effects relative to first-generation antipsychotics (FGA) (Vitiello et al., 2009). In France, the overall rate of AP prescribing has been stable in children and young adults over the period from 2006 to 2013, with SGA prescriptions increasing and FGA prescriptions decreasing (Verdoux et al., 2015).

SGA have limited approved indications in children and adolescents. Aripiprazole, olanzapine, quetiapine, and risperidone have been approved by the American Food and Drug Administration (FDA) for use in bipolar mania in children and adolescents (age 10–17 years; except olanzapine, age 13–17 years) and in adolescent schizophrenia (age 13-17 years). In addition, aripiprazole and risperidone have also been approved for behavioral disturbances (irritability and aggression) associated with autism spectrum disorders (ASD) and/or intellectual disability (ID) in children and adolescents (age 5–17 years). In France, the extent of legal authorization is even more restricted with risperidone approved for behavioral disorders associated with ID and/or ASD from the age of 5, and for schizophrenia from the age of 18; and aripiprazole for schizophrenia from the age of 15, and for manic episodes of bipolar I disorder from the age of 13. However, pharmacoepidemiological studies underline that SGA are frequently prescribed off-label in pediatric patients in several countries (McKinney et al., 2011).

In addition, a high number of sometimes severe AEs in children and adolescents treated with AP have been reported in the literature (Arango et al., 2014; Cohen et al., 2012; Ray et al., 2019). The most common AEs of SGA are metabolic (e. g. weight gain and metabolic complications), neuromotor (e.g. extrapyramidal syndrome), endocrine (e.g. hyperprolactinemia) and general symptoms (e.g. somnolence/sedation) (Keinänen et al., 2015; Menard et al., 2014; Pagsberg et al., 2017). Children must be considered to be a vulnerable group for adverse reactions, which tend to occur more frequently in the pediatric population than in adults (Correll et al., 2009).

Though concern has been expressed about the consequences of SGA after long-term exposure in the pediatric population (Ben Amor, 2012), their AEs are often underappreciated and poorly monitored. For example, among children, metabolic monitoring is carried out about two times less frequently than in the adult population (Morrato et al., 2010). The medium and long-term consequences of many AEs are poorly known for the pediatric population and non-industry funded pharmacovigilance studies on the long term effects of SGA are lacking (Persico et al., 2015).

Many countries have developed specific guidelines for the follow-up of AP treatments in children and adolescents (e.g. USA, Canada, United Kingdom and Spain, Raffin et al., 2014; Kendall et al., 2013; Ho et al., 2011), including clinical, physical and biological parameters.

The main objectives of our study were: (1) to determine the incidence of AEs of newly-prescribed AP drugs in a French pediatric population; (2) to document the clinical diagnosis that resulted in both label and off-label prescriptions in a naturalistic French context; (3) to determine the onset and duration of AEs during a one-year follow-up period; (4) to measure clinical benefit with a view to the discussion of the risk/benefit ratio in the context of these non-selected diagnoses.

2. Experimental procedures

2.1. Study design and participants

ETAPE is a naturalistic prospective multicenter study funded by the French National Agency for Medicines and Health Products Safety (ANSM, no 2012-004546-15) and approved by the local Ethics Committee “Sud Méditerranée V” (no 12.082). All patients and their parents signed informed consent upon enrollment in the study. The trial was registered at clinicaltrials.gov, number NCT02007928. In- and out-patients who met the inclusion criteria were recruited over a period of 25 months (from April 2013 to May 2015) in 15 departments of child and adolescent psychiatry in France. The inclusion criteria were: male or female inpatients aged from 6 to 18 years, treated with an AP drug for less than 28 days (naïve patients), never been treated or having received AP for less than 3 months, discontinued at least 6 months prior to inclusion (quasinaïve patients).

2.2. Assessments and measures

Details of the study protocol have been published elsewhere (Menard et al., 2016). Briefly, patients were included up to 28

days after the introduction of the AP drug. At inclusion, clinical diagnoses (DSM-IV) were evaluated by a recommended standardized instrument (Kiddie-SADS-PL or MINI-Kid) (Kaufman et al., 1997; Sheehan et al., 2010). AE assessments were performed at inclusion (0M) and at three (3M), six (6M), nine (9M) and 12 months (12M) follow-up visits. The follow-up of 12 months has been systematically proposed to all patients, independently of the duration of AP-treatment. Each assessment included a physical examination (weight, height, waist circumference, body mass index (BMI), Tanner stage), laboratory testing (full blood count, liver enzymes, creatine phosphokinase, glycaemia, cholesterol (total, HDL, LDL), triglycerides, prolactin, insulin, HbA1c, HOMA, vitamin D, thyroid hormones), and an electrocardiogram. Several clinical scales were administered at each assessment: PAERS for systematic reporting of AE occurring in children treated with psychotropic drugs in clinical studies (March et al., 2007); BFCRS for catatonia (Bush et al., 1996); AIMS for abnormal movement (Guy, 1976a); BARS for akathisia (Barnes, 1989); and SAS for extrapyramidal syndrome adverse effects (Simpson and Angus, 1970). The disease severity and its functional impact were assessed by CGI-S (Guy, 1976b) and CGAS (Endicott et al., 1976).

2.3. Definition and classification of AEs

The investigator determined if each AE was potentially attributable to the AP drug, and rated its severity (mild, moderate, severe, and extreme. AEs were classified into 12 clinical dimensions (neuromotor, metabolic, gastroenterological, psychiatric, eating disorders, hormonal, sleep disorders, dermatologic, cardiologic, hematologic, general symptoms and other) (Cohen et al., 2012; Rasimas and Liebelt, 2012).

Serious adverse events (SAEs) were defined as an AE that resulted in death or life threatening illness, required or prolonged hospitalization, caused persistent or significant disability or incapacity, or resulted in a congenital anomaly or birth defect. SAEs were reported to health authorities using a standardized and compulsory reporting process for treatment studies (https://www.has-sante.fr/portail/jcms/c_2787301/fr/declarer-les-evenements-indesirables-graves-eigs).

2.4. Statistical analysis

Characteristics of the study population are presented at baseline. Descriptive results of continuous variables are expressed as means (±SD), and as absolute numbers and relative frequencies for categorical variables. The incidence rate of AEs potentially attributable to the AP drug was calculated by dividing the number of patients with a new AE during the entire follow-up period by the number of person-years at risk. The 95% confidence interval (CI) is also presented.

