Pediatr Drugs (2015) 17:125–140
DOI 10.1007/s40272-015-0119-3

REVIEW ARTICLE

Use of Quetiapine in Children and Adolescents

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Published online: 17 February 2015

Abstract The atypical antipsychotic quetiapine has been used in different psychotic and non-psychotic disorders in children and adolescents in randomized clinical trials, open-label studies and chart reviews. Most of these studies suggest that quetiapine may be a promising agent with a potential for use in young patients. The aim of this paper is to critically review available literature on quetiapine in the treatment of children and adolescents with a variety of psychiatric disorders, including psychotic disorders, bipolar disorders (manic and depressive episodes), conduct disorder, autism spectrum disorder, Tourette's syndrome and personality disorders. Furthermore, we report on possible neurochemical pathways involved during treatment with quetiapine, and discuss some issues that are clinically relevant in daily practice, such as titration strategies, safety and tolerability, and monitoring possible side effects. Controlled studies support the short-term efficacy for treating psychosis, mania, and aggression within certain diagnostic categories. However, although quetiapine seems well tolerated in various pediatric populations during acute and intermediate treatments, and hyper-prolactinemia and extra-pyramidal side effects are consistently low among studies, weight gain and alterations in lipid profile need to be closely monitored. Furthermore, the distal benefit/risk ratio during long-term treatment remains to be determined.

Key Points

Empirical evidence supports the efficacy of quetiapine in adolescents with schizophrenic spectrum disorders and bipolar mania.

Quetiapine appears to be well tolerated in the short term and medium term, but long-term safety has not been clearly determined.

Weight gain and metabolic effects, namely the lipid profile, should be closely monitored also in the short term.

1 Introduction

Over the past 20 years, the use of second-generation antipsychotics (SGAs) in the treatment of children and adolescents with a range of psychiatric conditions and symptoms, including psychosis, bipolar disorder, aggressive and disruptive behavior, autism spectrum disorder (ASD), and tic disorders, has markedly increased. This rapid rise reflects the expectation of greater safety and tolerability, compared with first-generation antipsychotics (FGAs), particularly with respect to extra-pyramidal symptoms (EPS), although information about head-to-head

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differences in efficacy and tolerability of antipsychotics remains scarce in children and adolescents [1]. Findings from real life indicate that SGAs are prevalently used in off-label indications, are prevalently the sole antipsychotic (less than 10 % are in association with other SGAs), and have a low rate (16 %) of switch to other SGAs during the first year of treatment [2].

Quetiapine is a low-affinity dopamine D_2 receptor antagonist, frequently used in clinical child and adolescent psychiatric practice [3]. It has been approved by the FDA for the treatment of schizophrenia and bipolar disorder for ages 13–17 years, but it has not been approved by the European Medicines Agency (EMA) for use below age 18 years. The pharmacokinetics of the quetiapine immediate-release (IR) formulation has been studied in both adults and youth, while less information is available on the quetiapine extended-release (XR) formulation in children and adolescents. Patients aged 10–17 years receiving quetiapine IR, compared with a parallel adult population, presented similar pharmacokinetic, safety, and tolerability profiles by dose escalation, suggesting that no dosage adjustment is required when treating patients of these ages [4]. An analysis of quetiapine IR pharmacokinetics in adolescents revealed that at the end of weeks 2 and 8, quetiapine disposition was linear over the dose range studied [5, 6]. The elimination half-life of the drug averaged 3.9 and 2.9 h and total body clearance averaged 3.5 and 3.0 L/h/kg after study weeks 2 and 8, respectively. Recent research suggests that children and adolescents are likely to achieve a similar exposure following administration of either the XR formulation once daily or the IR formulation twice daily at similar total daily doses [7]. The relative exposure following administration of the XR formulation in adults, 13- to 17-year-olds, and 10- to 12-year-olds followed a similar pattern to the IR formulation.

The aim of the present descriptive review is to summarize all relevant articles on quetiapine use in several clinical conditions and discuss some issues that are clinically relevant in daily practice, such as titration strategies, safety and tolerability, and monitoring possible side effects.

A systematic Medline/PubMed search of the papers published in English between 1999 and December 2014 was conducted, using as key words "quetiapine" and "children". The search was then repeated adding the most important psychiatric disorders [schizophrenia, bipolar disorder/mania, depression, anxiety, conduct disorder, autism spectrum disorder, personality disorder, tic disorder/Tourette's syndrome (TS)]. Only studies including patients younger than 18 years of age were considered for this review. Table 1 provides a summary of the studies identified.

2 Early-Onset Schizophrenia

Three open-label studies, whose duration ranged between 3 and 12 weeks, firstly suggested a possible role of quetiapine at doses up to 800 mg in the treatment of early-onset schizophrenia (EOS) [5, 8, 9], but data relied on few patients and were uncontrolled.

More recently, a large randomized placebo-controlled study [10], tested the efficacy and safety of quetiapine monotherapy in 220 adolescents, aged 13–17 years, with schizophrenia and a Positive and Negative Syndrome Scale (PANSS) total score of $\geq$60. Patients were randomized to 6 weeks of quetiapine (400 or 800 mg/day) or placebo treatment. The primary efficacy measure was change in PANSS total score from baseline to day 42. Safety endpoints included adverse events and assessments of clinical chemistry values, suicidality, and EPS. The mean change in PANSS total score from baseline to endpoint was −27.31 with quetiapine 400 mg/day, −28.44 with quetiapine 800 mg/day, and −19.15 with placebo ($p = 0.043$ and 0.009 for quetiapine 400 and 800 mg/day, respectively). Several secondary efficacy outcomes, including Clinical Global Impression-Improvement (CGI-I) score, were consistent with the primary outcome measure in demonstrating significantly greater improvement in quetiapine groups than in the placebo group. Mean changes in body weight at day 42 were 2.2 and 1.8 kg for quetiapine 400 and 800 mg/day, respectively, and −0.4 kg for placebo. Mean changes in clinical chemistry, including total cholesterol and triglycerides, were numerically greater in the quetiapine groups than in the placebo group. Adverse events associated with quetiapine were mostly mild to moderate, and consistent with previous studies including adult schizophrenic patients.

