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Reviews

Aripiprazole in Children and Adolescents

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Abstract

Objective: To review the use of aripiprazole in children and adolescents.
Methods: Medline and Embase databases were systematically searched using the keywords *aripiprazole* and *child* or *adolescent* over the period from 2000 to 2019. The initial screen yielded 163 publications, from which 99 studies were reviewed.
Results: Aripiprazole is one of the most widely prescribed atypical antipsychotics. Like others, its use in children and adolescents is becoming commonplace and occurs in off-label indications. Aripiprazole has proven efficacy for several indications in children and adolescents, including schizophrenia, bipolar disorder, Tourette's syndrome, and behavioral impairments associated with autism and intellectual disability. Adverse effects are more important in children and adolescents than adults, particularly weight gain, drowsiness, extrapyramidal effects, and metabolic effects, even though the latter may appear less important than with other atypical antipsychotics. Severe adverse effects often occur in multiple-prescription settings. At present, postprescription monitoring is very poor.
Conclusion: Aripiprazole has proven efficacy for several indications in children and adolescents. However, its use requires clinical and paraclinical monitoring to assess the occurrence of adverse events that may challenge the benefit/risk ratio. In addition, off-label prescriptions should be limited, as they appear to account for a significant proportion of aripiprazole use worldwide.

Keywords: aripiprazole, child, adolescence

Introduction

General context: antipsychotics in children and adolescents

Available evidence shows that psychiatric consultations for children resulting in prescription of an antipsychotic notably increased about eightfold between 1993 and 2009 in the United States. By 2009, use of atypical antipsychotics became a trend of concern worrying U.S. control authorities since psychiatrists prescribing an antipsychotic do so much more often in children (68%) and adolescents (71%) than in adults (50%) (Olfson et al. 2012a). This increase in the prescription of antipsychotics is also found among very young children (2–5 years). Between 2000 and 2007, a study found that the prevalence of prescriptions in minors rose from 0.78% to 1.58% in extremely varied indications, such as autism spectrum disorders or intellectual disability (28%), attention-deficit/hyperactivity disorder (ADHD; 24%), and disruptive disorders (13%) (Olfson et al. 2010). In that study, more than half of the children had not been assessed by a psychiatrist.

It appears that in the United States, the prevalence of antipsychotic prescriptions is high and often does not comply with Food and Drug Administration (FDA) recommendations. Several estimates calculated from health insurance databases have yielded high figures: 4.2% of prescriptions among children 6–17 years of age (Crystal et al. 2009) and 2.7% of prescriptions among children in the care of Child Welfare (Dosreis et al. 2011). A study by Matone et al. (2012) distinguished age groups between 3 and 18 years and found prevalences of 0.4% between 3 and 5 years, 2.1% between 6 and 11 years, and 3.7% between 12 and 18 years. Finally, a study by Olfson et al. (2012a) on changes between 1993 and 2009 showed that in 2009, the prevalence of antipsychotic prescriptions was 1.83% in children and 3.76% in adolescents compared to 6.18% in adults. The reasons for this prescription boom are summarized elsewhere (Harrison et al. 2012). The main factors identified include a trend toward greater acceptance of psychotropic drug prescriptions in children, better knowledge of these drugs combined with an awareness of the disorders and frequency of psychological suffering in children, limited access to nonpharmacological

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treatments, a more pressing demand for rapid and inexpensive treatment, and a very wide disparity in time available and reimbursement rates for treatment of behavioral problems (this is particularly true in vulnerable populations in which treatment options are extremely limited in terms of supply and access to care).

Data regarding non-U.S. countries are sparse. While the prevalence of antipsychotic prescriptions for children and adolescents remained low from 2004 to 2008 (<4/10,000 per year), there has been a slight increase in recent years (Clavenna et al., 2011). This trend was found in Germany, with an increase of antipsychotic prescriptions from 2.3/10,000 in 2005 to 3.2/10,000 in 2012 (Bachmann et al. 2014). The most recent large comparative study by Hálfdánarson comparing up to 16 countries showed that the increase in prescription of atypical antipsychotic drugs still continues and varies for adolescents from country to country, with Lithuania prescribing the least and Taiwan and the United States prescribing the most (Hálfdánarson et al. 2017).

The case of aripiprazole

Aripiprazole is an atypical second-generation antipsychotic drug, which is a partial agonist of dopamine D2 receptors and serotonin 5-HT1A receptors and a partial antagonist of serotonin 5-HT2A receptors. It is metabolized primarily in the liver by CYP2-D6 and CYP3-A4 enzymes. Its elimination half-life is 75 hours for rapid metabolizers and 150 hours for slow metabolizers. However, it should be noted that these data were obtained primarily in adults. While it has been prescribed in adults since the early 2000s, studies in children and adolescents and their use are more recent. Worldwide marketing authorizations available for aripiprazole in children and adolescents are summarized in Table 1; the year of first marketing authorization is usually for only one indication.

The literature review presented in this study has endeavored to report as broadly as possible on the use of aripiprazole based on publicly available data. In terms of presentation, epidemiological studies in general or specific populations, short- and medium-term efficacy studies, and studies reporting side effects, whether in the context of efficacy or naturalistic studies, were distinguished. However, data exploited from pharmacovigilance resources and isolated case reports may enable us to identify recent trends, if any, as well as rare side effects that are sometimes only identified after prolonged use. As shown in Table 1, there is a fairly wide disparity in the years of first authorization of aripiprazole in children and adolescents since it occurred as early as 2007 in the United States, whereas for European countries and Canada, the first authorization occurred 5 years later (2012).

Methods

Medline and Embase databases were systematically searched with the keywords *aripiprazole* and *child* or *adolescent* from 2000 to 2019 (end of search, April 9, 2019). Titles and abstracts of selected articles were searched to ensure they were relevant to the use of aripiprazole in children and adolescents. Three subthemes were distinguished in this review: epidemiological data regarding aripiprazole, efficacy studies, and tolerance. For the latter two subthemes, a summary table was produced of the different studies selected and a corresponding flow chart was presented with the reasons each article was kept in the subtheme (list of excluded studies provided in the Supplementary Data).

Results

The results are presented distinguishing U.S. from non-U.S. epidemiological data (when available) to avoid extrapolations or shortcuts to national reality based on data that would only represent the United States. Indeed, the prescription of psychotropic drugs also depends on cultural and sociological aspects as well as access to care. Thereafter, the results detail efficacy and tolerance studies.

U.S. epidemiological data on aripiprazole

Several studies starting in 2010 have examined how prescribing physicians monitor children exposed to atypical or second-generation antipsychotic drugs, including aripiprazole. These studies also sought to distinguish which atypical antipsychotic was prescribed. They made it possible to assess the relative frequency of prescription of one drug compared to others within the same class, although rarely an estimate of prevalence (Raebel et al. 2014; Chen et al. 2018; Coughlin et al. 2018). In a large U.S. study on the monitoring of diabetic risk in 16,000 children and adolescents from 10 North American sites receiving an atypical antipsychotic, 31% were receiving aripiprazole (the first prescription being risperidone, 43%), leading to the conclusion that monitoring was very poor since only 11% of the children and adolescents had their glucose or hemoglobin A1C monitored (Raebel et al. 2014). Several U.S. states faced with a worrying increase in the prescription of atypical antipsychotic drugs in toddlers have decided to implement monitoring by prior agreement with an expert before prescription reimbursement. This control led to a moderate drop in prescriptions (by a factor of 1.31–1.75) after its implementation in the four states it was applied (Zito et al. 2018).

For aripiprazole, the most accurate data are from the FDA's pediatric focus safety review (Nevo et al. 2017). The number of patients receiving aripiprazole between June 2014 and November

Table 1. Aripiprazole in Children and Adolescents: Worldwide Agencies' Authorization (Until April 2019)

Country	*Year of first approval*	*SCZ*	*Bipolar disorder*	*Behavior impairments associated with autism or intellectual disability*	*Tourette's syndrome*
United States	2007	>13 Years	>10 Years	>6 Years	>6 Years
UE	2012		>13 Years		
Canada	2013	>15 Years	>13 Years		
France	2009 SCZ and 2016 BP	>15 Years	>13 Years		
Suisse	2018	>13 Years	>13 Years		
Indonesia	2018	Children	Children		
Philippines	2018				>6 Years

Modified from Perraudin et al. (2018).
BP, bipolar disorder; SCZ, schizophrenia.

Table 2. Nationally Estimated Number of Patients Who Received Prescriptions for Oral Aripiprazole from U.S. Outpatient Retail Pharmacies, Stratified by Patient Age, June 2014 Through November 2016

	Patients (N)	*Proportion (%)*
All ages	2,884,563	100
<17 Years	517,403	17.9
0–5 Years	9785	1.9
6–12 Years	209,527	40.5
13–17 Years	333,260	64.4
>18 Years	2,376,542	82.4
Age unknown	46,204	1.6

Summing across patient age bands is not advisable because this will result in overestimates of patient counts. Patient age subtotals do not sum exactly (>100%) due to patient aging during the study period. Patients may be counted more than once in the individual age categories.

Source: Nevo et al. (2017).

2016 in the United States is presented in Table 2 according to age; more than 500,000 minors received aripiprazole during that period. According to 10th revision of the International Classification of Diseases (ICD-10) diagnostic reports, the three most frequently reported indications were infantile autism, affect psychoses, and depressive disorder in 6- to 12-year olds and affect psychoses, manic-depressive illness, and infantile autism in 13- to 17-year olds. The same report summarized adverse events reported to the FDA adverse event reporting system from May 2011 to November 2016. The raw data show 1960 reports, including 891 serious and 37 fatal events in children younger than 17 years. After analysis, the FDA identified 78 cases (46 boys, 31 girls, and 1 case not specified) of serious/severe adverse events, including 14 deaths in children and adolescents. The children who died were exposed to aripiprazole dosages of 3–30 mg. Thirteen deaths occurred in children or adolescents 5–17 years of age, including five suicides, one overdose classified as unintentional, one malignant syndrome, one hyperthermia, one cardiorespiratory arrest, one metabolic disturbance, one malignant condition, and two unlabeled causes. The fourteenth death occurred in a premature infant who had transplacental exposure to aripiprazole prescribed to his mother. The death occurred at 6 days of age in the context of Fallot's tetralogy. No specific pattern of death was retained. The 64 severe nonlethal adverse events included 20 cases of clinical worsening with changes in dosage or formulation (including 16 cases of switching from the reference dosage form of Otsuka to a generic form), 15 cases of worsening (or lack of improvement) of pathology, 5 strokes, 3 gynecomastia, 3 with hallucinations, 2 with pancreatitis, 2 nonalcoholic liver steatoses, and 2 cases of false-positive amphetamine screening. Other severe adverse events ($n = 12$) were reported in isolation.