The onset of each AE was determined according to the date it was first recorded in the database, even if it persisted for more than one trimester. It was then assessed at each time point (3M, 6M, 9M, 12M). Statistical analyses were performed using SAS Enterprise Guide 7.1 (Copyright (c) 2017 by SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Characteristics of the study population

From April 2013 to May 2015, a total of 200 patients have been included in ETAPE study. Ten were excluded from statistical analyses because they did not meet full inclusion criteria. Fig. 1 summarizes the study flow diagram. In the total group of patients analyzed ($n = 190$), 109 (57.3%) patients never received any psychotropic treatment before inclusion. Among patients who had already received a psychotropic drug ($n = 81$): antidepressant ($n = 29$), stimulant ($n = 26$), antihistamine ($n = 24$), benzodiazepine ($n = 17$) and brief antipsychotic-treatment ($n = 16$). The study population characteristics at baseline are presented in Table 1. The mean age was 12 ± 3 years with the majority of participants being male (73.6%). AP prescription has principally been motivated by psychotic symptoms (28.9%), challenging behavior (19.5%), pervasive developpemental (10.5%) and mood disorder (10.0%). Main standardized diagnoses (DSM-IV) at inclusion are presented in Table 1 with 1.86+/−1.9 comorbid diagnoses per patient.

Table 1 Study population baseline characteristics ($n = 190$).

Age mean (±SD)	12.1	(2.9)
Girls *n* (%)	50	(26.3)
Boys *n* (%)	140	(73.7)
Tanner stage *n* (%)	190	(100)
I. Prepuberty	62	(32.6)
II-IV. Puberty in progress	81	(42.7)
V. Puberty completed	47	(24.7)
Weight, kg mean (±SD)	45.6	(16.3)
Height, m mean (±SD)	1.52	(0.2)
BMI, kg/m² mean (±SD)	18.9	(4)
CGI-S mean (±SD)	4.83	(0.84)
CGAS mean (±SD)	4.7	(1.07)
Clinical diagnoses (DSM IV)[a] *n* (%)	190	(100)
Anxiety disorder	116	(61)
Mood disorder	59	(31)
Attentional deficit	48	(25.3)
Oppositional defiant disorder	47	(25)
Psychosis	41	(21.6)
Intellectual disability	23	(12)
Tic	19	(10)
Conduct disorder	18	(9.5)
Eating disorder	10	(5.3)
Abuse	10	(5.3)
Enuresia/encopresia	6	(3)

SD = standard deviation; *n* = number; BMI = body max index; CGI-S = clinical global impression scale graduated from 1 (not at all ill) to 7 (among the most extremely ill patients); CGAS = children's global assessment scale graduated from 100 (superior functioning) to 1 (needs constant supervision); DSM: Diagnostic and Statistical Manual of Mental Disorders.

[a] Diagnoses based on K-SADS-PL (88%), MINI (5%) and clinician (7%).

The mean duration of follow-up was 8.36 months (± 4.54) with 108 patients (56.8%) completing study follow-up of 12 months. Within these 108 patients, the mean duration of antipsychotic treatment was 11.03 months (± 2.84).

AP, other psychotropic, and non-psychotropic drugs prescribed during the study period are summarized in Table 2. At inclusion, 92% of patients received a SGA, with risperidone (50%) and aripiprazole (36%) being the most frequently prescribed drugs. Most patients (74%) were prescribed only