Few comparative studies of SGAs have explored efficacy and safety in psychotic disorders in children and adolescents. Jensen et al. [11] conducted a pilot study to demonstrate the feasibility of the treatment and measurement protocols, to plan the design of a subsequent randomized controlled trial. Thirty children and adolescents (10–18 years) fitting diagnostic and statistical manual of mental disorders-fourth edition (DSM-IV) criteria for a schizophrenia-spectrum disorder (schizophrenia, schizoaffective, schizophreniform, psychotic disorder not otherwise specified) were randomized to receive 12 weeks of open-label, flexibly dosed treatment with either risperidone (3.4 ± 1.5 mg), olanzapine (14.0 ± 4.6 mg), or quetiapine (611 ± 253.4 mg). Twenty-one (70 %) of 30 subjects completed the study, without statistically significant difference in the change in PANSS total scores. However, the authors highlighted the possibility of a large differential treatment effect favoring risperidone relative to quetiapine (risperidone vs. quetiapine, $d = 1.10$ [95 % confidence interval (CI) 0.09–2.01]), suggested by the

Table 1 Summary of the reviewed studies (chronological order): focus on efficacy

References	No of patients	Methodology and duration	Daily doses	Measures	Main results
EOS/psychotic spectrum					
McConville et al. [5]	10 adolescents	Open-label, 23 days	Up to 400 mg	BPRS, CGI-S, MSANS	Well tolerated and effective
Shaw et al. [8]	15 adolescents	Open-label, 8 weeks	Range 300–800 mg (mean 467)	BPRS, CGI-S, PANSS, YMRS	Effective with a favorable side effect profile
Schimmelmann et al. [9]	56 adolescents	Open-label, 13 weeks	Range 200–800 mg	PANSS	Significant reduction on PANSS scores (total and positive)
Findling et al. [10]	220 adolescents	Randomized, double-blind, placebo-controlled, 6 weeks	400 or 800 mg or placebo	PANSS	Significant improvements in PANSS total score at 400 and 800 mg/day, generally well tolerated
Jensen et al. [11]	30 adolescents	Randomized comparative trial (risperidone, olanzapine, quetiapine), 12 weeks	Mean doses: risperidone 3.4 mg, olanzapine 14 mg, quetiapine 611 mg	PANSS	No overall statistically significant differences between treatments
Arango et al. [12]	50 adolescents	Randomized comparative trial (olanzapine, quetiapine), 6 months	Naturalistically determined	PANSS, CGI-S, C-GAS, HDRS-21, YMRS, SDQ	Significant reduction in all clinical scales in both groups
Castro-Fornieles et al. [13]	110 youth	Naturalistic longitudinal, 6 months (risperidone, olanzapine, quetiapine)	Naturalistically determined	PANSS, CGI-S, DAS, GAF	Similar clinical improvements among drugs
Bipolar spectrum (bipolar I, II, NOS, manic/hypomanic/mixed phases)					
Pathak et al. [16]	277 youth	Randomized, double-blind, placebo-controlled 3 weeks	400 or 600 mg or placebo	YMRS, CDRS-R, CGI-BP, C-GAS, MOAS	Significantly more effective than placebo at both doses in reducing manic symptoms; generally well tolerated
DelBello et al. [17]	30 adolescents	Randomized, double-blind, comparative trial (valproic acid + placebo, valproic acid + quetiapine), 6 weeks	Valproic acid blood level 80–130 mg/dL, quetiapine up to 150 mg	YMRS, PANSS-P, CDRS, C-GAS	Valproic acid + quetiapine significantly better valproic acid + placebo in reducing YMRS score
DelBello et al. [18]	50 adolescents	Randomized comparative trial (valproic acid, quetiapine), 28 days	Valproic acid blood level 80–120 mg/dL, quetiapine 400–600 mg	YMRS	Similar clinical improvement between drugs, but faster improvement of manic symptoms in quetiapine group
Joshi et al. [20]	49 children (30 preschool age, 19 school age)	Prospective, open-label trial, 8 weeks	Mean doses: preschool age 175.8 mg, school age 248.7 mg	YMRS, CDRS-R, HAM-A, ADHD-RS, BPRS, CGI-S, CGI-I	Improvements in all outcome measures a within 1 week of treatment and at endpoint
Scheffer et al. [21]	75 youth	Retrospective analysis of data collected prospectively	Range 400–1,000 mg, mean dose 750 mg	YMRS, CGI-I	Rapid load dosing (100 mg at day 1 and 400 mg at day 5 and then further increased based on clinical response) effective and well tolerated