Epidemiological non-U.S. data on aripiprazole

Specific aripiprazole data outside France, Germany, and Canada were not found, although the available prevalence of aripiprazole in children and adolescents was extracted from Halfdarnarson et al. and compared with the most prescribed antipsychotic in this age group (risperidone and quetiapine) by country (Fig. 1). Figure 1 shows that U.S. prescriptions are higher compared to European and Asian countries, with some exceptions, such as Taiwan (where the first prescribed antipsychotic was prochlorperazine), New Zealand,

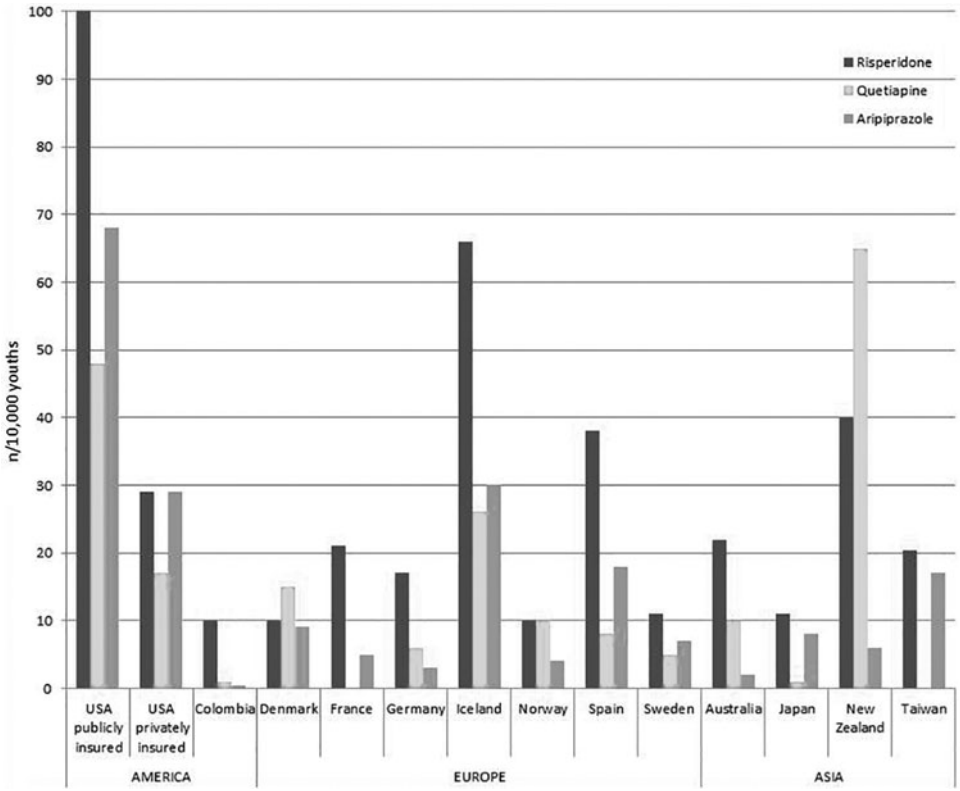

FIG. 1. 2014 Prevalence of aripiprazole, risperidone, and quetiapine in children and adolescents (≤19 years old) from 13 countries (data extracted from Hálfdánarson et al. 2017).

and Iceland. In most countries in 2014, aripiprazole prevalence was lower than 20/10,000.

In a Canadian general population study covering all of 2014, 7000 children receiving antipsychotic drugs were studied, including 4000 receiving risperidone, 2000 receiving quetiapine, and 1300 receiving aripiprazole (Chen et al. 2018). Again, indications were mostly off-label, such as ADHD, conduct disorder, and anxiety. The authors' observations were particularly worrying since the recommended monitoring of possible side effects was very limited and poorly carried out regardless of prescribed drug. Another study found the same results in terms of monitoring. In a longitudinal follow-up of 294 children and adolescents receiving an antipsychotic in a level 3 Canadian center, evaluation at 1 year showed very poor compliance with recommendations in terms of monitoring (Coughlin et al. 2018). In Germany, data from a statutory health insurance company from 2005 to 2012 yielded low rates of aripiprazole prescription. Of over 24,723 antipsychotic prescriptions for children and adolescents in 2012, only 4% related to aripiprazole (compared with 49.6% for risperidone) (Bachmann et al. 2014).

In France, two epidemiological studies explored changes in prescriptions over time. Based on health insurance data of a representative sample (at 1/97), Bénard-Laribière et al. (2019) found an increase in the use of antipsychotics in pediatric patients between 2007 and 2014 without an increase in off-label prescriptions (16% in period 1 vs. 11.1% in period 4). Nevertheless, the most frequently prescribed off-label drug was aripiprazole. This increase in antipsychotic drug use in pediatric patients was not found in adults over an almost identical period (2006–2013) (Montastruc et al. 2018). In the latter study, the increase in prescription of antipsychotics to minors was 39%. The prevalence data per drug were not described by age group, but for all ages. However, in the online supplements provided by Bénard-Laribière et al. (2019), drug-by-drug data found on off-label prescriptions in minors revealed aripiprazole was the drug most concerned, with an average off-label prescription prevalence varying from 15% to 29.4% .

Very little French data are available in a specific context (e.g., patients with autism). Nevertheless, the trends are identical. The prescription of psychotropic drugs outside legal authorization in pediatric hospitals appeared to be very frequent. In a 6-month study, including 1600 prescriptions for 472 patients, Winterfeld et al. (2009) found 68% of prescriptions were outside legal authorization, and 69% of these were for atypical antipsychotics, with risperidone being the most frequently prescribed. The most frequent off-label indications were anxiety, behavioral disorders, and pain. In addition, in a survey of parents of patients with autism ($n = 393$, mean age = 12 years), Cravero et al. (2017) reported that 52% received a psychotropic drug, of which 35% continued it. Atypical (23%) and typical antipsychotics (13%) were the most prescribed. The adverse effects reported by parents increased when atypical antipsychotics were prescribed, when there was polymedication, or when the prescription appeared to be off-label.

Finally, a study of French pharmacovigilance data between 1985 and 2017 found 247 reports of adverse reactions in children (2–12 years old) for atypical antipsychotics. A total of 210 patients received risperidone, 35 received aripiprazole, 1 received clozapine, and 1 received olanzapine. A total of 173 adverse reactions corresponded to off-label prescriptions, including all 35 cases reported for aripiprazole. Of the 173 off-label prescriptions, the study reported 90 nonserious and 83 severe adverse events, the majority of which were neurological (followed by endocrine and psychiatric). This study points out that the severity of adverse events inversely correlated with age (Poudroux et al. 2018). Unfortunately, few details were available as this study was only published as an abstract/poster in a congress.

Efficacy data

The flowchart corresponding to studies selected to explore and summarize efficacy data for aripiprazole is presented in Figure 2. Studies were separated according to their originality or meta-analytic nature.

Table 3 summarizes all of the efficacy studies found to include at least one arm with aripiprazole in children and adolescents. The studies were separated according to the quality of the methodology by distinguishing between randomized controlled studies by primary indication and other studies (open-label, randomized, and no control group). For each of these studies, Table 3 lists the authors and year, age and primary indication of the study, number of subjects included, dosage of aripiprazole received, nature of the control group when available, duration of the study, efficacy measures used, and main results with qualitative comments.

Four double-blind, randomized, controlled trials (RCTs) investigated aripiprazole in child and adolescent bipolar disorder and included 458 children and adolescents (Tramontina et al. 2009; Findling et al. 2012, 2013, 2017). Most studies found a significant improvement in the manic symptoms, leading to the authorizations listed in Table 1. For schizophrenia, there is only one major study involving 302 patients (Findling et al. 2008a). There, the improvement was significant and led to the approval of aripiprazole in this indication in some countries. Two RCTs that included 494 patients concerned Tourette's indication (Yoo et al. 2013; Sallee et al. 2017). Again, there was a significant improvement with aripiprazole, which has made it possible to obtain approval in some countries. Finally, four studies involving 493 patients were conducted on behavioral impairments associated with autism and/or intellectual disability (Marcus et al. 2009; Owen et al. 2009; Findling et al. 2014; Ichikawa et al. 2017). In most of the studies, aripiprazole was significantly superior to placebo, which led to its approval for this indication in some countries. The most recent RCT compared aripiprazole and risperidone for the indication of ADHD in children 3–6 years old (Razjouyan et al. 2018). While there was no significant difference between the two groups, both groups showed a substantial improvement in symptomatology at the end of the trial. No agency authorization is available to date for ADHD.

Finally, 14 studies that are less methodologically sound are also reported in Table 3: open-label studies with or without randomization (Findling et al. 2008b, 2009, 2011; Marcus et al. 2011a; Ercan et al. 2012; Ghanizadeh et al. 2014; Ghanizadeh 2016; Lamberti et al. 2016; Wang et al. 2016; Kim et al. 2018; Pan et al. 2018) and retrospective studies on files (Olfson et al. 2012b; Ercan et al. 2015; Akyol Ardic et al. 2017) in indications corresponding to FDA approval or off-label indications, such as ADHD, disruptive disorder, emotional regulation disorder, conduct disorder, and resistant obsessive-compulsive disorder. For most of these indications, a significant improvement is reported between the beginning and end of treatment, but the absence of a control group and, in particular, a placebo control group makes it very difficult to conclude that aripiprazole is useful for these nonauthorized indications.

Table 4 lists studies describing meta-analyses evaluating the efficacy of aripiprazole against placebo or possibly against another class of antipsychotic drugs, particularly risperidone. Surprisingly, only two indications were explored in the meta-analyses. First, behavioral impairments associated with autism and intellectual

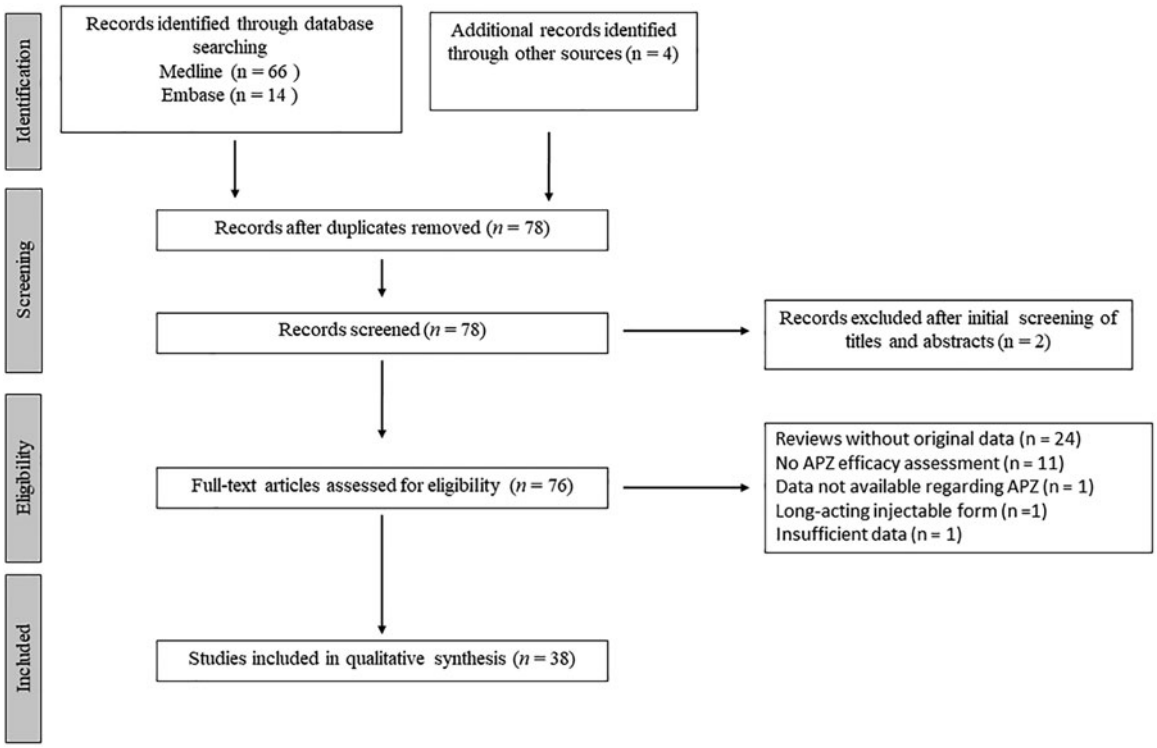

FIG. 2. Diagram of the study selection flowchart for evaluating aripiprazole efficacy.

disabilities were explored in eight different meta-analyses (Varni et al. 2012; Cohen et al. 2013; McQuire et al. 2015; Fung et al. 2016; Hirsch and Pringsheim 2016; van Schalkwyk et al. 2017; Maneeton et al. 2018; Fallah et al. 2019). These meta-analyses reported the superiority of aripiprazole over placebo, but no difference between aripiprazole and risperidone in improving behavioral problems associated with autism and intellectual disability was found. No meta-analysis reported efficacy for autistic symptoms. The second indication explored in meta-analyses concerns tics and Tourette's syndrome. This time, four meta-analyses compared aripiprazole with placebo and another atypical (risperidone) or typical (haloperidol and tiapride) antipsychotic drug or topiramate (Yang et al. 2015; Liu et al. 2016; Zheng et al. 2016; Wang et al. 2017). Aripiprazole was found to be superior to placebo in improving tics, but not superior to other antipsychotics.