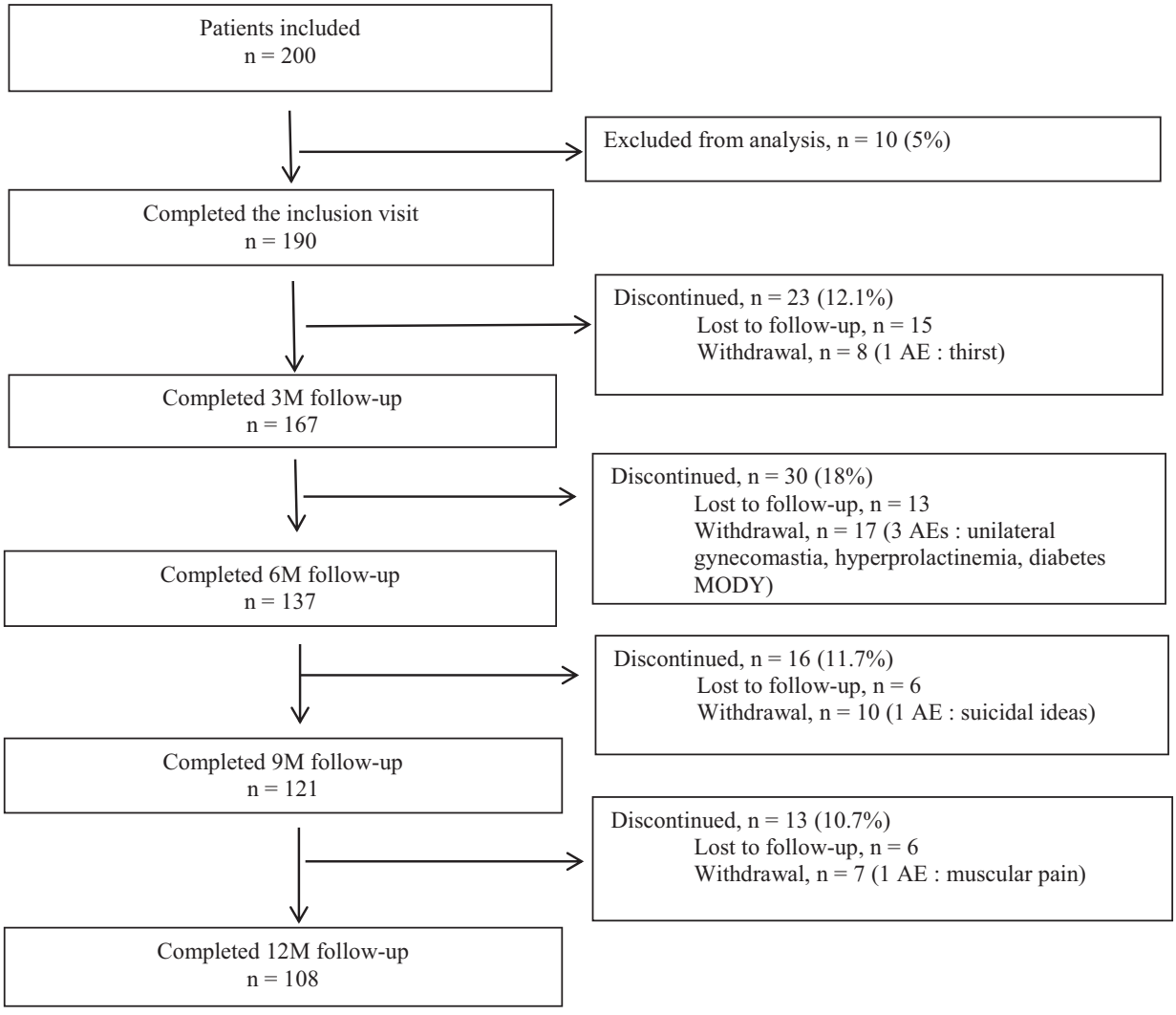


Fig. 1 Study flow diagram.
AE(s) = adverse event(s); 3M = 3 months, 6M = 6 months, 9M = 9 months, 12M = 12 months follow-up.

one drug. In patients receiving more than one drug, the most frequently associated prescriptions were of an anxiolytic (35%), another AP (26%), or an antidepressant (12%) drug. According to Table 1, 20.5% of AP prescriptions were for approved indications (21.9% for risperidone and 24.2% for aripiprazole). Among the 108 (56.8%) patients completing follow-up, most patients ($n = 73$, 67.7%) completed follow-up under the initial AP treatment.

3.2. Incidence of AEs potentially attributable to AP medication

During the 12-months follow-up, 2038 AEs potentially attributable to AP drug have been identified (Table 3). The most frequent AEs were neuromotor (15.4%), gastroenterological (14.8%), metabolic (12.2%), general (11.8%), hormonal (10.4%) and psychiatric (10.1%). The overall incidence rate was 11.52 AEs per person-year (IC 95% [9.83; 13.20]). Sex and age have not been found as risk factors in our sample.

Weight, BMI and z-BMI increased significantly respectively by 5.9 (±5.04), 1.54 (±1.84) and 0.53 (±0.69) in patients completing follow-up (Table 4).

AE severity followed a decreasing Poisson distribution with 1352 (66%) judged mild, 592 (29%) moderate, 88 (6.6%) severe and four (0.2%) extreme. Forty-six (24.2%) patients experienced at least one severe severity AE, which were classified as metabolic ($n = 22$), eating ($n = 19$), psychiatric ($n = 18$), neuromuscular ($n = 12$), and hormonal ($n = 4$). Three patients (1.6%) presented extreme severity AEs: assault of a caregiver with a knife ($n = 1$), hyperprolactinemia ($n = 1$), suicidal ideation ($n = 1$) and suicidal behavior ($n = 1$). The incidence rate of severe and extreme severity AEs was 0.44 [0.31; 0.57]. 25 serious adverse effects involving 16 patients have been reported to health authorities.

3.3. The onset and presence of AEs

In the 108 patients completing follow-up, more than half of AEs ($n = 718$, 52.7%) appeared during the first three months

Table 2 Distribution of AP treatments over follow-up.

	Inclusion		3M		6M		9M		12M	
	n = 190		*n* = 167		*n* = 137		*n* = 121		*n* = 108	
AP and co-medications	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Risperidone	107	***56.3***	116	***69.5***	67	***48.9***	54	***44.6***	47	***43.5***
Monotherapy[a]	85	*44.7*	91	*54.5*	62	*45.2*	50	*41.3*	44	*40.7*
Psychotropic polytherapy[a]	20	*10.5*	25	*15*	5	*3.6*	4	*3.3*	3	*2.8*
Association with non-psychotropic	24	*12.6*	52	*31.1*	8	*5.8*	6	*5*	4	*3.7*
Aripiprazole	82	***43.1***	69	***41.3***	82	***59.8***	35	***28.9***	34	***31.5***
Monotherapy[a]	60	*31.6*	55	*32.9*	39	*28.5*	30	*24.8*	28	*25.9*
Psychotropic polytherapy[a]	22	*11.6*	14	*8.4*	9	*6.6*	6	*4.9*	6	*4.9*
Association with non-psychotropic	22	*11.6*	36	*21.5*	2	*1.4*	2	*1.6*	2	*1.8*
Cyamemazine	20	*10.5*	3	*1.8*	3	*2.2*	3	*2.5*	3	*2.8*
Monotherapy[a]	17	*8.9*	3	*1.8*	2	*1.4*	2	*1.6*	2	*1.8*
Olanzapine	10	*5.3*	7	*4.2*	3	*2.2*	3	*2.5*	2	*1.8*
Monotherapy[a]	8	*4.2*	6	*3.6*	3	*2.2*	3	*2.5*	2	*1.8*
Loxapine	6	*3.1*	4	*2.4*	.	.	.	.	.	.
Monotherapy[a]	2	*1*	3	*1.8*	.	.	.	.	.	.
Quetiapine	2	*1*	13	*7.8*	6	*4.4*	6	*4.9*	4	*3.7*
Monotherapy[a]	1	.	9	*5.4*	4	*2.9*	5	*4.1*	3	*2.8*
Haloperidol	.	.	.	.	.	.	1	*0.8*	1	*0.8*
No AP medication	0	*0*	18	*10.7*	13	*9.5*	20	*16.5*	20	*18.5*

AP = antipsychotic.
[a] Possible association with non-psychotropic medication; 3M = 3 months, 6M = 6 months, 9M = 9 months, 12M = 12 months follow-up.

of AP-treatment (Fig. 2(A)). They concerned general symptoms ($n = 95$, 61.3%), eating disorders ($n = 75$, 58.6%), hormonal ($n = 88$, 57.1%), gastroenterological ($n = 101$, 55.2%), or metabolic ($n = 95$, 53.4%) AEs (see Table S1, available online). Nevertheless, new AEs continued to arise throughout the entire follow-up period (Fig. 2(A)). AEs were persistent in all clinical categories (see Table S2, available online). At 12M follow-up (Fig. 2(B)), 70.4% of patients had experienced at least one metabolic AE, 65.7% a hormonal abnormality, 50% eating disorders, 41% a gastroenterological AE, 33.3% a psychiatric AE, and 28.7% had experienced some disorder of sleep.