Table 1 continued

References	No of patients	Methodology and duration	Daily doses	Measures	Main results
Bipolar depression					
DelBello et al. [22]	32 adolescents	Randomized, double-blind, placebo-controlled trial, 8 weeks	300 mg (possibly up to 600 mg)	CDRS-R, YMRS, HAM-A, CGI-BP	Quetiapine no more effective than placebo in improving symptoms of depression
Findling et al. [23]*	193 adolescents	Randomized, double-blind, placebo-controlled trial, 8 weeks	Range 150–300 mg, mean dose 204.9 mg	CDRS-R, CGI-BP	No significant differences between quetiapine and placebo for primary (depressive symptoms) and secondary outcomes
Bipolar + disruptive behavior disorders					
Barzman et al. [24]	33 adolescents	Randomized, double-blind, comparative trial (divalproex and quetiapine), 28 days	Divalproex blood level 80–120 μg/mL; quetiapine 400–600 mg	PANSS EC	Quetiapine and divalproex equally effective in reducing impulsivity and reactive aggression
Masi et al. [25]	40 adolescents	Open-label study, 3 months	Range 100–600 mg	CGI-I, CGI-S, C-GAS	Global improvements in 55 % of patients; reduction of suicidality; comorbidity with ADHD associated with poorer response
Disruptive behavior disorders (ADHD, oppositional defiant disorder, conduct disorder)					
Connor et al. [26]	19 adolescents	Randomized, double-blind, placebo-controlled study, 5 weeks	Range 200–600 mg	CGI-I, CGI-S, OAS, CPRS-CP	Significant global clinical improvement; no improvement in OAS and CPRS-CP
Findling et al. [6]	17 adolescents	Open-label study, 8 weeks	Mean dose at endpoint 4.4 mg/kg/day	RAAPPS, NCBRF, CPRS-48	Global improvement in aggression and conduct problems
Findling et al. [27]	9 adolescents	Open-label study, 26 weeks (continuation of previous study)	Range 75–350 mg	RAAPPS, NCBRF, CPRS-48, CGI-S, C-GAS	Persistence of the improvement evidenced in the previous report
Kronenberger et al. [28]	30 adolescents	Open-label study, 9 weeks	OROS MPH 54 mg, quetiapine 50–300 mg	RAAPPS, CGI-S, ADHD-RS,	Clinical global improvement in patients non-responders to MPH only; quetiapine + MPH reduced ADHD symptoms and aggression
Autism spectrum disorders					
Findling et al. [29]	9 adolescents	Open-label study, 12 weeks	Range 300–750 mg	CGI-I	Only two patients improved
Hardan et al. [30]	10 adolescents	Retrospective study, 22 ± 10 weeks	Mean dose 477 ± 212 mg	CPS, CGI-I	Improvement in conduct, inattention, and hyperactivity
Golubchik et al. [31]	11 adolescents	Open-label study, 8 weeks	Range 50–150 mg	CGI-S, OAS, CSHQ	Improvement in aggressive behavior and sleep disturbance; no improvement in autistic behavior

Table 1 continued

References	No of patients	Methodology and duration	Daily doses	Measures	Main results
Borderline personality disorder					
Podobnik et al. [32]	22 adolescents	Open-label, prospective study, 24 weeks	SSRI + quetiapine 75–600 mg	C-GAS, MOAS, KADS-6	Improvement in aggressive behavior, intentional self-injury, chronic anxiety and affective instability, depression, suicidal tendencies and irritability
Tic disorder and Tourette's syndrome					
Mukaddes et al. [33]	12 adolescents	Open-label study, 8 weeks	Mean dose 72.9 ± 22.5 mg	YGTSS	Significant reduction in tic scores
Copur et al. [34]	20 adolescents	Retrospective study, 22 ± 10 weeks	Mean dose 175.0 ± 116.8 mg	YGTSS	Significant reduction in tic scores

ADHD-RS Attention Deficit Hyperactivity Disorder Rating Scale, *BPRS* Brief Psychiatric Rating Scale, *CDRS-R* Children's Depression Rating Scale-Revised, *C-GAS* Children's Global Assessment Scale, *CGI-BP* Clinical Global Impression-Bipolar, *CGI-I* Clinical Global Impression-Improvement, *CGI-S* Clinical Global Impression-Severity, *CPRS-48* Conners' Parent Rating Scale 48 items, *CPRS-CP* Conners' Parent Rating Scale conduct problems subscale, *CPS* Conners' Parent Scale, *CSHQ* Child Sleep Habits Questionnaire, *DAS* Disability Assessment Schedule, *EOS* Early-Onset Schizophrenia, *GAF* Global Assessment of Function, *HAM-A* Hamilton Anxiety Rating Scale, *HDRS-21* Hamilton Depression Rating Scale, *KADS-6* Kutcher Adolescent Depression Scale 6 items, *MOAS* Modified Overt Aggression Scale, *MSANS* Modified Scale for the Assessment of Negative Symptoms, *NCBRF* Nisonger Child Behavior Rating Form, *NOS* Not Otherwise Specified, *OAS* Overt Aggression Scale, *OROS MPH* Oral Release Osmotic System methylphenidate, *PANSS* Positive and Negative Syndrome Scale, *PANSS EC* Positive and Negative Syndrome Scale Excited Component, *PANSS-P* Positive and Negative Syndrome Scale-Positive, *RAAPPS* Rating of Aggression Against People and/or Property Scale, *SDQ* Strength and Difficulties Questionnaire, *SSRI* Selective Serotonin Reuptake Inhibitors, *YGTSS* Yale Global Tic Severity Scale, *YMRS* Young Mania Rating Scale

* Quetiapine extended release

point estimate. They proposed further research with larger samples and only two treatment arms aiming to explore clinically significant differential treatment effect between risperidone and quetiapine.

Arango et al. [12] compared efficacy, safety, and tolerability of quetiapine and olanzapine in 50 adolescents aged 16 ± 1.2 years, with first episode psychosis. The participants were randomized to quetiapine or olanzapine in a 6-month open-label study, and 32 patients, 16 for each treatment group, completed the trial. At the end of the study, a significant reduction in all clinical scales was recorded in both treatment groups, with the exception of the negative scale of the PANSS for olanzapine, and the general psychopathology scale of the PANSS for quetiapine. The only difference between treatment arms on the clinical scales was observed on the patients' Strength and Difficulties Questionnaire (SDQ) scale, with greater improvement for olanzapine. However, patients on olanzapine increased much more their body mass index (BMI), gaining 15.5 kg versus 5.5 kg for patients on quetiapine.

The efficacy of pharmacotherapy with antipsychotics, including quetiapine, was assessed in the Child and Adolescent First-Episode Psychosis Study (CAFEPS), a naturalistic longitudinal study of early-onset first psychotic episode [13]. Data from the first year of study from six different centers compared the most frequently used agents after 6 months treatment in 110 patients (9–17 years), 38.2 % with psychotic disorder not otherwise specified, 39.1 % with schizophrenia-type disorder, 11.8 % with depressive disorder with psychotic symptoms, and 10.9 % with bipolar disorder, manic episode with psychotic symptoms. Efficacy and safety measures were the PANSS, CGI, Disability Assessment Schedule (DAS), and Global Assessment of Function (GAF) scales, administered at baseline and at 6 months, and the Udvalg for Kliniske Undersøgelser (UKU) at 6 months. The most frequently used antipsychotic agents were risperidone ($n = 50$), quetiapine ($n = 18$), and olanzapine ($n = 16$). Patients who received olanzapine or quetiapine had more negative and general symptoms at baseline. No significant differences were found in the reductions on any scale in patients treated with risperidone, quetiapine, or olanzapine for 6 months. Weight increase was greater with olanzapine than with risperidone ($p = 0.020$) or quetiapine ($p = 0.040$). More neurological side effects were reported with risperidone than with olanzapine ($p = 0.022$). All side effects were mild or moderate.