Tolerance data

Figure 3 summarizes studies retained to assess aripiprazole tolerance in children and adolescents. These studies were classified according to their design, distinguishing between RCTs and open-label trials where the primary objective was to study the tolerance of aripiprazole in children and adolescents, meta-analyses, and case reports describing mainly rare side effects in children and adolescents. It was important to retain these case reports as rare side effects are usually identified in these postmarketing reports.

Table 5 summarizes tolerance studies, in RCT (Mankoski et al. 2013; Findling et al. 2014), open-label (Marcus et al. 2011b; Ho et al. 2012; Ichikawa et al. 2018), naturalistic (Germanò et al. 2014; Carbon et al. 2015; Al-Dhaher et al. 2016; Rafaniello et al. 2016; Pringsheim et al. 2017; Pozzi et al. 2019), or retrospective studies (Diomšina et al. 2015; Kimura et al. 2015; Rubin et al. 2015; Jakobsen et al. 2016; Yoon et al. 2016; Palanca-Maresca et al. 2017; Stassinos and Klein-Schwartz 2017). Table 5 does not include efficacy studies described in previous tables as the main objective in these studies was efficacy, especially as they generally describe tolerance, most often in the short term. These studies were in any case included in the meta-analyses.

All known side effects of other antipsychotic drugs are present in the studies listed in Table 5, particularly weight gain, which is more pronounced in children who have never been exposed to antipsychotic drugs and more common in younger subjects (Mankoski et al. 2013). Neurological and extrapyramidal effects as well as drowsiness are also quite common. A 16-month study by Findling et al. (2014) reported 25% weight gain, 15% drowsiness, 17% extrapyramidal effects, and a few cases of respiratory infections, constipation, and vomiting. However, in that long-term study, the authors did not describe any difference in metabolic parameter changes or an increase in prolactin, but rather a decrease in serum prolactin. Open or naturalistic studies of a certain duration clarify certain points: overall, the majority of side effects are mild or moderate in severity (Ichikawa et al. 2018).

For example, a 10-month study comparing patients on aripiprazole and risperidone showed that weight gain on aripiprazole may be slightly lower at the start of treatment, but higher afterward (Pringsheim et al. 2017), and discontinuation of therapy due to metabolic or extrapyramidal effects occurred in 17% and 10% of cases, respectively. A few studies have also investigated the effects on cardiac conduction and, in particular, some electrocardiogram (ECG) parameters (Germanò et al. 2014; Palanca-Maresca et al. 2017). A 20-month study of $\sim$50 patients on aripiprazole reported the incidence of corrected QT interval (QTc) prolongation (>450 mseconds) was 8.7%, with only one case of QTc prolongation detected after 12 months (Palanca-Maresca et al. 2017). Interestingly, most of the QTc abnormalities found were in patients taking ADHD medication, and no case of sudden death was reported. Another report involving a database of 22,000 patients revealed

Table 3. Efficacy Studies Including One Arm with Aripiprazole in Children and Adolescents

Authors (year)	*Age, indication*	N	*Treatment group, daily dose*	*Control group, daily dose*	*Duration*	*Efficacy measures*	*Outcomes*	*Comments*
Randomized, double-blind, controlled trials								
Bipolar spectrum disorders								
Tramontina et al. (2009)	8–17 Years, BP (manic or mixed) with ADHD	43	APZ, 13.6 ± 5.4 mg	PBO	6 Weeks	YMRS total score (primary outcome); SNAP-IV total score (primary outcome); CGI-S; CMRS-P; CDRS-R; KADS	Significant improvement in manic symptoms (YMRS, $p=0.02$, effect size = 0.80, 95% CI, 0.15–1.41; CMRS-P, $p=0.02$, effect size = 0.54) with APZ compared with PBO; no significant difference between APZ and PBO in ADHD symptoms (SNAP-IV, $p=0.39$)	Significant improvement in CGI-S with APZ compared with PBO ($p=0.04$, effect size = 0.28); no significant difference between APZ and PBO in depressive symptoms (CDRS-R, KADS)
Findling et al. (2012)	4–9 Years, BP	60	APZ, 0.26 ± 0.11 mg/kg	PBO	72 Weeks	Time to study discontinuation due to a mood event	Significantly longer time to study discontinuation with APZ due to a mood event ($p=0.005$) and discontinuation for any reason ($p=0.003$) compared with PBO	Substantial rates of withdrawal from maintenance treatment over the initial 4 weeks with both APZ and PBO (50% for APZ and 90% for PBO), suggesting a possible nocebo effect; 16 weeks of OLT with APZ before randomization
Findling et al. (2009)	10–17 Years, BP-I (manic or mixed)	296	APZ, 10 or 30 mg/day	PBO	4 Weeks	YMRS total score (primary outcome); CGI	Significant decrease of YMRS total score starting at week 1 and maintaining at week 4 with both doses of APZ compared with PBO ($p<0.05$)	Significant improvement with both doses of APZ in YMRS and CGI responder rates compared with PBO
Findling et al. (2013)	10–17 Years, BP-I (manic or mixed)	296	APZ, 10 or 30 mg/day	PBO	30 Weeks	YMRS total score (primary outcome); CGI; CGAS; CDRS-R; GBI; ADHD-RS-IV; PQ-LES-Q; treatment response; time to discontinuation	Significant improvement in manic symptoms (YMRS total score) with both doses of APZ compared with PBO ($p<0.001$)	Significant improvement with both doses of APZ in CGI, functioning (CGAS), and ADHD symptoms (ADHD-RS-IV) compared with PBO; significantly superior treatment response rate and longer time to discontinuation with both doses of APZ compared with PBO; no significant difference in depressive symptoms (CDRS-R) and self-reported quality of life (PQ-LES-Q)

(*continued*)

Table 3. (Continued)

Authors (year)	*Age, indication*	N	*Treatment group, daily dose*	*Control group, daily dose*	*Duration*	*Efficacy measures*	*Outcomes*	*Comments*
Findling et al. (2017)	5–17 Years, CYC or BP-NOS	59	APZ, 7.1 ± 3.7 mg/day	PBO	12 Weeks	YMRS total score (primary outcome); CGI-S; CGAS; CDRS-R; ARS-IV	Significant improvement in manic symptoms (YMRS total score) with APZ compared with PBO at week 12 ($p < 0.0005$)	Significant improvement in manic symptoms (YMRS total score) with APZ compared with PBO by week 3; large effect size of time by treatment interaction (Cohen's $d = 1.16$); average scores in the euthymic range by 6 weeks (YMRS <12); significant improvement in CGI-S, ADHD symptoms (ARS-IV), and functioning (CGAS) with APZ compared with PBO; no significant difference in depressive symptoms (CDRS-R)
SCZ								
Findling et al. (2008a)	13–17 Years, SCZ	302	APZ, 10 or 30 mg/day	PBO	6 Weeks	PANSS total (primary outcome), positive and negative subscale scores; CGI-S, -I; CGAS; PQ-LES-Q	Significant improvement in SCZ symptoms (PANSS total score) with both 10 and 30 mg/day doses of APZ at week 6 compared with PBO ($p = 0.05$ and $p < 0.01$, respectively)	Significant improvement in positive symptoms (PANSS positive subscale score), CGI-S, -I, functioning (CGAS) and patient quality of life (PQ-LES-Q overall score) with both doses of APZ at week 6 compared with PBO; significant improvement in negative symptoms (PANSS negative subscale score) with the 10 mg/day dose of APZ only at week 6 compared with PBO; significant improvement in PANSS total and positive subscale scores as well as CGI-S at week 1 with the 30 mg/day dose of APZ only compared with PBO
TS								
Yoo et al. (2013)	6–18 Years, TS	61	APZ	PBO	10 Weeks	YGTSS total score (primary outcome); CGI-S	Significant improvement in tics (YGTSS total score) with APZ compared with PBO ($p = 0.196$)	Significant improvement in CGI-S with APZ compared with PBO

(*continued*)

Table 3. (Continued)

Authors (year)	*Age, indication*	N	*Treatment group, daily dose*	*Control group, daily dose*	*Duration*	*Efficacy measures*	*Outcomes*	*Comments*
Sallee et al. (2017)	7–17 Years, TS	133	APZ low dose, 5 mg/day if <50 kg; 10 mg/day if ≥50 kg; APZ high dose, 10 mg/day if <50 kg; 20 mg/day if ≥50 kg	PBO	8 Weeks	YGTSS total score (primary outcome); CGI; SNAP-IV; CY-BOCS; CDRS-R; PARS	Significant improvement in tics (YGTSS total tic score) at week 8 with both low ($p = 0.002$) and high ($p < 0.0001$) doses of APZ compared with PBO	Significant improvement in tics (YGTSS total score) compared with PBO from weeks 1 to 8 for high-dose APZ and at all time points, but week 2 for low dose; noticeable separation between the low and high doses of APZ on the YGTSS total score by week 4; significant improvement in CGI from weeks 1 to 8 with both doses of APZ compared with PBO; significant improvement in ADHD/ODD symptoms (SNAP-IV) with the high dose of APZ only compared with PBO; no significant difference in both doses compared with PBO in obsessive-compulsive (CY-BOCS), depressive (CDRS-R), and anxiety (PARS) symptoms
ASD or ID with behavioral disorders								
Marcus et al. (2009)	6–17 Years, ASD	218	APZ, 5, 10 or 15 mg/day	PBO	8 Weeks	ABC-I (primary outcome); response rate; ABC-H, -IS, -S, -SW; CGI-S, -I; CY-BOCS (compulsions only); CGSQ, PedsQL	Significant improvement in irritability (ABC-I) with all APZ doses (5, 10 and 15 mg/day) compared with PBO at week 8 ($p < 0.05$, $p < 0.01$, and $p = 0.001$, respectively)	Early significant improvement by week 2 at least (all subjects receiving 5 mg/day at this time); significantly higher response rate with 5 mg/day APZ dose only compared with PBO; significant improvement with all APZ doses in CGI-I, ABC-H, and -S compared with PBO; significant improvement in CGI-S with both 10 and 15 mg/day APZ doses compared with PBO; no significant difference in ABC-SW with any dose of APZ compared with PBO; significant improvement in ABC-IS, compulsive symptoms (CY-BOCS), patients' and caregivers' quality of life (CGSQ, PedsQL) with 15 mg/day APZ dose only compared with PBO

(*continued*)

Table 3. (Continued)