3.4. Clinical improvement and social functioning

At baseline, the mean score of 4.78±0.97 on the CGI-S scale, on which a score of 4 represents "moderate illness" and 5 "marked illness", was consistent with the burden of severe mental illness in the study population. This was also reflected in the measurement of social functioning with a mean CGAS score of 47±10.7 (score of 50–41 represents a "moderate degree of interference" and 40–31 a "major impairment in social functioning". Significant improvements in the CGI-S scores (from 4.78±0.97 to 3.88±1.22; $p < 0.0001$) as well as in the CGAS scores (from 47±10.7 to 57.3 ± 15.8; $p < 0.0001$) were observed between baseline and 12M, suggesting clinical efficacy of treatment.

4. Discussion

ETAPE study is the first prospective study of AP-related AEs in a large, AP-naïve pediatric population in France. The naturalistic design included a population with access to publicly-funded care.

Twelve-month studies evaluating AP drug safety in pediatric populations are unusual (Baeza et al., 2017; Ronsley et al., 2015). Others studies concern 6-months (Arango et al., 2014) or shorter follow-up (Raffin et al., 2018). Assuring follow-up in mental health research is a recognized difficulty, and significant rates of loss to follow-up are the norm. Although 43.2% of the initial ETAPE study patient population were lost to follow-up by twelve months, this compares favorably with other studies (72–83%) (Baeza et al., 2017; Ronsley et al., 2015). Raffin et al. had lost 29% of their study population to follow-up by three months (Raffin et al., 2018) and Arango et al. had lost 36% at six months (Arango et al., 2014). Telephone reminders during ETAPE study might explain this difference.

The main result of ETAPE study is the disturbing high incidence ratio of potentially AP-related AE (11.52 AEs per person-years). Even if most AE had mild to moderate severity, about one quarter of patients exposed to an AP drug experienced a severe or extreme severity AE. Nonetheless, the impact of additional factors has to be considered, such as concomitant medication, psychiatric diagnosis and subjective clinician judgment.

Among the diverse potentially AP-related AEs, some have been confirmed in the literature before (e.g. metabolic, hormonal, neuromotor) and others are less documented (e.g. hepatic, hematologic) (Cohen et al., 2012). Psychiatric AEs such as aggressiveness or suicidal attempts are poorly described in the pediatric population treated by AP (Kimura et al., 2015). They may be associated to mental illness, but relation with AP-treatment cannot be ruled out, warranting additional research in this field.

The extended duration of ETAPE study provides additional evidence of the persistence of AEs. In particular, metabolic

Table 3 Potentially attributable AEs to antipsychotic drug.

Total AEs *n* (%)	2038	(100)
Incidence rate per person-years *n* (CI)	11.5	[9.8;13.2]
AEs with functional impact *n* (%)	348	(17.2)
Neuromotor *n* (%)	315	(15.4)[c]
Headache[a]	65	(20.6)
Muscular weakness[a]	56	(17.8)
Akathisia	28	(8.9)
Tremor	25	(7.9)
Muscle cramps	25	(7.9)
Creatine kinase elevation[a] (>150 UI/L)	24	(7.6)
Dyskinesia[a]	22	(7)
Extrapyramidal signs[a]	17	(5.4)
Other (e.g. muscle pain, tic, hypertonia, dystonia)[a]	53	(16.8)
Gastroenterological *n* (%)	302	(14.8)[c]
Dry mouth[a]	81	(26.8)
Abdominal pain	52	(17.2)
Nausea, vomiting	50	(16.5)
Thirst	47	(15.6)
Transit disorders	36	(11.9)
Abnormal liver function (ASAT>30 UI/L; ALAT>35 UI/L)	21	(6.9)
Other (e.g. hypersialorrhea, gastroesophageal reflux)	15	(4.9)
Metabolic *n* (%)	248	(12.2)[c]
Weight gain (+1 standard deviation over 3 months follow-up)[a]	110	(44.3)
Lipid disorders[a] (total cholesterol >1,7 g/l; triglyceride ≥ 1 g/l)	90	(36.3)
Excess abdominal fat (waist circumference/waist ratio > 0.5)[a,b]	20	(8)
Glycemic disorders[a] (≥1 g/l)	18	(7.2)
Other (e.g. weight loss)	10	(4)
General symptoms *n* (%)	241	(11.8)[c]
Asthenia[a]	152	(63.1)
Dizziness	58	(24.1)
Chest pain[a]	17	(7)
Malaise, syncope	14	(5.8)
Hormonal *n* (%)	213	(10.4)[c]
Hyperprolactinemia (> 25 ng/ml)[a,b]	82	(38.5)
Vitamin D deficiency (< 30 ng/mL)[a]	78	(36.6)
Hypoprolactinemia (< 2 ng/ml)[a]	18	(8.4)
Mammary disorder	15	(7)
Thyroid abnormality	12	(5.6)
Other (e.g. amenorrhea, dysmenorrhea, …)	8	(3.7)
Psychiatric *n* (%)	207	(10.1)[c]
Apathy, reduced affects, lack of interest[b]	31	(14.9)
Suicidal thoughts, suicide attempt[a,b]	26	(12.5)
Exalted mood	25	(12)
Attention deficit[a]	20	(9.7)
Sadness[a]	18	(8.7)
Aggressiveness, impulsiveness, anger[a,b]	18	(8.7)
Irritability, emotional lability[a]	17	(8.2)
Agitation	11	(5.3)
Other (e.g. anxiety, sexual disorder, hallucination, flight of ideas, psychiatry relapse …)[a,b]	41	(3.4)
Eating disorders *n* (%)	178	(8.7)[c]
Increased appetite, hyperphagia[a]	122	(67.4)
Loss of appetite[a]	27	(15.2)

(*continued on next page*)

Table 3 (*continued*)

Total AEs *n* (%)	2038	(100)
Binge eating, bulimia[a]	26	(12.3)
Other (e.g. cat food, food theft)	3	(0.6)
Sleep disorders *n* (%)	109	(5.3)[c]
Hypersomnia[a]	85	(18.3)
Insomnia	20	(78)
Other	4	(3.7)
Hematologic *n* (%)	69	(3.4)[c]
Epistaxis, hematomas	17	(24.6)
Neutropenia (< 15,000/mm³)	11	(15.9)
Other (e.g. abnormalities of the blood count)	41	(59.4)
Dermatologic *n* (%)	63	(3.1)[c]
Skin rash	30	(47.6)
Acne[a]	23	(36.5)
Itching	7	(11.1)
Other (e.g. alopecia)	3	(4.8)
Cardiologic *n* (%)	55	(2.7)[c]
Palpitations[a]	18	(32.7)
Tachycardia	12	(21.8)
Conduction disorder	7	(12.7)
Prolonged QT interval (QTc>440 ms)	6	(10.9)
Bradycardia	5	(9.1)
Rhythm disorder	3	(5.4)
Other (e.g. repolarization disorder, hypertension ...)	4	(7.3)
Other (e.g. accommodation disorder, CRP elevation, sensation of cold, dyspnea, hot flushes ...)	38	(1.7)[c]

AE(s) = adverse event(s).
[a]Severe and extreme severity AE.
[b]Serious AE.
[c]percentage of all AEs (gray area) and percentage by clinical dimension (white area).