Another comparative study assessed the efficacy and tolerability of quetiapine in adolescents with first onset psychosis, using risperidone as a comparator [14]. Twenty-two patients were randomized to receive quetiapine (up to 800 mg/day) or risperidone (up to 6 mg/day) for 6 weeks. No statistical differences in outcome symptom ratings emerged in terms of efficacy or tolerability between the two drugs, although some clinically significant differences seem to favor the efficacy of risperidone over quetiapine. Patients taking quetiapine showed less clinical improvement in total positive and negative symptoms, clinical global severity and depression at 6 weeks, compared with those taking risperidone. Interestingly, in this study both treatments were associated with weight gain and sedation, but more patients on quetiapine experienced over 10 % weight gain. Risperidone was significantly more likely to be associated with elevation in serum prolactin levels, EPS and/or need for anticholinergic medication.

Robles et al. [15] explored the effects of quetiapine on some cognitive measures in patients with early-onset psychosis after 6-months treatment. Fifty adolescents were randomized to receive quetiapine ($n = 24$) or olanzapine ($n = 26$) in a single-blind study. According to a neuropsychological battery administered at baseline and after 6-months' treatment, in the 32 patients (quetiapine, $n = 16$; olanzapine, $n = 16$) who completed at least 6-months of treatment, no changes were observed in cognitive performances with the assigned medications, there was no evidence of any differential efficacy of olanzapine or quetiapine on cognitive improvement, and neither group showed statistically significant gains, although some trends toward cognitive improvement were observed for the olanzapine group.

In summary, studies have shown that quetiapine 200–800 mg/day improves psychotic symptoms in patients aged 11–17 years with EOS, and presents acceptable safety and tolerability, with no serious unexpected events reported. Compared with a parallel adult population, there were similar pharmacokinetic, safety and tolerability profiles by dose escalation, suggesting that no dosage adjustment is required when treating patients of these ages. Some comparative studies including risperidone and olanzapine suggest that quetiapine may be less effective, but with less severe side effects.

3 Bipolar Disorder (Mania/Hypomania/Bipolar Spectrum)

The only randomized, placebo-controlled trial in bipolar children and adolescents is a large study [16] exploring the efficacy and safety of quetiapine monotherapy in 277 bipolar patients aged 10–17 years, with a manic episode and Young Mania Rating Scale (YMRS) total score of ≥20, randomized to 3 weeks of quetiapine (400 or 600 mg/day) or placebo. The change in YMRS total score from baseline to endpoint was −14.25, −15.60, and −9.04 for quetiapine 400 mg/day, quetiapine 600 mg/day, and placebo, respectively ($p < 0.001$, each quetiapine dose vs.

placebo). Significant improvement in YMRS score versus placebo first appeared at day 4 ($p = 0.015$) with quetiapine 400 mg/day, and day 7 ($p < 0.001$) with quetiapine 600 mg/day. Mean changes in body weight at day 21 were 1.7 kg for both quetiapine doses and 0.4 kg for placebo. Larger mean increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides were observed more frequently with quetiapine than placebo, broadly consistent with the known profile of quetiapine in adults with bipolar disorder.

DelBello et al. [17] explored the efficacy and tolerability of quetiapine in combination with divalproex in bipolar adolescents with acute mania in a randomized, double-blind, placebo-controlled study. Quetiapine plus divalproex were compared with divalproex alone in 30 manic or mixed bipolar I adolescents (12–18 years), who firstly received divalproex at a dose of 20 mg/kg, and were then randomized to 6 weeks of combination therapy with quetiapine (450 mg/day) ($n = 15$) or placebo ($n = 15$). According to a change from baseline to endpoint in YMRS score and YMRS response rate, the divalproex + quetiapine treatment was associated with a statistically significantly greater improvement in YMRS score from baseline to endpoint ($p = 0.03$), as well as a significantly greater YMRS response rate (87 vs. 53 %, Fisher's exact test, $p = 0.05$), compared to the divalproex alone treatment. Group differences in safety measures were not found, but mild to moderate sedation was significantly more common in the divalproex + quetiapine group.

In a subsequent study, DelBello et al. [18] further explored comparative efficacy of quetiapine and divalproex in 50 bipolar patients aged 12–18 years, with manic or mixed episode, randomized to quetiapine (400–600 mg/day) or divalproex (serum level 80–120 μg/mL) for 28 days in a double-blind study. According to a change in YMRS score, no statistically significant group differences were evident across the 28 days of the study ($p = 0.3$), but improvement in YMRS scores occurred more rapidly in the quetiapine than in the divalproex group for both the last-observation carried forward ($p = 0.01$) and observed data ($p = 0.03$). Response and remission rates were significantly greater in the quetiapine than in the divalproex group ($p < 0.03$). Adverse events did not differ significantly between groups.

Finally, DelBello et al. [19] have explored the efficacy and tolerability of quetiapine in the treatment of adolescents at high risk for developing bipolar I disorder. Twenty adolescents aged 12–18 years, with mood symptoms not fitting diagnostic and statistical manual of mental disorders-fourth edition, text revised (DSM-IV-TR) diagnostic criteria for bipolar I disorder (11 with bipolar disorder not otherwise specified (BD-NOS), three with bipolar disorder type II (BD II), three with dysthymia, two with cyclothymia, and one with major depressive disorder) and with at least one first-degree relative with bipolar I disorder, prospectively received quetiapine in a single-blind, 12-week study. These patients presented a YMRS score of ≥12 or a Children's Depression Rating Scale-Revised (CDRS-R) score of ≥28 at baseline. According to an endpoint CGI-I scale score of 1 or 2 ("much" or "very much" improved), 87 % of patients were responders at week 12 (endpoint dose = 460 ± 88 mg/day). YMRS scores decreased from 18.1 ± 5.5 at baseline to 8.7 ± 7.9 at endpoint ($p < 0.0001$), and CDRS-R scores decreased from 38.2 ± 9.8 to 27.7 ± 9.3 ($p = 0.0003$). Somnolence, headache, musculoskeletal pain, and dyspepsia were the most frequently reported adverse events, but no subjects discontinued because of adverse events.