Authors (year)	*Age, indication*	N	*Treatment group, daily dose*	*Control group, daily dose*	*Duration*	*Efficacy measures*	*Outcomes*	*Comments*
Owen et al. (2009)	6–17 Years, ASD	98	APZ, 5, 10 or 15 mg/day	PBO	8 Weeks	ABC-I (primary outcome); response rate; ABC-H, -IS, -S, -SW; CGI-S, -I; CY-BOCS (compulsions only); CGSQ, PedsQL	Significant improvement in irritability (ABC-I) with APZ compared with PBO at week 8 ($p < 0.001$)	Significant improvement in ABC-I with APZ by week 1 compared with PBO; significantly higher response rate and improvement in CGI-I, -S, ABC-H, - IS, and -S, compulsive symptoms (CY-BOCS), patients' and caregivers' quality of life with APZ compared with PBO; no significant difference in ABC-SW with APZ compared with PBO
Ichikawa et al. (2017)	6–17 Years, ASD	92	APZ, 8.2 ± 4.9 mg/day	PBO	8 Weeks	ABC*-I (primary outcome); response rate; ABC-J (ABC Japanese translation)-H, -IS, -S, -SW, -response rate; CGI-S; CY-BOCS; CGAS; ABC-J	Significant improvement in irritability (ABC-I) with APZ compared with PBO at week 8 ($p < 0.01$)	Significant improvement in irritability (ABC-I) with APZ compared with APZ by week 3; significantly higher response rate and greater improvement in ABC-H, CGI-S and functioning (CGAS) with APZ compared with PBO; no significant difference in the other ABC subscales and obsessive-compulsive symptoms (CY-BOCS)
Findling et al. (2014)	6–17 Years, ASD	85	APZ, 9.7 ± 4.9 mg/day	PBO	16 Weeks	Time to relapse (irritability as measured by ABC-I and CGI-I, or study discontinuation due to irritability)	No significant difference in the time to relapse between APZ and PBO ($p = 0.97$)	Relapse rate of 35% at week 16 for APZ and 52% for PBO
ADHD								
Razjouyan et al. (2018)	3–6 Years, ADHD	34	APZ, 1.25–5 mg/day	RSP, 0.25–1 mg/day	12 Weeks	ADHD-RS-IV; CPRS; CGAS	Significant improvement in ADHD symptoms (ADHD-RS-IV, CPRS) and functioning (CGAS) at week 12 ($p < 0.001$) for both APZ and RSP, without a significant between-group difference	Earlier response with APZ (second week) compared with RSP (fourth week)
Randomized, OLTs								
Ghanizadeh et al. (2014)	4–18 Years, ASD	59	APZ, 5.5 ± 2.2 mg/day	RSP, 1.12 ± 0.9 mg/day	8 Weeks	ABC-I, -H, -IS, -S, -SW (primary outcome); CGI-S, -I	No significant difference between APZ and RSP in the reduction in autistic symptoms (all ABC subscale scores, $p > 0.05$)	No significant difference in CGI-S and CGI-I between APZ and RSP

(*continued*)

Table 3. (Continued)

Authors (year)	*Age, indication*	N	*Treatment group, daily dose*	*Control group, daily dose*	*Duration*	*Efficacy measures*	*Outcomes*	*Comments*
Ghanizadeh (2016)	6–18 Years, Tic disorder	36	APZ twice weekly, 4.5 mg	APZ daily, 4.0 mg	8 Weeks	YGTSS	No significant between-group difference ($p = 0.3$)	No significant time by treatment interaction with both doses ($p = 0.4$); both groups received APZ daily (up to 7.5 mg/day) during 2 weeks before
Lamberti et al. (2016)	6–13 Years, ASD with ADHD	44	APZ, 6.6 ± 4.4 mg/day	RSP, 1.7 ± 0.5 mg/day	24 Weeks	ADHD-RS; CPRS-H, -I; CGI-I, -S; CGAS	Significant differences between APZ and RSP at week 12 (better scores with APZ in ADHD-RS, CGI-I, and CGAS), but not at week 24	Significant improvement in ADHD symptoms (ADHD-RS and CPRS-H) and CGI-S with both APZ and RSP at week 24 compared with baseline; significant improvement in CPRS-I and CGAS with APZ only at week 24 compared with baseline; ADHD-RS and CPRS only validated for patients with ADHD without ASD; no concomitant assessment of ASD symptoms (i.e., with ABC)
Open-label, nonrandomized trials								
Findling et al. (2008b)	8–12 Years, ADHD	23	APZ, 6.7 ± 2.4 mg/day	None	6 Weeks	ADHD-RS-IV; CGI-S, -I; CGAS; neuropsychological measures (CPT, SCWT, and WJ-III-ACH)	Significant improvement in all ADHD-RS-IV subscale scores (inattention, hyperactivity/impulsivity, total), CGI-S and functioning (CGAS) ($p < 0.001$)	No significant difference in neuropsychological measures at week 6 compared with baseline
Findling et al. (2009)	6–17 Years, CD	23	APZ, ~0.2 mg/kg	None	2 Weeks ±36-month extension	RAAPP; CGI-S, -I; neuropsychological measures (WCST, CPT, and VFT)	Improvement in aggressive behaviors (RAAPP, CGI) suggested at week 2 and month 36	No statistical analysis; minor improvements in neuropsychological performances suggested at month 6 (WCST, CPT, and VFT)
Ercan et al. (2012)	6–16 Years, ADHD with CD	20	APZ, 8.55 ± 1.73 mg/day	None	8 Weeks	T-DSM-IV; CGI-S, -I; CBCL; TRF	Significant improvement in all T-DSM-IV subscale scores (inattention, hyperactivity/impulsivity, ODD, CD, total; $p < 0.001$)	Significant improvement in several CBCL and TRF subscale scores (e.g., attention problems, social problems, delinquent and aggressive behaviors, and anxiety/depression)

(*continued*)

Table 3. (Continued)

Authors (year)	*Age, indication*	N	*Treatment group, daily dose*	*Control group, daily dose*	*Duration*	*Efficacy measures*	*Outcomes*	*Comments*
Findling et al. (2011)	4–9 Years, BP	96	APZ, 6.5 ± 2.3 mg/day	None	16 Weeks	YMRS; CDRS-R; CGAS; CGI-S	Significant improvement in all scales at week 6 ($p < 0.001$)	Large to very large effect sizes (YMRS, $d = 2.57$; CDRS-S, $d = 0.68$; CGAS, $d = 2.07$; and CGI-S, $d = 2.54$)
Marcus et al. (2011a)	6–17 Years, ASD	330	APZ, 10.6 mg/day	None	52 Weeks	ABC-I (primary outcome); ABC-H, -IS, -S, -SW; CGI-S, -I; CY-BOCS (compulsions only); CGSQ, PedsQL	Improvement in irritability (ABC-I) suggested to be maintained up to 52 weeks	No statistical analysis; open-label extension of 8-week PBO-controlled trials (three groups of subjects: *de novo*, prior PBO, and prior APZ); early irritability (ABC-I) improvement suggested within the first few weeks followed by further improvement up to week 8 in *de novo* and prior PBO subjects; improvements (*de novo* and prior APZ subjects) or stability (prior APZ subjects) suggested at week 52 in the other ABC subscales, CGI-S, compulsions (CY-BOCS), patients' and caregivers' quality of life (CGSQ, PedsQL; no statistical analysis); frequent comedications
Wang et al. (2016)	7–20 Years, TS	26	APZ, 9.4 ± 3.7 mg/day	None	8 Weeks	YGTSS; SAICA; PSI	Significant improvement in all YGTSS subscale scores (motor tics, phonic tics, total tic score, and impairment; $p < 0.001$)	Significant improvement in home behaviors (SAICA, $p < 0.01$) and parental stress (PSI child domain, $p < 0.05$)
Kim et al. (2018)	6–17 Years, ASD	67	APZ, 5.1 ± 2.5 mg/day	None	12 Weeks	ABC-I (primary outcome); ABC-H, -IS, -S, -SW; CGI-S; CY-BOCS; VABS; PSI-SF	Significant improvement in irritability (ABC-I; $p < 0.001$)	Significant improvement in all other ABC scores ($p < 0.001$), as well as compulsive symptoms (CY-BOCS, compulsions only), CGI-S, adaptive behavior (VABS), and parental stress (PSI-SF)

(*continued*)

Table 3. (Continued)

Authors (year)	*Age, indication*	N	*Treatment group, daily dose*	*Control group, daily dose*	*Duration*	*Efficacy measures*	*Outcomes*	*Comments*
Pan et al. (2018)	7–17 Years, DMDD with ADHD	24	APZ with MPH, 4.17 ± 1.20 mg/day (APZ); 22.71 ± 8.47 mg/day (MPH)	None	6 Weeks	SNAP-IV; CBCL; BYI-II; neuropsychological measures (CPT-II and CCTT)	Significant improvement in all SNAP-IV subscale scores (irritability, inattention, hyperactivity, and ODD; $p < 0.001$); significant improvement in several CBCL (e.g., attention problems, social problems, delinquent and aggressive behaviors, and anxiety/depression) and BYI-II subscale scores (anxiety, depression, and angry)	Significant improvement in CPT-II variability ($p = 0.007$); no significant change in other neuropsychological measures; no comparison of the bitherapy with PBO or other monotherapy
Retrospective chart review studies								
Olfson et al. (2012b)	6–17, EOS	173 (APZ), 805 (RSP)	APZ; NR	RSP; NR	180 Days	Time to discontinuation; time to psychiatric hospital admission	No significant differences in adjusted HR of both time to discontinuation and time to psychiatric hospital admission with APZ compared with RSP	Prevalence of discontinuation with APZ: 76.5%, of psychiatric hospital admission: 7.2%; mean time to discontinuation with APZ: 57.8 ± 35.8 days, to psychiatric hospital admission: 38.8 ± 42.8 days; no dose–effect relationship analysis
Ercan et al. (2012)	NR, treatment-resistant OCD	16	APZ monotherapy, 4.75 mg/day	None	12 Weeks	CY-BOCS; CGI-S, -I	Significant improvement in all CY-BOCS subscale scores (obsessions, compulsions, total; $p \leq 0.001$)	Small sample, frequent comorbidities (mostly ADHD); no control with PBO or potentiation strategy (APZ+SSRI and/or CBT); CGI results at week 12 NR
Akyol Ardic et al. (2017)	6–17 Years, treatment-resistant OCD	48	APZ with SSRI, 3.4 ± 2.2 mg/day (APZ); 142.9 ± 87.9 imipramine eq/day (SSRI)	None	12 Weeks	CY-BOCS; CGI-S, -I	Significant improvement with APZ potentiation, with or without concomitant SSRI escalation ($p < 0.001$ for all scores, in both cases)	Nonrandomized, PBO-controlled trial; CY-BOCS subscale scores NR (mean score only)

95% CI, 95% confidence interval; ABC, Aberrant Behavior Checklist; ABC-H, ABC-Hyperactivity/noncompliance; ABC-I, ABC-Irritability; ABC-IS, ABC-Inappropriate speech; ABC-S, ABC-Stereotypic behavior; ABC-SW, ABC-Lethargy/social withdrawal; ADHD, attention-deficit/hyperactivity disorder; ADHD-RS-IV, ADHD-Rating Scale-IV; APZ, aripiprazole; ARS-IV, DSM-IV ADHD Rating Scale; ASD, autism spectrum disorder; BP (-I, NOS), bipolar disorder (type I, not otherwise specified); BYI-II, Beck Youth Inventories-second edition; CBCL, Child Behavior Checklist; CBT, Cognitive Behavioral Therapy; CCTT, Children's Color Trails Test; CD, conduct disorder; CDRS-R, Children's Depression Rating Scale-Revised; CGAS, Children's Global Assessment Scale; CGI (-S, -I), Clinical Global Impression scale (-Severity, -Improvement); CGSQ, Caregiver Strain Questionnaire; CMRS-P, Child Mania Rating Scale-Parental Version; CPRS (-H, -I): Conners' Parent Rating Scale (-Hyperactivity, -Inattention); CPT (-II), Conners' Continuous Performance Test (-version II); CY-BOCS, Child Yale–Brown Obsessive-Compulsive Scale; CYC, cyclothymic disorder; DMDD, disruptive mood dysregulation disorder; EOS, early-onset schizophrenia; GBI, Global Behavior Inventory; HR, hazard ratio; ID, intellectual disability; KADS, Kutcher Adolescent Depression Scale; MPH, methylphenidate; NR, not reported; OCD, obsessive-compulsive disorder; ODD, oppositional defiant disorder; OLT, open-label trial; PANSS, Positive And Negative Syndrome Scale; PARS, Pediatric Anxiety Rating Scale; PBO, placebo; PedsQL, Pediatric Quality of Life Inventory; PQ-LES-Q, Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire; PSI (-SF), Parenting Stress Index (-Short Form); RAAPP, Rating of Aggression Against People and Property; RSP, risperidone; SAICA, Social Adjustment Inventory for Children and Adolescents; SCWT, Stroop Color and Word Test; SCZ, schizophrenia; SNAP-IV, Swanson, Nolan, and Pelham, version IV; SSRI, selective serotonin reuptake inhibitor; T-DSM-IV, Turgay DSM-IV based child and adolescent behavior disorders screening and rating scale; TRF, Teachers Report Form; TS, Tourette's syndrome; VABS, Vineland Adaptive Behavior Scale; VFT, Verbal Fluency Test; WCST, Wisconsin Card Sorting Test; WJ-III-ACH, Woodcock-Johnson III Achievement test; YGTSS, Yale Global Tic Severity Scale; YMRS, Young Mania Rating Scale.