Table 4 Evolution of weight, BMI, z-BMI.

A - Study population ($n = 190$)

Parameters	Baseline $n = 188$	3M $n = 157$	6M $n = 134$	9M $n = 109$	12M $n = 104$	*p* value
Weight (mean ± SD) (kg)	45.57 ± 16.33	48.19 ± 16.98	48.13 ± 17.40	49.02 ± 17.96	49.76 ± 18.12	*<0.001*[a]
BMI (mean ± SD) (kg/m²)	18.98 ± 4.04	19.95 ± 4.33	20.01 ± 4.26	20.38 ± 4.29	20.46 ± 4.42	*<0.001* [a]
z-BMI (mean ± SD)	−0.13 ± 1.26	0.27 ± 1.11	0.36 ± 1.05	0.47 ± 1.05	0.48 ± 1.11	*<0.001* [a]

B - Patients completing the study ($n = 108$)

Parameters	Baseline $n = 107$	3M $n = 102$	6M $n = 105$	9M $n = 98$	12M $n = 104$	*p* value
Weight (mean ± SD) (kg)	42.80 ± 16.05	45.90 ± 16.99	47.80 ± 17.51	49.52 ± 18.20	49.76 ± 18.12	*<0.001*[a]
BMI (mean ± SD) (kg/m²)	18.65 ± 3.85	19.68 ± 4.11	20.15 ± 4.28	20.59 ± 4.37	20.46 ± 4.42	*<0.001*[a]
z-BMI (mean ± SD)	−0.13 ± 1.22	0.26 ± 1.10	0.40 ± 1.08	0.52 ± 1.02	0.48 ± 1.11	*<0.001*[a]

3M = 3 months, 6M = 6 months, 9M = 9 months, 12M = 12 months follow-up; *n* = number; BMI = body mass index; SD = standard deviation.
[a]Baseline < 3-month, $p < 0.001$; baseline < 6-month, $p < 0.001$; baseline < 9-month, $p < 0.001$; baseline < 12-month, $p < 0.001$.

AEs during the first year of prescribing are of major concern in young patients. Like Baeza et al. (2017), we observed a significant increase in BMI. The consequences of these AEs in the longer term are poorly known (Ronsley et al., 2015). Like Raffin et al. (2018), we observed high rates of hyperprolactinemia, which may have long term impacts on osteoporosis, particularly in girls. Carbon et al. (2015) showed that neuromotor AEs were present after 12 weeks AP treatment; also persisting at 12M follow-up in ETAPE study. In addition, we found many gastroenterological, cardiac, psychiatric or sleep AEs in young patients treated with AP drugs which are less well documented in the literature.

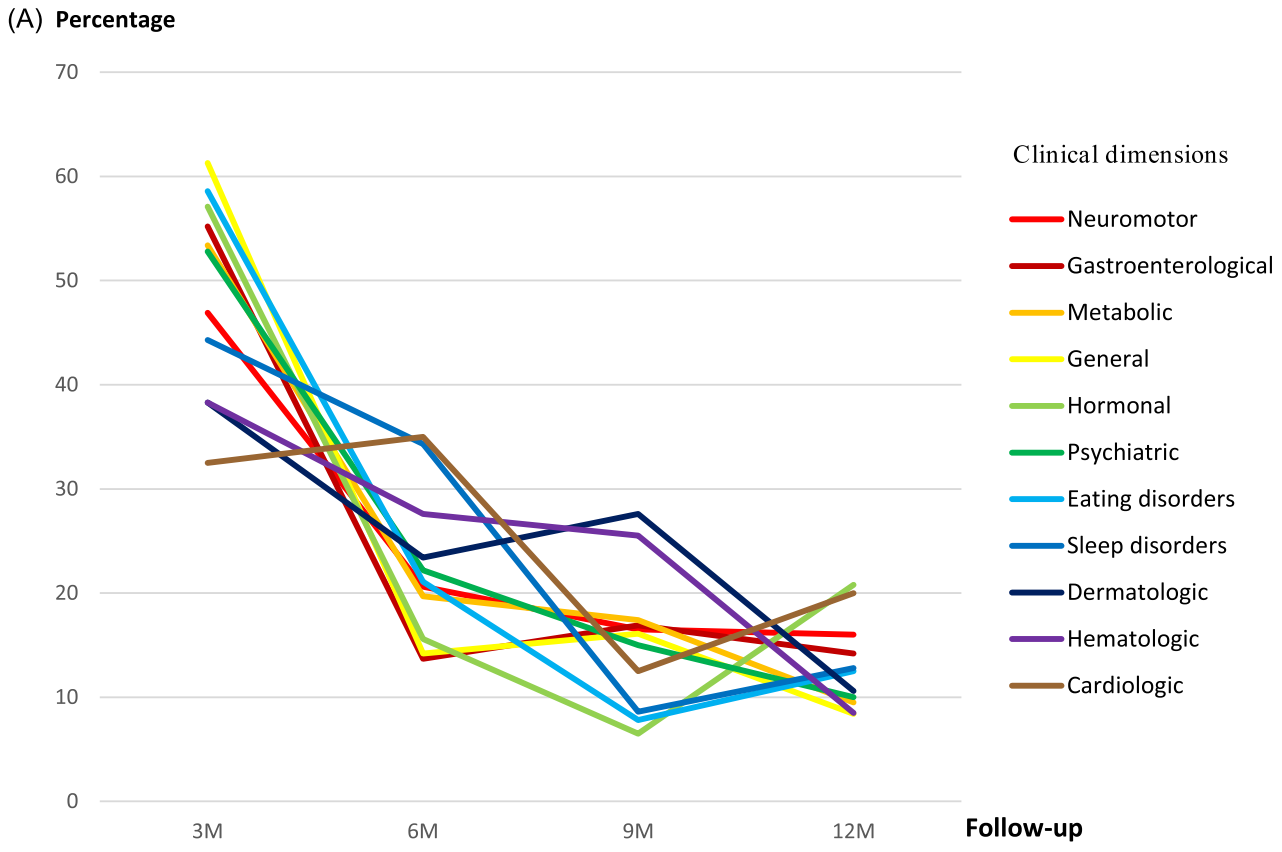


Fig. 2 Onset and presence of AEs in patients completing 12-months follow-up ($n = 108$).
(A) Onset of AEs in patients completing the study.
(B) Presence of AEs in patients completing the study.
3M = 3 months, 6M = 6 months, 9M = 9 months, 12M = 12 months follow-up.