An open-label study [20] has addressed the important issue of efficacy and safety of quetiapine monotherapy in very young bipolar children in the preschool and school-age years. The study was an 8-week, prospective, open-label trial including 30 preschool children (age 4–6 years) and 19 school-age children (age 6–15 years) with bipolar spectrum disorders. Baseline YMRS at entry was 34.5 ± 5.5 in preschoolers and 30 ± 6.5 in school-age children. Twenty preschool and 14 school-age patients completed the trial. Quetiapine was titrated to a mean endpoint dose of 175.8 ± 63.8 mg/day in preschool and 248.7 ± 153.1 mg/day in school-age children. At endpoint, treatment was associated with similar and statistically significant improvement in mean YMRS scores in preschool (−14.5 ± 11.5, $p < 0.001$) and school-age (−13 ± 9.8, $p < 0.001$) children. Treatment-limiting adverse events were reported in 3/30 preschool and 1/19 school-age children, namely weight gain (+3.1 ± 1.8 and +7.4 ± 7.7 lb, respectively, $p < 0.001$).

Scheffer et al. [21] have explored the effects of a rapid loading of quetiapine in 75 bipolar children and adolescents (6–16 years) with acute manic or hypomanic episode. The medication started at 100 mg/day, increased to 400 mg/day by day 5, with subsequent dose adjustments according to the clinical picture. Based on a clinical response defined as a ≥50 % reduction in baseline scores on the YMRS, and CGI-I scores of 1 (very much improved) or 2 (much improved) as secondary measures of response, and remission defined as a YMRS score of ≤12, 94 % of the sample had a CGI-I score of ≤2 at 8 weeks and 70 % were in remission at 6 months. Sedation was reported by 50 % of subjects during the first week, but this rate dropped to 5.6 % at 6 months. Blood pressure, weight change, somnolence, EPS, and akathisia did not occur during the study.

According to these studies, quetiapine monotherapy (400 or 600 mg/day) is better than placebo and at least as effective as divalproex, with a faster improvement of manic symptoms in favor of quetiapine. Furthermore, some data suggest that quetiapine may be used even in younger

bipolar patients in preschool and school years, and in adolescents with mood disorders and high risk for bipolar disorder based on the YMRS score, even with a rapid loading. Tolerability was similar to divalproex, even though lipid profile and weight deserve close attention.

4 Bipolar Depression

Two double-blind, placebo-controlled studies have addressed the complex issue of the pharmacological treatment of adolescent patients with bipolar depression. In the first study, DelBello et al. [22] compared quetiapine and placebo during depressive episodes in 32 adolescents with bipolar I disorder. The patients were randomized to quetiapine (300–600 mg/day) or placebo for 8 weeks. According to the primary efficacy measure CDRS-R from baseline to endpoint, there was no statistically significant treatment group difference ($p = 0.89$, effect size $= -0.05$, 95 % CI -0.77 to 0.68). CDRS-R average rate of change over the 8-week study period did not differ between groups ($p = 0.95$). Furthermore, there were no statistically significant differences in response (placebo 67 % vs. quetiapine 71 %) or remission (placebo 40 % vs. quetiapine 35 %) rates. Also secondary efficacy measures, Hamilton Anxiety Rating Scale (HAM-A), YMRS, and CGI-Bipolar Version Severity (CGI-BP-S) scores were not statistically different ($p > 0.7$) between treatment groups. Dizziness was more commonly reported in the quetiapine group (41 %) than in the placebo group (7 %) (Fisher's exact test, $p = 0.04$). According to these results, quetiapine monotherapy was no more effective than placebo, even though the high placebo response rate may have strongly affected the interpretation of the results.

More recently, Findling et al. [23] assessed the efficacy of quetiapine XR (dose range 150–300 mg/day) in 193 pediatric outpatients aged 10–17 years with bipolar I or II disorder (current or most recent episode depressed) in a large, multicenter, double-blind, randomized, placebo-controlled study. The participants were treated for up to 8 weeks. In the 144 patients who completed the study [$n = 70$ (75.3 %) in the quetiapine XR group; $n = 74$ (74.0 %) in the placebo group], according to the primary study outcome, the CDRS-R total score, mean changes at week 8 were -29.6 [standard error (SE 1.65)] with quetiapine XR and -27.3 (SE 1.60) with placebo. The rates of response and remission did not differ significantly between treatment groups. The safety profile of quetiapine XR was consistent with previous adult studies using quetiapine XR and pediatric studies of quetiapine IR, including elevations in triglycerides (9.3 % quetiapine XR; 1.4 % placebo group) and thyroid stimulating hormone (TSH) (4.7 % quetiapine XR; 0 % placebo group).

These two studies do not support the efficacy of quetiapine monotherapy in children and adolescents with bipolar depression, although the high placebo response may have affected the results. Safety data are consistent with studies with other psychiatric disorders, with the important inclusion of the increase in TSH.

5 Bipolar Disorder and Comorbid Disruptive Behavior Disorders

There are no placebo-controlled studies exploring the efficacy of quetiapine in bipolar patients with comorbid disruptive behavior disorders (DBD). Barzman et al. [24] compared the efficacy and tolerability of quetiapine and divalproex to improve impulsivity and reactive aggression in adolescents with co-occurring bipolar disorder and DBD. Inclusion criterion was a current diagnosis of bipolar I disorder, manic or mixed episode, and a lifetime and/or current diagnosis of DBD that is a conduct disorder (CD) or oppositional defiant disorder. Furthermore, patients presented a score of ≥ 14 on the PANSS Excited Component (EC) and ≥ 4 on at least one of the PANSS EC items. Thirty-three (92 %) of the 36 subjects with bipolar disorder and DBD met the PANSS EC inclusion criteria, and they were randomized to quetiapine (400–600 mg/day) or divalproex (serum level 80–120 μg/mL) for 28 days in a double-blinded study. According to a change in PANSS EC score over the study period, a statistically significant within-treatment-group effect for divalproex (from 20.6 to 13.3, $p < 0.0001$) and quetiapine (from 18.8 to 10.8, $p < 0.0001$) was reported, without statistically significant treatment group differences ($p = 0.7$, $d = 0.14$). Furthermore, there was no significant difference in the rate of improvement in the PANSS EC scores between the two treatment groups.