Table 4. Meta-Analyses Available Assessing Aripiprazole Efficacy in Children and Adolescents by Indications

Authors (year)	*Studies included (type)*	*Age, indication*	N *studies (control group)*	N *patients*	*Duration*	*Efficacy measures*	*Outcomes*	*Comments*
ASD								
Varni et al. (2012)	RBCT	6–17 Years, ASD	2 (PBO)	316	8 Weeks	PedsQL	Significant improvement in health-related quality of life with APZ compared with PBO	Significant improvement in the PedsQL combined-scale total score (MD = 7.8; 95% CI, 3.8–11.8; $p < 0.001$), as well as the scores of all three PedsQL scales (emotional, social, and cognitive functioning)
Cohen et al. (2013)	RBCT	6–17 Years, ASD	2 (PBO)	316	8 Weeks	CGI	Significant improvement in CGI response rate with APZ compared with PBO (OR = 6.09; 95% CI, 2.3–12.63)	No significant difference with RSP
McQuire et al. (2015)	RBCT	6–17 Years, ASD	2 (PBO)	316	8 Weeks	ABC-I	Significant improvement in irritability with APZ compared with PBO ($p < 0.001$)	SMD = −1.09 (95% CI, −0.91 to −0.36; $I^2 = 12\%$)
Fung et al. (2016)	RBCT	6–17 Years, ASD	2 (PBO)	316	8 Weeks	ABC-I	Significant improvement in irritability with APZ compared with PBO ($p < 0.001$)	Effect size: $d = 0.78$; substantial heterogeneity ($I^2 = 72\%$), with dose-dependent effects
Hirsch and Pringsheim (2016)	RBCT	6–17 Years, ASD	2 (PBO)	316	8 Weeks	ABC-I, -H, -IS, -S, -SW	Significant improvement in irritability (ABC-I), hyperactivity (ABC-H), inappropriate speech (ABC-IS), and stereotypy (ABC-S) with APZ compared with PBO	ABC-I: MD = −6.17 (95% CI, −9.07 to −3.26; $p < 0.00001$; $I^2 = 33\%$); no significant difference in social withdrawal
van Schalkwyk et al. (2017)	RBCT	6–17 Years, ASD or BP-I (manic or mixed)	3 (PBO)	704	4–8 Weeks	ABC-I (ASD); YMRS-disruptive/ aggressive behavior line item (BP-I)	Significant improvement in overall irritability and aggression with APZ compared with PBO (SMD = 0.68; 95% CI, 0.50–0.86; $p < 0.00001$; z = 7.5)	No significant difference with RSP; no significant difference based on diagnosis indication; no overall dose–effect

(*continued*)

Table 4. (Continued)

Authors (year)	*Studies included (type)*	*Age, indication*	N *studies (control group)*	N *patients*	*Duration*	*Efficacy measures*	*Outcomes*	*Comments*
Maneeton et al. (2018)	RBCT	6–17 Years, ASD	3 (PBO)	408	8 Weeks	ABC-I, -H, -IS, -S, -SW	Significant improvement in irritability, hyperactivity, inappropriate speech, and stereotypy with APZ compared with PBO	ABC-I: MD = −5.41 (95% CI, -7.58 to −3.24; $p < 0.00001$; $I^2 = 10\%$); no significant difference in social withdrawal
Fallah et al. (2019)	RBCT	4–18 Years, ASD	3 (PBO), 1 (RSP)	467	8 Weeks	ABC-I	Significant improvement in irritability with APZ compared with PBO	MD = −6.62 (95% CI, −10.88 to −2.22); no meta-analysis performed with APZ versus PBO (only one study available)
Tic disorders								
Yang et al. (2015)	RBCT, RCT, OLT	4–18 Years, Tic disorders	7 (total): 4 (HLP), 2 (TIA), 1 (RSP)	600	8–12 Weeks	YGTSS	No significant difference in the reduction in the YGTSS total score with APZ compared with overall control medications ($p = 0.87$), as well as with HLP ($p = 0.60$) and TIA ($p = 0.45$) separately	No significant difference between APZ and overall control medications in the reduction in the YGTSS subscale scores (motor, vocal and total tics, and impairment); no significant difference between APZ and both HLP and TIA in all subscale scores, but the vocal tics score (lower efficacy of APZ compared with HLP); no meta-analysis performed with APZ versus RSP separately, nor versus PBO (only one study available for each)

(*continued*)

Table 4. (Continued)

Authors (year)	*Studies included (type)*	*Age, indication*	N *studies (control group)*	N *patients*	*Duration*	*Efficacy measures*	*Outcomes*	*Comments*
Liu et al. (2016)	RBCT, OLT	4–19 Years, TS	1 RBCT (PBO), 9 OLTs	302	6–14 Weeks	YGTSS; CGI-S	Significant improvement in the YGTSS total tic score and CGI-S with APZ ($p<0.001$)	Effect sizes ($p<0.001$): YGTSS total score: -1.99 (95% CI, -2.26 to -1.72); CGI-S: -2.34 (95% CI, -2.96 to -1.73); significant between-study heterogeneity for the YGTSS total score ($I^2=57.8\%$), depending on the year of publication; mostly OLTs
Zheng et al. (2016)	OLT	5–17 Years, TS	2 (TIA)	260	8–12 Weeks	YGTSS	No significant difference between APZ and TIA in the reduction in the YGTSS total score ($p=0.42$)	Only two studies, with high between-study heterogeneity ($I^2=90\%$)
Wang et al. (2017)	RBCT, RCT, OLT	3–17 Years, Tic disorders	10 (total): 6 (HLP), 2 (TIA), 1 (RSP), 1 (TOP), 1 (PBO)	817	4–12 Weeks	YGTSS	No significant difference in the reduction in the YGTSS total score with APZ compared with overall control medications, as well as with HLP and TIA separately	No significant difference between APZ and overall control medications in the reduction in all YGTSS subscale scores (motor tics, vocal tics, and impairment), as well as between APZ and HLP separately; no meta-analysis performed with APZ versus TOP or RSP separately, nor versus PBO (only one study available for each)

95% CI, 95% confidence interval; ABC, Aberrant Behavior Checklist; ABC-H, ABC-Hyperactivity/noncompliance; ABC-I, ABC-Irritability; ABC-IS, ABC-Inappropriate speech; ABC-S, ABC-Stereotypic behavior; ABC-SW, ABC-Lethargy/social withdrawal; ADHD, attention-deficit/hyperactivity disorder; APZ, aripiprazole; ASD, autism spectrum disorder; BP (-I), bipolar disorder (type I); CGI (-S), Clinical Global Impression scale (-Severity); HLP, haloperidol; MD, mean difference; OLT, open-label trial; OR, odds ratio; PBO, placebo; PedsQL, Pediatric Quality of Life Inventory; RBCT, randomized blinded controlled trial; RCT, randomized controlled trial; RSP, risperidone; SMD, standardized mean difference; TIA, tiapride; TOP, topiramate; TS, Tourette's syndrome; YGTSS, Yale Global Tic Severity Scale; YMRS, Young Mania Rating Scale.

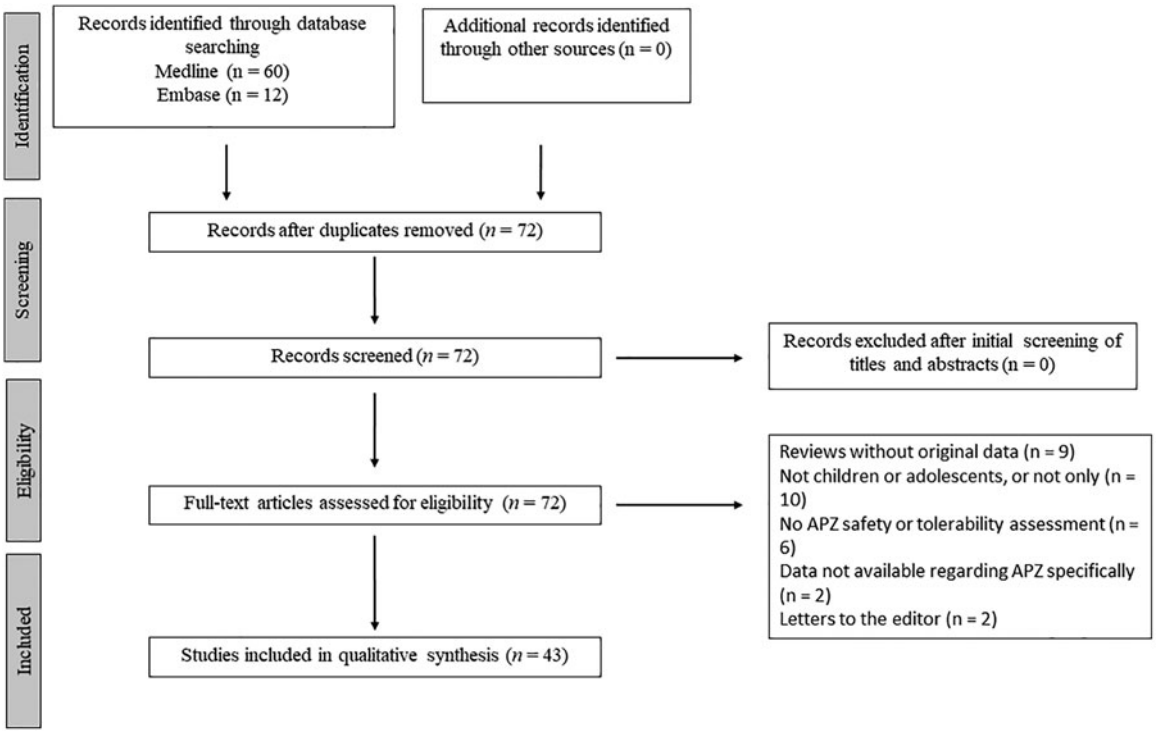

FIG. 3. Diagram of the study selection flowchart for evaluating aripiprazole tolerance.

that those exposed to aripiprazole as the first treatment had a 1.58-fold higher risk of type II diabetes versus those taking risperidone, which is the reference in this database analysis (Rubin et al. 2015). Nevertheless, the risk of diabetes for all atypical antipsychotic drugs combined was 1.51. Two years before the FDA report on serious adverse events with aripiprazole published in 2017, an FDA database search found that 2500 cases reported had serious side effects defined as neuroleptic malignant syndrome, QT prolongation, leukopenia, and suicide attempts (Kimura et al. 2015). A significant signal was retained regarding the potential of aripiprazole to induce neuroleptic malignant syndrome and suicide attempts. Finally, a study of poison control center database reports of accidental exposure to aripiprazole in children younger than 6 years revealed that side effects were mostly minor, and only 0.8% major side effects were reported, with no deaths (Stassinos and Klein-Schwartz 2017).