AP drugs are commonly prescribed in the pediatric population. In another French community-based study in persons aged 0–25 years, though two thirds of patients prescribed AP drugs were aged 16 years and over, 14% concerned children less than 10 years of age (Verdoux et al., 2015). Our finding that boys are more exposed to AP drugs is consistent with other studies (Baeza et al., 2017; Olfson et al., 2015; Ronsley et al., 2015; Verdoux et al., 2015).

A meta-analysis of data from 16 countries (Asia, Europe, Oceania, and America) showed that risperidone was the most frequently used AP drug in children and adolescents, followed by quetiapine and aripiprazole (Halfdanarson et al., 2017); consistent with the ETAPE study population, in which more than 56% of patients have been treated by risperidone and 43.1% by aripiprazole at inclusion.

Prescribing of more than one psychotropic drug in the ETAPE study, was also similar to other published studies, with anxiolytics most commonly prescribed, followed by antidepressants, mood stabilizers and stimulants (Acquaviva et al., 2012; Olfson et al., 2015; Verdoux et al., 2015).

We found high rates of off-label prescribing with only 20% of prescriptions in the ETAPE study for approved indications in France. Off-label SGA prescribing has been rising dramatically in the pediatric population (Acquaviva et al., 2012) for several indications including psychotic as well as non-psychotic mental disorders, such as hyperkinetic, anxiety or mood disorders, impulsive or aggressive behaviors associated with ADHD, disruptive behavior disorders, and ASD (Edelsohn et al., 2017; Harrison et al., 2012; Olfson et al., 2015). The heterogeneity of diagnoses identified in ETAPE study is typical of clinical practice. In addition, anxiety disorders, presented by 61% of the ETAPE study population, are common and frequently comorbid with other mental disorders (e.g. depressive disorders) (Essau et al., 2018). However, off-label use of AP is often supported by evidence from controlled studies of effectiveness (Vitiello et al., 2009).

Among the limitations, one is the lack of a control group that prevents cause-effect relationship to be drawn with certainty. In addition, the naturalistic design of ETAPE study without definition of clinical profiles and indications of AP prescriptions might bias study results. Moreover, a minor part of included participants had received short-term AP treatment in the past. The inclusion period of 28 days following the first administration of AP might also bias analysis. Another limitation is the treatment of most patients with risperidone or aripiprazole. Thus, conclusions are mainly driven by the use of these two medications and generalization of observed AEs is limited.

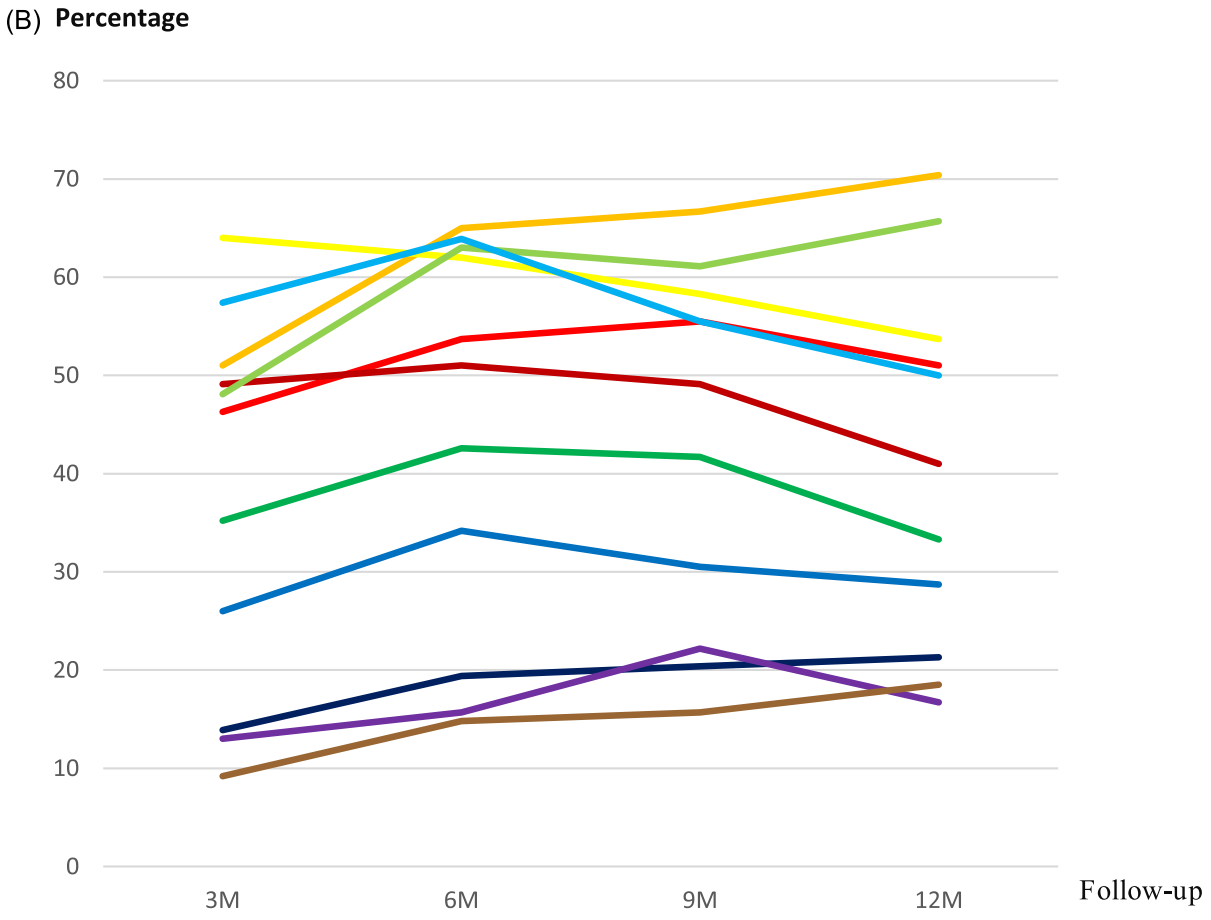


Fig. 2 Continued

5. Conclusion

In France, as in the rest of the world, SGA are frequently prescribed in children and adolescents for both psychotic and non-psychotic disorders (Edelsohn et al., 2017; Olfson et al., 2015), of which many are off-label prescriptions (Acquaviva et al., 2012). The ETAPE study found a high incidence of AEs throughout the 12M follow-up, concerning onset as well as a persistence of AEs. Thus, prescribers should continuously monitor AEs during AP prescribing.