A consecutive series of 40 adolescents with bipolar disorder comorbid with CD (24 males, age range 12–18 years, mean age 14.9 ± 2.0 years) were enrolled to assess the efficacy of quetiapine monotherapy in an open-label study (mean final dose 258 ± 124 mg/day, range 100–600 mg/day) [25]. According to the response criteria at the endpoint (3 months) [CGI-I 1 or 2, CGI-Severity (CGI-S) 3 or less and improvement of at least 30 % Children's Global Assessment Scale (C-GAS) during 3 consecutive months], 22 patients (55 %) were responders. Both CGI-S and C-GAS significantly improved ($p < 0.0001$). Of note, nine out of the 16 patients with suicidality (56.3 %) improved this severe symptom during the follow-up. An attention deficit hyperactivity disorder (ADHD) comorbidity was associated with a worse response rate. Eight patients (20 %) experienced moderate to severe sedation and eight (20 %) increased appetite and weight gain.

Thus, according to these non-controlled studies, quetiapine may be useful as monotherapy and as similarly effective as divalproex for the treatment of impulsivity and reactive aggression in adolescents with bipolar and DBD.

6 Conduct Disorder

The only randomized, double-blind, placebo-controlled study exploring the efficacy of quetiapine in youth with CD is a small pilot study with two parallel arms, including nine youths who received quetiapine and ten youths who receive placebo [26]. The primary outcome measures were the clinician-assessed CGI-S and CGI-I scales. Secondary outcome measures included parent-assessed quality of life, the Overt Aggression Scale (OAS), and the conduct problems subscale of the Conners' Parent Rating Scale (CPRS-CP). The final mean dose of quetiapine was 294 ± 78 mg/day (range 200–600 mg/day). Quetiapine was superior to placebo on all the clinician-assessed measures and on the parent-assessed quality-of-life rating scale, while no differences were found on the parent-completed OAS and CPRS-CP. No EPS occurred in patients receiving active drug, but one patient randomized to quetiapine developed akathisia, requiring medication discontinuation.

An open-label study explored the effectiveness and pharmacokinetics of quetiapine in aggressive children with CD in an 8-week trial, including 17 patients aged 6–12 years (16 boys, mean age 8.9 years) [6]. Outcome measures included the Rating of Aggression Against People and/or Property Scale (RAAPPS), Nisonger Child Behavior Rating Form (NCBRF), and the 48-item Conners' Parent Rating Scale (CPRS-48). The mean dose at week 8 was 4.4 ± 1.1 mg/kg. Significant decreases in the baseline scores of the RAAPPS and several subscales of the NCBRF and the CPRS were found by the end of the study ($p < 0.05$). No patient discontinued because of an adverse event. No patient experienced EPS side effects.

A study from the same research group explored the persistence of efficacy of quetiapine in the 18-week follow-up of the abovementioned acute trial, including nine aggressive males aged 6–12 years (mean 8.9 ± 1.2 years), who had participated in the previous 8-week, open-label trial [27]. Psychometric measures included the RAAPPS, the NCBRF, the CPRS-48, the CGI-S, and the C-GAS. At a median dose at the end of the study of 150 mg/day (range 75–350 mg/day), the mean psychometric scores did not change substantially from baseline (corresponding to the end of the 8-week trial), supporting a persistent efficacy of quetiapine treatment. No patient discontinued treatment because of an adverse event.

Kronenberger et al. [28] investigated the safety and efficacy of add-on quetiapine to ongoing oral release osmotic system methylphenidate (OROS MPH) in the treatment of adolescents aged 12–16 years with ADHD and co-occurring severe aggression poorly responsive to MPH monotherapy. Participants openly received for 3 weeks OROS MPH monotherapy titrated to 54 mg/day, followed by 9 weeks of combination quetiapine–MPH in the 24 out of 30 participants who failed to meet criteria for significant improvement of aggression with MPH alone. Investigator and parent ratings of ADHD symptoms, aggression, and global functioning improved significantly during both MPH monotherapy treatment and during combined MPH–quetiapine treatment. At the conclusion of combined treatment, 42 % of the sample met all criteria for clinically significant improvement and 79 % showed minimal aggression. Mild and transient sedation was reported by about half the cases. Weight loss (0.9 kg) during MPH treatment was offset by weight gain (1.2 kg) during combination treatment.

These data, even based on a small controlled study and few open studies, suggest that quetiapine may be a possible treatment option in aggressive youth with CD, with a good stability over time after a good response to an acute treatment. Furthermore, quetiapine may be a well-tolerated adjunctive option in aggressive children with ADHD responding poorly to MPH alone.

7 Autism Spectrum Disorder

ASD constitutes a broad diagnostic category for which SGAs are frequently prescribed off-label, while the FDA approved risperidone and aripiprazole for the treatment of irritability associated with autism in 2006 and 2009, respectively.

Only a few open studies with small sample sizes have explored possible efficacy of quetiapine in aggression and irritability associated with ASD. A small study evaluated the effectiveness of quetiapine in nine adolescents aged 10–17 years with ASD in a 12-week, open-label study [29]. Quetiapine was gradually titrated up to a daily dose of 300 mg, with possible further increases to a maximum daily dose of 750 mg/day. According to the primary outcome measure, the CGI-I, only two patients were "much" or "very much" improved, and only these same two patients continued quetiapine after the end of the study, according to the parents' will.