Table 6 summarizes the six available meta-analyses evaluating the safety of aripiprazole in children and adolescents, generally in comparison to other antipsychotic drugs or placebo (De Hert et al. 2011; Pringsheim et al. 2011a; Robb et al. 2011; Cohen et al. 2012; Almandil et al. 2013; Jensen et al. 2015). Only two are detailed in this study, the first by Cohen et al. (2012) because it is the most important in terms of inclusion of patients on atypical antipsychotics using a Bayesian method. Their meta-analysis summarizes the side effects of each antipsychotic relative to placebo in a semiquantitative mode and shows that aripiprazole has a particular profile of side effects, including somnolence/sedation, weight gain, and relatively frequent extrapyramidal effects. In contrast, aripiprazole had no hyperprolactinemic effect and little short-term effect on metabolic parameters. The second study detailed herein was by Jensen et al. (2015) because it focused on cardiac side effects reported in 14 studies with aripiprazole arms for a total of 862 exposed patients. It appears that, on average, aripiprazole significantly decreases the QTc interval. The change in QTc correlated with the dosage received since the higher the dose, the more QTc tends to decrease.

Finally, Supplementary Table S1 lists all 19 case reports (corresponding to a total of 22 observations) mentioning aripiprazole tolerance problems in children and adolescents (McLaren et al. 2010; Patel et al. 2011; Star et al. 2012; Stern and Trieu 2012; Panigrahi et al. 2013; Thabet et al. 2013; Párraga and Sherman 2015; Hoşoğlu et al. 2016; Mohapatra 2016; Pinnaka et al. 2016; Binici and Güney 2017; Fatima and Mottola 2017; Gunes 2017; Han et al. 2017; Lamberti et al. 2017; LeRiger et al. 2017; Sridaran and Nesbit 2017; Boyer et al. 2018; Işik and Çam Ray 2019). Accountability is sometimes difficult to attribute since 11 of the 22 observations were in a polyprescription context and 4 adverse events occurred when a similar history was known or when an autoimmune medical comorbidity was reported. In total, eight observations report known side effects that are not detailed in this study (in particular, observations of particularly severe neurological side effects). In one case, rhabdomyolysis in the context of coprescription was observed (Star et al. 2012). Another rather complex case of a 3-year-old girl reports a history of epilepsy and encephalopathy in a context without any previous history (Thabet et al. 2013). Observation of neuroleptic malignant syndrome without fever that clinically evokes malignant catatonia was described in an 8-year-old boy after 3 days of aripiprazole initiation (Sridaran and Nesbit 2017), and one case of pseudoneutropenia was reported (Pinnaka et al. 2016). Three cases of epistaxis have also been reported, including one with gingival bleeding (Hoşoğlu et al. 2016; Binici and Güney 2017). Finally, two cases of secondary enuresis were reported (Gunes 2017), as well as one case of urinary retention in an 11-year-old boy with severe intellectual disability (Boyer et al. 2018).

Table 5. Studies Assessing Aripiprazole Safety and Tolerability in Children and Adolescents

Authors (year)	*Age, indication*	N	*Daily dose*	*Duration*	*Safety and tolerability measures*	*Outcomes*	*Comments*
Randomized, double-blind, controlled trials							
ASD							
Findling et al. (2013)	6–17 Years, ASD	157 (phase 1); 85 (phase 2)	9.0±4.5 mg (phase 1); 9.7±4.9 mg (phase 2)	13–26 Weeks (phase 1); 16 Weeks (phase 2)	Any clinical AE, weight (BMI, z-score), EPS measures (SAS, BARS, AIMS), metabolic parameters (Glu, LDL-CHL, HDL-CHL, total CHL, TG), PRL level	Phase 2 (double-blind randomized, APZ vs. PBO): AEs in 56.4% of cases (vs. 32.6%), with upper respiratory tract infection (10.3% vs. 2.3%), constipation (5.1% vs. 0%), vomiting (5.1% vs. 4.7%), movement disorder (5.1% vs. 0%); EPS-related AEs: 7.7% versus 7.0%; significant weight gain with APZ compared with PBO, mean difference (z-score): 0.15 SDs (95% CI, 0.06–0.24, $p=0.001$), weight gain (LOCF): 2.2 kg versus 0.6 kg; significant decrease in PRL level with APZ compared with PBO, mean difference: −4.8 ng/mL (95% CI, −6.8 to −2.9); no significant differences in metabolic parameters between APZ and PBO; no differences in sexual maturation; no serious AEs or discontinuations due to AEs; most AEs of mild intensity	Phase 1 (single blind with APZ): AEs in 80% of cases, mainly weight gain (25.2%), somnolence (14.8%), vomiting (14.2%); EPS-related AEs in 17.4%, with tremor in 6.5%; weight gain: 3.2 kg (LOCF); minimal changes in metabolic parameters: -6.0 mg/dL (total CHL), -3.0 mg/dL (LDL-CHL), -1.0 mg/dL (HDL-CHL), 0 mg/dL (Glu), 4.0 mg/dL (TG); main AEs leading to discontinuation: aggression and weight gain (1.3% each); most AEs of mild intensity
Mankoski et Cal. (2013)	6–17 Years, ASD	316	NR	8 Weeks	Any clinical AE, weight (BMI, z-score), EPS measures (SAS, BARS, AIMS), metabolic parameters (Glu, LDL-CHL, HDL-CHL, total CHL, TG)	Stratification by PAE: 259 (82%) AN subjects, 57 (18%) subjects with PAE; significant weight gain with APZ compared with PBO in AN subjects only, mean difference: 1.2 kg (95% CI, 0.5–1.9), RR of clinically significant weight gain: 4.6 (95% CI, 1.8–12.1); high baseline weight z-score and young age (6–12 years) significant predictors of weight gain; no significant difference in metabolic parameters between APZ and PBO in both AN and PAE subjects; sedation, somnolence, and fatigue more common in AN subjects than in subjects with PAE (22.7 vs. 11.1%, 11.9 vs. 2.8%, and 17.0 vs. 13.9%, respectively), as well as vomiting (15.3 vs. 5.6%), pyrexia (10.2 vs. 2.8%), salivary hypersecretion (6.8 vs. 0%), and EPS (6.8 vs. 2.8%); low rates of discontinuation when subtracting PBO to APZ rates: 3.3% (AN subjects) and 3.5% (subjects with PAE)	Most common AEs reported in AN subjects treated with APZ: sedation (22.7%), fatigue (17.0%), somnolence (11.9%), vomiting (15.3%), increased appetite (13.1%), pyrexia (10.2%), drooling (9.7%), tremor (9.7%), diarrhea (8.0%), decreased appetite (7.4%), nasopharyngitis (7.4%), headache (7.4%), EPS (6.8%); main AEs leading to discontinuation in AN subjects: sedation (3.4%), drooling and tremor (2.3% each)

(*continued*)

Table 5. (Continued)

Authors (year)	*Age, indication*	N	*Daily dose*	*Duration*	*Safety and tolerability measures*	*Outcomes*	*Comments*
Open-label, nonrandomized trials							
ASD							
Marcus et al. (2011b)	6–17 Years, ASD	330	9.6 mg	52 Weeks	Any clinical AE, weight (BMI, z-score), metabolic parameters (Glu, LDL-CHL, HDL-CHL, total CHL, TG), PRL level, vital signs, ECG	Prevalence of AEs: overall of 86.7%, with increased weight (23.0%), vomiting (18.8%), nasopharyngitis (13.3%), increased appetite (13.0%), pyrexia (11.8%), upper respiratory tract infection (11.5%), and insomnia (10.0%). Rate of discontinuation due to AEs: 10.0% (*de novo* subjects: 10.5%, prior PBO subjects: 14.3%, and prior APZ subjects: 8.0%); most frequent AEs leading to discontinuation in the overall population: aggression (2.1%) and weight increase (2.1%); serious AEs in 2.7% (*de novo* subjects: 3.5%, prior PBO subjects: 1.4%, and prior APZ subjects: 2.9%). Weight gain, mean change (LOCF): 6.3 kg; following >9 months of APZ exposure, mean change in weight z-score of 0.33, in BMI z-score of 0.31. At >9 months, metabolic abnormalities: Glu (1.9%), HDL-CHL (30.1%), LDL-CHL (6.5%), total CHL (5.2%), TG (4.6%); no discontinuation due to metabolic abnormalities. Decrease in PRL level, mean change: -5.6, -5.4, -6.0, and -6.3 ng/mL following total exposure times of ≤3, 3–6, 6–9, and >9 months, respectively. EPS-related AEs: overall prevalence of 14.5%, with tremor (3.0%), psychomotor hyperactivity (2.7%), akathisia (2.4%), and dyskinesia (2.4%); mean changes in AIMS, SAS, and BARS (LOCF) of -0.3, -0.0, and 0.0, respectively. No discontinuation due to ECG or vital sign abnormalities; one case of QTc prolongation (479 mseconds) in a patient without PAE; clinically relevant increase and decrease in sitting systolic blood pressure in 10.6% and 34.0%, respectively; clinically relevant increase and decrease in sitting diastolic blood pressure in 5.3% and 33.0%, respectively; clinically relevant increase in sitting heart rate in 2.2%, no clinically relevant decreases	Open-label study with subjects from two previous 8-week RBCTs comparing APZ ($n=174$) with PBO ($n=70$), and *de novo* enrolled subjects ($n=86$); CNS comedications in 64.2% of cases: analgesics and antipyretics (35.5%), anxiolytics (15.8%), psychostimulants (15.8%), antidepressants (15.2%)

(*continued*)

Table 5. (Continued)

Authors (year)	*Age, indication*	N	*Daily dose*	*Duration*	*Safety and tolerability measures*	*Outcomes*	*Comments*
Ho et al. (2012)	5–17 Years, ASD	24	7.8 mg	14 Weeks	ECG parameters (PR, QRS, RR QT, QTcB, QTcN, QTcF)	No significant differences in ECG parameters, including QTc before and after APZ initiation. No significant correlation between APZ dose and percent change in the QTc. No posttreatment QTc >440 mseconds	One posttreatment ECG only (at week 14)
Ichikawa et al. (2018)	6–17 Years, ASD	86	8.5 ± 4.7 mg	694.9 ± 390.7 days	Any clinical AE, weight (BMI, z-score), metabolic parameters (Glu, total CHL, TG), PRL level, ECG	Most common AEs (≥20% of patients): nasopharyngitis (61.6%), somnolence (32.6%), influenza (29.1%), increased weight (24.4%). And EPS-related AEs: 12.8%, mostly salivary hypersecretion (7.0%) and akathisia (4.7%); all mild in severity. Majority of AEs mild or moderate in severity. Discontinuation rate due to AEs: 11.6%; most frequent AEs leading to discontinuation: increased weight (3.5%), worsening of primary disease (3.5%), and increased appetite (2.3%). Decrease in PRL level, among prior PBO subjects, mean difference (LOCF): -12.5 ± 12.2 ng/mL. No clinically relevant changes in weight, BMI, metabolic or ECG parameters in the overall population (prior PBO and APZ subjects). Mean weight and BMI z-score changes among prior PBO subjects: 0.33 and 0.39 at week 48 and 0.21 and 0.24 at end point, respectively.	Open-label extension study of previous 8-week RBCT comparing APZ with PBO; continuation rate at week 48: 81%; no statistical analysis; ECG parameters NA
Naturalistic studies							
Germanò et al. (2014)	4–15 Years, mental health disorders	29	7.4 ± 3.1 mg	8 Weeks	ECG parameters (heart rate, PR, RR, QRS, QTc, QTd)	Significant increase in QTd compared with baseline, without being pathological (40.6 ± 6.5 mseconds vs. 46.3 ± 7.2 mseconds, $p < 0.01$). No other significant difference in ECG parameters, including QTc. No QTc >450 mseconds, no QTd >100 mseconds (before and after APZ initiation). No significant correlation between APZ dose and ECG parameters	One posttreatment ECG only (at week 8) Diagnoses NR for APZ patients specifically Diagnoses (total APZ and RSP patients): PDD, ODD, ADHD, ID with psychotic disorder, TS and other tic disorders