Further studies are needed in order to evaluate medium and long-term consequences of AP drugs in children both in term of efficacy and AE, to delineate proper recommendations to clinicians regarding care strategy. In the current stage of knowledge, cautiousness is required.

ETAPE Study Group

Michel Boublil, MD (CAMPS de Grasse, Grasse, France); Jean Chambry, MD (Fondation Vallée, Gentilly, France); Dorothée Charvet, MD (Unité de Soins pour Adolescents Ulysse, Saint Jean de Dieu Hospital, Lyon, France); Mona Cseterky, MD (Princess Grace Hospital Centre, Monaco); Eric Fontas, MD (Department of Clinical Research and Innovation, Nice University Hospital, Nice, France); Pierre Fourneret, MD, PhD (Hôpital Femme Mère Enfant, Fondation Hospices Civils de Lyon, Lyon, France); Ludovic Gicquel, MD, PhD (Henri Laborit Hospital, Poitiers, France); Bernard Kabuth, MD, PhD (Department of Child and Adolescent Psychiatry, Brabois Vandoeuvre-les-Nancy Hospital, France); Bernard Leroy, MD (Pôle Parents-Femme-Enfant, Cannes Hospital, France); Fanny Maria (University Department of Child and Adolescent Psychiatry, Children's Hospitals of Nice CHU-Lenval, Nice, France); Pamela Moceri, MD (Children's Hospitals of Nice CHU-Lenval, Nice, France); Bertrand Olliac, PhD-MD (Department of Child and Adolescent Psychiatry, Esquirol Hospital, Limoges, France); Nadège Parassol-Girard (University Department of Child and Adolescent Psychiatry, Children's Hospitals of Nice CHU-Lenval, NICE, France); Brigitte Ravis (CIC 1407 Inserm - Hospices Civils de Lyon, Lyon, Franc); Jean-Philippe Raynaud, MD, PhD (University Department of Child and Adolescent Psychiatry, Toulouse University Hospital, Toulouse, France); Jean-François Roche, MD (Department of Child and Adolescent Psychiatry, Esquirol Hospital, Limoges, France); Thierry Rochet, MD (Hospital Center Le Vinatier, Bron, France).

Role of the funding source

The French National Agency for Medicines and Health Products Safety

Contributions

Drs Menard was the principal investigator, contributed to the conceptualization of ETAPE study and the design of this protocol and has been involved in drafting the first version of the manuscript.

Prof Bonnot, Prof Cohen contributed to the conceptualization of ETAPE study and the design of this protocol.

Prof Askenazy contributed to the conceptualization of ETAPE study and the design of this protocol and has been involved in drafting the first version of the manuscript.

Drs Thümmler has been involved in drafting the first version of the manuscript.

Drs Giannitelli has been involved in drafting the first version of the manuscript.

Miss Cruzel did all the statistical analyzes.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflict of interest

In the last five years, DC has consulted for or received honoraria from Otsuka, Shire, Lundbeck and IntegraGen. OB has consulted for or received honoraria from Otsuka, Shire, Orphan Europe and Actelion. The other authors have no conflicts of interest to report.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2019.10.006.

References

Acquaviva, E., Peyre, H., Falissard, B., 2012. Panorama de la prescription et de la consommation des psychotropes chez l'enfant et l'adolescent en France. Neuropsychiatr. Enf. Adolesc. 60, 77–85.

Arango, C., Giraldez, M., Merchan-Naranjo, J., et al., 2014. Second-generation antipsychotic use in children and adolescents: a six-month prospective cohort study in drug-naïve patients. J. Am. Acad. Child Adolesc. Psychiatry 53, 1179–1190.

Baeza, I., Vigo, L., de la Serna, E., et al., 2017. The effects of antipsychotics on weight gain, weight-related hormones and homocysteine in children and adolescents: a 1-years follow-up study. Eur. Child Adolesc. Psychiatry 26, 35–46.

Barnes, T., 1989. A rating scale for drug induced akathisia. Br. J. Psychiatry 154, 672–676.

Ben Amor, L., 2012. Antipsychotics in pediatric and adolescent patients: a review of comparative safety data. Affect. Disord. 138, S22–S30.

Bush, G., Fink, M., Petrides, G., et al., 1996. Catatonia I. Rating scale and standardized examination. Acta Psychiatr. Scand. 93, 129–136.

Caccia, S., 2013. Safety and pharmacokinetics of atypical antipsychotics in children and adolescents. Paediatr. Drugs 15 (3), 217–233.

Carbon, M., Kapoor, S., Sheridan, E., et al., 2015. Neuromotor adverse effects in 342 youth during 12 weeks of naturalistic treatment with 5 s-generation antipsychotics. J. Am. Acad. Child Adolesc. Psychiatry 54 (9), 718–727.

Cohen, D., Bonnot, O., Bodeau, N., et al., 2012. Adverse effects of second-generation antipsychotics in children and adolescents: a Bayesian meta-analysis. J. Clin. Psychopharmacol. 32, 309–316.

Correll, C.U., Manu, P., Olanshanskiy, V., et al., 2009. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. JAMA 302 (16), 1765–1773.

Edelsohn, G.A., Karpov, I., Parthasarathy, M., et al., 2017. Trends in antipsychotic prescribing in medicaid-eligible youth. J. Am. Acad. Child Adolesc. Psychiatry 56 (1), 59–66.

Endicott, J., Spitzer, R.L., Fleiss, J.L., 1976. The global assessment scale: a procedure for measuring overall severity of psychiatric disturbance. Arch. Gen. Psychiatry 33, 766–771.

Essau, C.A., Lewinsohn, P.M., Lim, J.X., et al., 2018. Incidence, recurrence and comorbidity of anxiety disorders in four major developmental stages. J. Affect. Disord. 228, 248–253 1.