These findings are consistent with a previous retrospective study including ten consecutive outpatients (12.0 ± 5.1 years) receiving quetiapine (477 ± 212 mg/day) for a mean of 22.0 ± 10.1 weeks [30]. Six of these patients were considered responders on the basis of impressions from chart review and Conners' Parent Rating Scale (CPRS). Conduct, inattention, and hyperactivity subscales of the CPRS presented the greatest improvements. Quetiapine was well

tolerated, mild sedation being the most common side effect, and no patient required treatment termination.

An 8-week open-label study included 11 adolescents (eight boys, 13–17 years) [31]. The severity of the clinical picture was assessed using the CGI-S, OAS, and Child Sleep Habits Questionnaire (CSHQ). Non-significant changes were obtained in autistic behavior (CGI-S 4.0 ± 0.6 vs. CGI-S after 3.1 ± 1.1, $p = 0.08$), while aggressive behavior improved significantly (OAS 2.1 ± 0.94 vs. 1.3 ± 0.64, respectively, $p = 0.028$). Also sleep disturbances improved significantly (CSHQ 49.0 ± 12 vs. 44.1 ± 9.6, $p = 0.014$).

These few findings do not support a strong efficacy of quetiapine in ASD, compared with other available pharmacological treatments (risperidone, aripiprazole).

8 Borderline Personality Disorder

A small open-label, prospective study explored the efficacy of quetiapine in children and adolescents with borderline personality disorder (BPD), refractory to previous treatment with selective serotonin reuptake inhibitors (SSRIs) (fluvoxamine, sertraline, or fluoxetine), who had pronounced symptoms of depression, aggression, irritability, and suicidal tendencies [32]. The open trial included 11 male and 11 female patients 9–17 years old (mean 15.4 ± 1.7); diagnosis was categorized as developing BPD, according to DSM-IV criteria and the Revised Diagnostic Interview for Borderline Patients (DIB-R). Quetiapine (75–600 mg/day, mean 390 ± 153.3 mg/day) was used as an add-on therapy to various SSRIs for 24 weeks. The treatment increased ($p < 0.001$) the total C-GAS scores and significantly decreased total Modified Overt Aggression Scale (MOAS) total score and scores in MOAS aggression, irritability and suicidality subscales ($p < 0.001$) and six-item Kutcher Adolescent Depression Scale (KADS-6) ($p < 0.001$). The clinical improvement remained stable over 24 weeks of study. Transient somnolence, dry mouth, and fatigue were evident in some patients during the first 2 weeks of the trial, but resolved spontaneously; no other clinical side effects were recorded.

Given the paucity of data supporting pharmacological treatment in adolescents with BPD, quetiapine may be a possible option, with its good tolerability profile compared with other antipsychotic agents (namely weigh gain and sedation, which may increase the poor compliance of these complex patients).

9 Tic Disorders and Tourette's Syndrome

Only small open studies tested the efficacy of quetiapine in children and adolescents with tic disorders or TS. A first study [33] was an 8-week, open-label trial that included 12 subjects (mean age 11.4 ± 2.4 years). Mean dose of quetiapine at the end of the study was 72.9 ± 22.5 mg/day. According to the primary outcome measure, the Yale Global Tic Severity Scale (YGTSS), a statistically significant improvement in tic scores was found, ranging from 30 to 100 %.

Another retrospective study included 20 patients aged 8–18 years [34]. The main outcome measure was the YGTSS score. Quetiapine was started at 25 mg/day, and the mean final dose was 114.6 ± 51.6 mg/day and 175.0 ± 116.8 mg/day at the fourth and eighth weeks of treatment, respectively. The YGTSS score significantly improved at 4 and 8 weeks ($p < 0.003$), without abnormalities in routine laboratory parameters and serum prolactin level, but with mild but significant increases in BMI at 4 and 8 weeks compared with baseline. Neither biochemical, electroencephalogram (EEG) and electrocardiogram (ECG) changes, nor relevant neurological or autonomic symptoms between the baseline and the end of study were found in the follow-up [35].

Although TS treatment is often unsatisfactory, as most of the effective drugs are associated with severe side effects, and spontaneous waxing and waning of symptoms limit the strength of the conclusions on treatment efficacy, available evidence supports a greater efficacy of other SGAs, particularly risperidone [36] and aripiprazole [37].

10 Possible Neurochemical Pathways Involved During Treatment with Quetiapine

Some studies have explored possible neurochemical pathways involved in the therapeutic effect of quetiapine in bipolar youth. It has been hypothesized that concentrations of *N*-acetylaspartate (NAA) may be a putative measure of neuronal integrity and metabolism in the central nervous system (CNS), and that therapeutic mechanisms may be reflected in changes in NAA concentrations in the prefrontal cortex. Chang et al. [38] examined the effects of quetiapine monotherapy on these putative neurochemical systems and their potential role as predictors of response in 26 adolescents (nine boys, 15.6 years) with bipolar depression participating in an 8-week placebo-controlled trial. Subjects were scanned at baseline and after 8 weeks with proton magnetic resonance spectroscopy (1H-MRS) in the right and left dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC), to calculate absolute concentrations of NAA and myo-inositol (mI). Of these subjects, five out of 16 subjects receiving quetiapine and five out of ten receiving placebo were responders (50 % decrease in CDRS score). There were no differences in NAA concentration changes between the quetiapine and placebo groups. Regarding the

NAA levels, there were no significant differences in the changes in ACC and DLPFC between quetiapine and placebo groups. Although baseline ACC mI did not predict responder status, responders had significantly lower post-treatment ACC mI values than non-responders ($p = 0.004$). In summary, only post-treatment, but not baseline ACC mI levels were associated with response to quetiapine in adolescents with bipolar depression.