(*continued*)

Table 5. (Continued)

Authors (year)	*Age, indication*	N	*Daily dose*	*Duration*	*Safety and tolerability measures*	*Outcomes*	*Comments*
Carbon et al. (2015)	4–19 Years Mental health disorders	66 (APZ) 342 (all SGAs)	NR	12 Weeks	Neuromotor AEs (reported with TESS) EPS measures (SAS, BARS, AIMS)	Significant increase in drug-induced parkinsonism (SAS total score, restricted to AN subjects) with APZ at week 12 compared with baseline ($p<0.001$). No significant dose–effect relationship for any of EPS (parkinsonism, dyskinesia, akathisia). 3-Month incidences with APZ: parkinsonism: 27.3%; akathisia: 6.3%; dyskinesia: 4.5%; anticholinergic medication: 4.8%; discontinuation due to EPS: 6.2%.	High rates of dyskinesia (10.8%) and parkinsonism (9.1%) at baseline; diagnoses: mood, SCZ, and disruptive/aggressive behavior spectrum disorders; not only AN subjects; no statistical comparison of APZ specifically with other SGAs
Al-Dhaher et al. (2016)	4–19 Years, mental health disorders	41 (APZ); 257 (all SGAs)	NR	12 Weeks	Activating and sedating AEs (reported with TESS)	High rates of activating and sedating AEs at baseline in all groups, including APZ (i.e., drowsiness: 60.0% and insomnia: 32.5%). Significant increase in hypersomnia reports and significant decrease in insomnia reports with APZ at 4, 8, and 12 weeks compared with baseline. No other significant changes in the prevalences of activating and sedating AEs reported with APZ over time compared with baseline. No significant changes in activating and sedating AE severity ratings with APZ over time compared with baseline, except at 4 weeks (lower psychomotor activation item severity, higher malaise item severity). No significant dose–effect relationship with APZ. Rates of discontinuation with APZ: 5.9% for any reason, 2.0% due to sedation; no discontinuation due to activating AEs	Significantly more activating ($p=0.018$) and less sedating AEs ($p=0.018$) with APZ compared with other SGAs; no significant difference between SGAs, including APZ, in the rate of discontinuation due to sedation, but a nonsignificant trend ($p=0.059$) toward more discontinuations with QTP compared with other SGAs; diagnoses: mood, SCZ, and disruptive/aggressive behavior spectrum disorders; AN subjects only
Rafaniello et al. (2016)	<18 Years Mental health disorders	33 (APZ) 184 (all SGAs)	8.54 ± 5.34 mg	NR	Any clinical AE, blood tests, ECG	No significant difference between APZ and other SGAs (RSP, QTP, OLP) in the prevalence of overall AEs. Significantly lower PRL level with APZ compared with RSP ($p<0.001$). Prevalences of AEs reported with APZ: overall: 78.8%; nervous system disorders: 30.8% (i.e., sedation and headache); psychiatric disorders: 21.2% (i.e., agitation); gastrointestinal disorders: 13.5% (i.e., abdominal pain); abnormal investigations: 13.5% (i.e., elevated CPK or ALP); cardiac disorders: 11.5% (i.e., tachycardia); metabolism/nutrition disorders: 5.8% (i.e., hyperphagia); general disorders and administration-site conditions (3.8%, i.e., drug failure).	Diagnoses: ASD, disruptive behavioral disorders, ID, psychosis spectrum disorders, TS and other tic disorders, others; no statistical comparison between APZ and other SGAs regarding more specific AE prevalences; seriousness of AEs NR for APZ specifically, discontinuation rate with APZ NR; data regarding ECG measures (i.e., QTc) and blood tests other than serum PRL level measure not precisely reported

(*continued*)

Table 5. (Continued)

Authors (year)	*Age, indication*	N	*Daily dose*	*Duration*	*Safety and tolerability measures*	*Outcomes*	*Comments*
Pringsheim et al. (2017)	6–17 Years, TS	30 (APZ); 27 (RSP)	6.0 mg (APZ); 1.1 mg (RSP)	10 Months (mean, total APZ and RSP subjects; range 1–30 months)	EPS measure (ESRS), clinical (weight, BMI, waist circumference), and laboratory (Glu, LDL-CHL, HDL-CHL, TG, insulin, AST, ALT) metabolic parameters	Significant increase in BMI over time ($p<0.001$), with significant time by drug interaction ($p=0.041$): smaller gain in the first months with APZ, and faster increase later compared with RSP. Significant increase in waist circumference over time ($p<0.001$), without significant drug by time interaction. Significant increase in EPS after treatment ($p<0.001$), without significant drug by time interaction. No significant difference between APZ and RSP in any laboratory metabolic parameter at 3 (or 6) and 12 months. Incidence of EPS with APZ: 43%, with parkinsonism (37%) and akathisia (13%). Incidences of metabolic AEs with APZ: weight gain: 24%; LDL-CHL increase, HDL-CHL decrease, insulin increase, AST and ALT increases: 3% each; no Glu or TG increase; discontinuation rate with APZ due to metabolic AEs: 17%, due to EPS: 10%.	Hypothesis of a nonlinear pattern of BMI gain with APZ based on visual inspection of BMI change over time only; no statistical analysis of laboratory metabolic changes over time with APZ specifically; no PRL level measurement in patients treated with APZ
Pozzi et al. (2019)	<18 Years, mental health disorders	24 (APZ); 103 (RSP)	0.11 mg/kg (children); 0.13 mg/kg (adolescents)	NR	BMI z-score	Significant BMI z-score increase over time with APZ (mean, 95% CI): in children, at 3 (0.198, 0.087–0.306) and 6 months (0.396, 0.174–0.612); in adolescents, at 3 (0.117, 0.024–0.207), 6 (0.234, 0.048–0.414), and 12 months (0.468, 0.096–0.828).	Higher BMI z-score increase with APZ in children than in adolescents (at 3 and 6 months); shorter PAE in children (3 months) than in adolescents (4.5 months) regarding APZ; treatment with RSP associated with trends of BMI z-score increase in children and decrease in adolescents, possibly due to longer PAE in adolescents as well; no statistical comparison between APZ and RSP (only visual analysis of weight-change trajectories with both drugs)

(*continued*)

Table 5. (Continued)

Authors (year)	*Age, indication*	N	*Daily dose*	*Duration*	*Safety and tolerability measures*	*Outcomes*	*Comments*
Retrospective chart review studies							
Diomšina et al. (2015)	9–18 Years, mental health disorders	33	4.65 ± 3.52 mg	Mean NR (minimum 4 weeks, maximum 5 years)	Any clinical AE, weight, blood tests (including CHL and PRL levels), blood pressure, ECG	Majority of good tolerability (57%), with no AEs (42%) or slight transient effects (15%), such as fatigue (9%) and tremor of hands (3%). Increased appetite/weight gain: main AE (42%) and main cause of discontinuation (18% over 24%). Rare hyperprolactinemia (3%) and persistent fatigue (3%). No dyslipidemia or cardiac AE.	Diagnoses: ADHD, PDD, TS and other tic disorders, ID, psychotic disorders, anxiety disorders, OCD, adaptation and attachment disorders; exclusion of patients if not treated ≥4 weeks (exclusion of 1 patient presenting akathisia after 1 week of treatment); only subjective report of some AEs by patients or parents; comedications not taken into account; no dose or treatment duration-related analyses; data regarding blood tests and ECG NR, no measure of Glu level
Kimura et al. (2015)	0–12 Years	2553	NR	NR	Serious AEs (defined as NMS, QT prolongation, leukopenia, and suicide attempt) reported to the FAERS from 1997 to 2011	APZ signals detected for NMS and suicide attempt.	Indications/diagnoses NR
Rubin et al. (2015)	10–18 Years, mental health disorders	22,214	NR	NR	Incidence of type 2 diabetes mellitus (identified through visit and pharmacy claims) in Medicaid-enrolled youths starting APZ from 2003 to 2007	OR of incident type 2 diabetes mellitus among APZ initiators: 1.58 (95% CI, 1.21–2.07; $p = 0.001$).	Diagnoses NR for APZ initiators specifically; evaluation of risk in case of association with antidepressants or stimulants only performed for overall SGAs initiators
Jakobsen et al. (2016)	<18 Years, mental health disorders	19	5.2 mg	9 Months	AEs (neurological, metabolic, or psychiatric) reported to the safety database of the Danish Medicines Agency from 2003 to 2015	Neurological AEs reported: akathisia, balance problems, blurred and stiffened gaze, chronic insomnia, convulsions, dizziness, dystonia, facial muscle spasms, fatigue, hand tremor, hypersalivation, involuntary movements of arms and legs, involuntary throat sounds, motor rigidity, mydriasis, parkinsonism, tics, spasms, and sedation. Psychiatric AEs reported: aggressive behavior, anxiety, hallucinations, mental tics, NMS, overeating, and suicidal behavior. Metabolic and other AEs reported: weight gain between 7 and 19 kg and hypercholesterolemia; loss of hair, and restlessness also reported.	Diagnoses: SCZ, psychosis not otherwise specified, ADHD, anorexia nervosa, anxiety, ASD, brain damage, developmental disturbances and ID, TS, epilepsy, OCD, enuresis; APZ dose, duration, and comedications, not always reported; no use of any AE rating scales; no causality assessment
Stassinos and Klein-Schwartz (2017)	<6 Years	5018	NR	NR	Exposure calls (from the public or health professionals) received by poison centers and reported to the AAPCC/NPDS from 2005 to 2013	Mainly unintentional exposures (96.5%). Most frequent AE reported: drowsiness (47.6%). Mostly no (40.5%), minor (43.0%), or moderate (15.7%) medical outcome. Major medical outcome in 0.8% of cases, no deaths.	No dose evaluation; no coingestants reports; telephonic symptom record; population <6 years

(*continued*)

Table 5. (Continued)

Authors (year)	*Age, indication*	N	*Daily dose*	*Duration*	*Safety and tolerability measures*	*Outcomes*	*Comments*
Yoon et al. (2016)	2–19 Years, ASD and/or ID	66 (APZ); 202 (all SGAs)	NR	1.22±0.97 Years (mean, all SGAs)	BMI z-score	Significant increase in BMI z-score with APZ (mean: 0.19; 95% CI, 0.00–0.38; $p=0.0496$). Significantly superior BMI z-score increase with OLP; no significant difference with other SGAs.	Differences between SGA groups in age and baseline BMI; control for duration of treatment and concomitant medications, but not for SGA dosage
Palanca-Maresca et al. (2017)	4–17 Years, mental health disorders	46	6.0 mg	20 Months (mean)	QTc, QTd	Prolonged QTc (>450 mseconds) incidence (APZ): 8.7%. One case of QTc prolongation detected >12 months. No prolonged QTc >500 mseconds; no QTd >100 mseconds; no case of TdP or sudden cardiac death. QTc changes mostly asymptomatic and spontaneously resolutive. For all APs: significant association of QTc abnormalities with concomitant ADHD medications; nonsignificant association with cardiovascular family history.	Diagnoses NR for patients treated with APZ specifically; period of the study unspecified; low mean daily dose; no dose–effect relationship evaluation

95% CI, 95% confidence interval; AAPCC, American Association of Poison Control Centers; ADHD, attention-deficit/hyperactivity disorder; AE, adverse effect; AIMS, Abnormal Involuntary Movement Scale; AN, AP naive; AP, antipsychotic; APZ, aripiprazole; ASD, autism spectrum disorder; BARS, Barnes Akathisia Rating Scale; BFCRS, Bush Francis Catatonia Rating Scale; BMI, body mass index; BP, bipolar disorder; CHL, cholesterol; CNS, central nervous system; ECG, electrocardiogram; EPS, extrapyramidal symptoms; ESRS, extrapyramidal Symptom Rating Scale; FAERS, Food and Drug Administration Adverse Event Reporting System; Glu, glucose; HDL-CHL, high-density lipoprotein-CHL; ID, intellectual disability; LDL-CHL, low-density lipoprotein-CHL; LOCF, last observation carried forward; NMS, neuroleptic malignant syndrome; NPDS, National Poison Data System; NR, not reported; OCD, obsessive-compulsive disorder; ODD, oppositional defiant disorder; OLP, olanzapine; OR, odds ratio; PAE, prior antipsychotic exposure; PBO, placebo; PDD, pervasive developmental disorder; PRL, prolactin; QTc, corrected QT interval, Bazett's (QTcB), United States Food and Drug Administration (FDA) Neuropharmacology Division (QTcN), and Fridericia's (QTcF) formulas; QTd, QT interval dispersion; QTP, quetiapine; RBCT, randomized blinded controlled trial; RR, relative risk; RSP, risperidone; SAS, Simpson-Angus Scale; SCZ, schizophrenia; SD, standard deviation; SGA, second-generation antipsychotic; TdP, torsade de pointes; TESS, Treatment Emergent Symptoms Scale; TG, triglycerides; TS, Tourette's syndrome.