Guy, W., 1976a. ECDEU. Assessment Manuel for Psychopharmacology: Revised (DHEW Publication Number ADM 76-338). US Department of Health, Education and Welfare, Public Health Service, Rockville, MD Alcohol, Drug Abuse and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs, 534-537.

Guy, W., 1976b. Clinical global impressions. In: Guy, W (Ed.), ECDEU. Assessment Manuel for Psychopharmacology. National Institute of Mental Health, Rockville, MD, pp. 217–222 Revised ed.

Halfdanarson, O., Zoëga, H., Aagaard, L., et al., 2017. International trends in antipsychotic use: a study in 16 countries, 2005–2014. Eur. Neuropsychopharmacol. 27, 1064–1076.

Harrison, J.N., Cluxton-Keller, F., Gross, D., 2012. Antipsychotic medication prescribing trends in children and adolescents. J. Pediatr. Health Care 26, 139–145.

Ho, J., Panagiotopoulos, C., McCrindle, B., et al., 2011. Management recommendations for metabolic complications associated with second generation antipsychotic use in children and youth. J. Can. Acad. Child Adolesc. Psychiatry 20, 3.

Kalverdijk, L.J., Bachmann, C.J., Aagaard, L., et al., 2017. A multi-national comparison of antipsychotic drug use in children and adolescents, 2005–2012. Child Adolesc. Psychiatry Ment. Health 11, 55.

Kaufman, J., et al., 1997. Schedule for affective disorders and schizophrenia for school-age children-resent and lifetime version (K-SADS-PL): initial reliability and validity data. J. Am. Acad. Child Adolesc. Psychiatry 36 (7), 980–988.

Keinänen, J., Mantere, O., Kieseppä, T., et al., 2015. Early insulin resistance predicts weight gain and waist circumference increase in first-episode psychosis – a one year follow-up study. Schizophr. Res. 169 (1–3), 458–463.

Kendall, T., Hollis, C., Stafford, M., et al., 2013. Recognition and management of psychosis and schizophrenia in children and young people: summary of NICE guidance. BMJ 346, f150.

Kimura, G., Kadoyama, K., Brown, J.B., et al., 2015. Antipsychotics-associated serious adverse events in children: an analysis of the FAERS database. Int. J. Med. Sci. 12 (2), 135–140, 5.

McKinney, C., Renk, K., 2011. Atypical antipsychotic medications in the management of disruptive behaviors in children: safety guidelines and recommendations. Clin. Psychol. Rev. 31, 465–471.

March, J., Karayal, O., Chrisman, A., 2007. CAPTN: the pediatric adverse event rating scale. In: Novins, D.K., DeYoung (Eds.). The Scientific Proceedings of the 2007 Annual Meeting of the American Academy of Child and Adolescent Psychiatry. Boston, Edited by. p. 241, 23-28 October 2007.

Menard, M.L., Thümmler, S., Auby, P., et al., 2014. Preliminary and ongoing French multicenter prospective naturalistic study of adverse events of antipsychotic treatment in naive children and adolescents. Child Adolesc. Psychiatry Ment. Health 8, 18.

Menard, M.L., Thümmler, S., Giannitelli, M., et al., 2016. Incidence of adverse events in naïve children and adolescents treated with antipsychotic drugs: a French multicenter naturalistic study protocol (ETAPE). BMJ Open 6, e011020.

Morrato, E., Nicol, G.E., Maahs, D., et al., 2010. Metabolic screening in children receiving antipsychotic drug treatment. Arch. Pediatr. Adolesc. Med. 164, 344–351.

Olfson, M., King, M., Schoenbaum, M., 2015. Treatment of young people with antipsychotic medications in the United States. JAMA Psychiatry 72, 867–874.

Pagsberg, A.K., Katrine, A., Jeppesen, P., et al., 2017. Quetiapine extended release versus aripiprazole in children and adolescents with first-episode psychosis: the multicentre, double-blind, randomised tolerability and efficacy of antipsychotics (TEA) trial. Lancet Psychiatry 4 (8), 605–618.

Persico, A.M., Arango, C., Buitelaar, J.K., et al., 2015. Unmet needs in paediatric psychopharmacology: present scenario and future perspectives. Eur. Neuropsychopharmacol. 25, 1513–1531.

Raffin, M., Bonnot, O., Giannitelli, M., et al., 2018. Hormonal risk factors for osteoporosis: different profile among antipsychotics. J. Child Adolesc. Psychopharmacol. 13. doi:10.1089/cap.2017.0158.

Raffin, M., Giannitelli, M., Consoli, A., et al., 2014. Management of adverse effects of second-generation antipsychotics in youth. Cur. Treat Opt. Psychiatry 1, 84–105.

Rasimas, J.J., Liebelt, E.L., 2012. Adverse effects and toxicity of the atypical antipsychotics: what is important for the pediatric emergency medicine practitioner. Clin. Pediatric Emerg. Med. 13 (4), 300–310.

Ray, W.A., Stein, C.M., Murray, K.T., et al., 2019. Association of antipsychotic treatment with risk of unexpected death among children and youths. JAMA Psychiatry 76 (2), 162–171.

Ronsley, R., Nguyen, D., Davidson, J., et al., 2015. Increased risk of obesity and metabolic dysregulation following 12 months of second-generation antipsychotic treatment in children: a prospective cohort study. Can. J. Psychiatry 60 (10), 441–450.

Santoch, P.J., Belle, L., Fiori, F., et al., 2017. Pediatric antipsychotic use and outcomes monitoring. J. Child Adolesc. Psychopharmacol. 27 (6), 546–554.

Sheehan, D.V., Sheehan, K.H., Shytle, R.D., et al., 2010. Reliability and validity of the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). J. Clin. Psychiatry 71 (3), 313–326.

Simpson, G.M., Angus, J.W.S., 1970. A rating scale for extra-pyramidal side effects. Acta Psychiatr. Scand. 212, 11–19.

Verdoux, H., Pambrun, E., Cortaredona, S., et al., 2015. Antipsychotic prescribing in youths: a French community-based study from 2006 to 2013. Eur. Child Adolesc. Psychiatry 24, 1181–1191.

Vitiello, B., Correll, C., van Zwieten-Boot, B., et al., 2009. Antipsychotics in children and adolescents: increasing use, evidence for efficacy and safety concerns. Eur. Neuropsychopharmacol. 19, 629–635.