Table 6. Meta-Analyses Available Assessing the Safety and Tolerability of Aripiprazole in Children and Adolescents

Authors (year)	*Studies included (type)*	*Age, indication*	N *studies (control group)*	N *patients*	*Duration*	*Safety/tolerability measures*	*Outcomes*	*Comments*
De Hert et al. (2011)	RBCT	≤18 Years, mental health disorders	5 (PBO)	579	4–8 Weeks	Weight	Significant weight gain with APZ compared with PBO, mean difference: 0.79 kg (95% CI, 0.54–1.04; $p<0.00001$; $I^2=0\%$)	Diagnoses: ASD (2 studies), SCZ (1), BP (manic or mixed) (1), BP (manic or mixed) with ADHD (1); short-term trials; no meta-regression analyses; mean daily-dose NR
Pringsheim et al. (2011a)	RBCT	≤18 Years, mental health disorders	5 (PBO)	861	4–8 Weeks	Weight, BMI, EPS, metabolic parameters, PRL level, ECG (QTc), heart rate, and blood pressure	Significant weight and BMI gains with APZ compared with PBO, mean differences: 0.85 kg (95% CI, 0.58–1.13; $p<0.00001$; $I^2=0\%$) and 0.27 kg/m^2 (95% CI, 0.11–0.42; $p=0.0007$; $I^2=17\%$), respectively. Significant decrease in PRL level compared with PBO, mean difference: −5.03 ng/mL (95% CI, −7.80 to −2.26; $p=0.0004$; $I^2=47\%$). Significantly higher risk for EPS (OR = 3.70; 95% CI, 2.37–5.77; $p<0.00001$; $I^2=0\%$). No significant difference in metabolic parameters, ECG (QTc), heart rate, and blood pressure.	Diagnoses: ASD (2 studies), SCZ (1), BP (manic or mixed) (1), BP (manic or mixed) with ADHD (1); short-term trials; no meta-regression analyses; mean daily-dose NR
Robb et al. (2011)	RBCT	6–17 Years, ASD	2 (PBO)	313	8 Weeks	Clinical AEs, weight, EPS measures (SAS, BARS, AIMS), metabolic parameters (Glu, LDL-CHL, HDL-CHL, TG)	Significantly higher weight gain (LOCF) with APZ compared with PBO (1.6 vs. 0.4 kg, $p<0.001$). Mixed results regarding EPS measures: significant difference between APZ and PBO on the mean change (LOCF) in SAS (0.1 vs. -0.4, $p=0.03$); significantly greater improvement in AIMS with APZ (-0.4 vs. 0, $p=0.005$); no difference in BARS (0 vs. 0.1, $p=0.106$). No significant differences in metabolic changes. Dose–response relationship with fatigue only ($p<0.05$).	Common AEs (APZ vs. PBO): sedation 20.8% vs. 4.0%), fatigue (16.5% vs. 2.0%), vomiting (13.7% vs. 6.9%), increased appetite (12.7% vs. 6.9%), somnolence (10.4% vs. 4.0%), tremor (9.9% vs. 0%); EPS-related AEs (APZ vs. PBO): overall, 20.8% versus 9.9%, tremor 9.0% versus 0%, drooling, 9.0% versus 0%, extrapyramidal disorder (≥2 EPS), 6.1% versus 0%, akathisia, 3.3% versus 8.9%; discontinuation rates due to EPS (APZ vs. PBO): overall, 4.2% versus 3.0%, tremor, 1.9% versus 0.0%, drooling, 1.9% versus 0%, extrapyramidal disorder, 1.4% versus 0%; discontinuation rates due to AEs (APZ vs. PBO): overall, 10.4% versus 6.9%, subjects 6–12 years, 10.8% versus 5.1%, subjects 13–17 years, 8.9% versus 13.6%; most AEs mild or moderate in intensity; serious AEs in 0.9% (1 case of presyncope and 1 case of aggression)

(*continued*)

Table 6. (Continued)

Authors (year)	*Studies included (type)*	*Age, indication*	N *studies (control group)*	N *patients*	*Duration*	*Safety/tolerability measures*	*Outcomes*	*Comments*
Cohen et al. (2012)	RBCT	≤18 Years, mental health disorders	10 arms (APZ); 93 arms (total)	671 (APZ); 4015 (total)	3–12 Weeks	Weight, EPS, somnolence/sedation, metabolic parameters (Glu, CHL, TG), PRL level	Significant weight gain with APZ compared with PBO: OR = 4.44 (95% CI, 2.0–8.88). Mean weight change from baseline with APZ: 0.89 kg (95% CI, 0.26–1.51 kg). Significantly increased risk of EPS with APZ compared with PBO: OR = 3.79 (95% CI, 2.17–6.17). Significantly increased risk of somnolence/sedation with APZ compared with PBO: OR = 6.07 (95% CI, 2.79–12.22). No significant difference in metabolic parameters (Glu, CHL, TG) with APZ compared with PBO.	Trend to an increase in Glu level with APZ compared with PBO, mean difference: 2.21 mg/dL (95% CI, -0.63 to 5.09 mg/dL); no meta-analysis performed with APZ regarding PRL level; diagnoses NR for APZ specifically; short-term trials; no meta-regression analyses; mean daily-dose NR
Almandil et al. (2013)	RBCT	≤18 Years, mental health disorders	4 (PBO)	848	6–8 Weeks	Weight	Significant weight gain with APZ compared with PBO, mean difference: 0.94 kg (95% CI, 0.65–1.24; $p < 0.00001$; $I^2 = 0\%$).	Diagnoses: ASD (2 studies), SCZ (1), BP (manic or mixed) with ADHD (1); short-term trials; no meta-regression analyses; mean daily-dose NR
Jensen et al. (2015)	RBCT, OLT	<18 Years, mental health disorders	10 RBCT (PBO); 4 OLT	814	15.0 ± 3.9 Weeks	ECG (QTc)	Significant decrease in QTc with APZ compared with PBO ($p = 0.007$). Mean change from baseline: -1.44 (95% CI, -2.63 to -0.26; $p = 0.017$).	Trend toward an inverse dose-dependency ($p = 0.059$); diagnoses: TS and other tic disorders (4 studies), ASD (3), BP (2), CD (2), SCZ (2), any diagnosis (1); mean daily dose: 14.0 ± 3.7 mg

95% CI, 95% confidence interval; ADHD, attention-deficit/hyperactivity disorder; AE, adverse effect; AIMS, Abnormal Involuntary Movement Scale; APZ, aripiprazole; ASD, autism spectrum disorder; BARS, Barnes Akathisia Rating Scale; BMI, body mass index; BP, bipolar disorder; CD, conduct disorder; CHL, cholesterol; ECG, electrocardiogram; EPS, extrapyramidal symptoms; Glu, glucose; HDL-CHL, high-density lipoprotein-CHL; LDL-CHL, low-density lipoprotein-CHL; LOCF, last observation carried forward; NR, not reported; OLT, open-label trial; OR, odds ratio; PBO, placebo; PRL, prolactin; QTc, corrected QT interval; RBCT, randomized blinded controlled trial; SAS, Simpson-Angus Scale; SCZ, schizophrenia; TG, triglycerides; TS, Tourette's syndrome.

Conclusion

In total, the following trends can be identified. First, aripiprazole is one of the most widely prescribed atypical antipsychotics, probably due to a well-established efficacy profile in two to four approved indications according to various countries and a safety profile that is somewhat different from other atypical antipsychotics (Cohen et al. 2012). Like other atypical antipsychotics, its use in children and adolescents is becoming commonplace and occurs in off-label indications. Second, compared with what is known about aripiprazole in adults, it appears that adverse effects are more important in children and adolescents, particularly weight gain, drowsiness, extrapyramidal effects, and metabolic effects, even though the latter may appear less important than with other atypical antipsychotics (Table 5).

Moreover, severe adverse effects often occur in polyprescription settings. Third, the fact that aripiprazole was marketed contemporaneously with the Pediatric Act has been very beneficial in terms of the number of studies available. These studies detail relatively well clinical (e.g., weight gain and extrapyramidal symptoms) and paraclinical (e.g., serum prolactin; serum cholesterol; and ECG) adverse events. This is not necessarily the case for older atypical antipsychotics, such as olanzapine. On the other hand, if the prescription of atypical antipsychotics and aripiprazole is regarded as straightforward by the physician or psychiatrist because of potentially overly positive representations, the counterpart is very poor postprescription monitoring. Consequently, even if there is no evidence of risk in this population, information to prescribers should be reinforced, particularly in terms of postprescription monitoring.

In terms of recommendations, it seems useful to limit the use of aripiprazole to the FDA-approved indications and make non-FDA prescriptions subject to specialist advice. Indeed, review of the literature highlights the need to propose aripiprazole treatment in children in certain indications where efficacy has been noted and where approval has not been obtained in some countries (e.g., Tourette's syndromeand behavioral disorders associated with autism and intellectual disability). It would also be useful to ask clinicians to reexamine polyprescriptions because it is in these contexts that the most serious adverse effects have been reported. In particular, prescribers should be informed of the need to monitor and track adverse events according to existing recommendations (Pringsheim et al. 2011b). Pharmacoepidemiology and pharmacovigilance studies should also be continued to clarify possible risks at the population level or rare side effects (e.g., suicide induction), bearing in mind that to date, there is no risk in terms of public health. Finally, given the high prevalence of off-label prescription, new evidence-based studies on these specific indications should be provided to ensure whether other indications than the FDA-approved ones are legitimate.

Clinical Significance

Aripiprazole has proven efficacy for several indications in children and adolescents, including schizophrenia, bipolar disorder, Tourette's syndrome, and behavioral impairments associated with autism and intellectual disability. However, its use requires clinical and paraclinical monitoring to assess the occurrence of adverse events that may challenge the benefit/risk ratio. In addition, off-label prescriptions should be limited as they appear to account for a significant proportion of aripiprazole use worldwide.

Disclosures

During the last 3 years, D.C. reported past consultation for or the receipt of honoraria from Otsuka, Shire, Lundbeck, Roche, and Janssen. N.C. and M.-L.M. have no financial relationship with any pharmaceutical company. Authors were independent in selecting the data and analyzing them, and writing the article.

Supplementary Material

Supplementary Data
Supplementary Table S1

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