Adler et al. [39] used magnetic resonance spectroscopy to examine prefrontal NAA in 31 patients receiving quetiapine for bipolar mania, compared with 13 healthy controls, at baseline and after 8 weeks of treatment. Bipolar subjects received openly quetiapine monotherapy (mean dose 584 ± 191 mg); 14 remitted (YMRS ≤12), 11 patients did not, and six patients were lost to follow-up. Bipolar and healthy subjects did not significantly differ in baseline NAA or degree of change during the 8 weeks. However, remitters showed greater mean baseline NAA concentrations in the right ventro-lateral prefrontal cortex compared with non-remitters ($p < 0.05$). In the ACC, remitters showed near significantly decreased baseline NAA concentrations at baseline ($p < 0.06$) and significant differences in NAA change during the 8 weeks of treatment ($p < 0.03$). Manic patients who remitted with quetiapine presented distinct patterns of baseline prefrontal NAA concentration, coupled with decreased NAA in the ACC with treatment, possibly related to an effect of medication on neuronal metabolism. These data support the suggestion that therapeutic effects of quetiapine involve metabolic effects on specific prefrontal regions.

It has been hypothesized that aggressive behavior may be associated with dysfunctions in an affective regulation network, with prefrontal regions orbitofrontal cortex (OFC), ACC, and DLPFC controlling the amygdala. A modulation of the prefrontal–amygdala system may account for anti-aggressive effects of medications effective in improving disruptive behavior in various disorders. An in vivo observation of pharmacological influences on cortico-limbic projections during human aggressive behavior was explored in a double-blind, placebo-controlled study [40]. This study compared quetiapine and placebo, administered for 3 successive days prior to an functional magnetic resonance imaging (fMRI) experiment assessing functional brain connectivity during a virtual aggressive behavior in a violent video game and an aggression-free control task in a non-violent modification. Quetiapine increased the functional connectivity of ACC and DLPFC with the amygdala during virtual aggression, whereas OFC–amygdala coupling was attenuated. These effects were observed neither for placebo nor for the non-violent control. These results indicate a pharmacological modification of aggression-related brain networks in a naturalistic setting, and suggest a neurobiological model for the anti-aggressive effects of quetiapine through a modulation of prefrontal–amygdala networks.

11 Safety: Monotherapy and Comparative Studies in Short- and Long-Term Trials

In general, SGAs have superior tolerability profiles compared with conventional agents [41]; however, clear differences in tolerability exist among the new generation antipsychotics [42]. Metabolic and hormonal side effects in children and adolescents during SGAs are currently a serious cause for concern.

Only two studies specifically explored the long-term safety of quetiapine. In the first study, McConville et al. [43] explored long-term safety of quetiapine in five boys and five girls, aged 12.3–15.9 years, with schizoaffective disorder or bipolar disorder with psychotic features in a single-site, 88-week, open-label extension of a clinical trial. In the open-label trial, which followed directly after this trial, with ending doses ranging from 300 to 800 mg/day, tolerability and safety were supported by clinical laboratory tests, physical examinations, measurements of EPS, vital signs, interviews for selective symptomatology, and ECGs. No EPS or evidence of tardive dyskinesia were reported. There was a non-significant increase in mean weight and BMI at week 64. This long-term study suggests that quetiapine is a well-tolerated antipsychotic agent, although conclusions are limited by small sample size [5].

In the second study, Findling et al. [44] evaluated the safety of quetiapine monotherapy in children and adolescents aged 13–17 years with schizophrenia or mania in a 26-week, open-label, continuation study including patients who participated in one of two acute, double-blind, placebo-controlled studies of IR quetiapine. Youth were enrolled with flexible doses between 400 and 800 mg/day, with options to reduce dosing to 200 mg/day on the basis of tolerability. Of 381 patients enrolled in the open-label study ($n = 176$, schizophrenia; $n = 205$, bipolar disorder), 237 patients (62.2 %) completed the study period (71 %, schizophrenia; 54.6 %, bipolar disorder). The most common side effects reported during the study included somnolence, headache, sedation, weight increase, and vomiting. A total of 14.9 % of patients experienced a shift to potentially clinically significant low levels of high-density lipoprotein (HDL) cholesterol, and 10.2 % of patients experienced a shift to potentially clinically significant high triglyceride levels. Weight gain of ≥7 % was reported in 35.6 % of patients between open-label baseline and final visit. After adjustment for normal growth, 18.3 % of study participants experienced clinically significant weight gain (i.e., increase in BMI ≥0.5 standard deviations from baseline).

Other comparative studies have addressed the safety of different SGAs. Fraguas et al. [45] explored safety in 66 children and adolescents (44 males, 15.2 ± 2.9 years) with schizophrenia or other psychoses who were treated for

6 months with risperidone ($n = 22$), olanzapine ($n = 20$), or quetiapine ($n = 24$). At the 6-month follow-up, 33 patients (50 %) showed significant weight gain. After 6 months, BMI z scores increased significantly in patients receiving olanzapine and risperidone, but not with quetiapine. Patients were considered "at risk for adverse health outcome" if they met at least one of the following criteria: (1) ≥85th BMI percentile plus presence of one or more negative weight-related clinical outcome; or (2) ≥95th BMI percentile. The number of patients at risk for adverse health outcome increased from 11 (16.7 %) to 25 (37.9 %) ($p = 0.018$). The latter increase was significant only in the olanzapine group ($p = 0.012$). Total cholesterol levels increased significantly in patients receiving olanzapine ($p = 0.047$) and quetiapine ($p = 0.016$). Treatment with quetiapine was associated with a significant decrease in free thyroxin ($p = 0.011$).

Noguera et al. [46] reported on the 24-month follow-up of the Child and Adolescent First-Episode Psychosis Study, a longitudinal study including 110 patients aged 9–17 years, with early-onset first psychotic episodes, and specifically focused on discontinuation rates, reasons for discontinuation, and adverse effects of different SGAs. Risperidone, quetiapine, and olanzapine were the most commonly SGAs used. The discontinuation rate was 44.5 % at 6 months, 59.1 % at 12 months, and 70.9 % at 24 months. Discontinuation rates or reasons for discontinuation (adverse reaction, insufficient response, and other) did not differ significantly among antipsychotics. At 6 months, significant differences were found in BMI increase and BMI z score increase, which were higher with olanzapine, and in neurological effects, which were higher with risperidone; at 12 and 24 months, these differences were no longer significant.

Patel et al. [47] have analyzed changes in short-term weight and BMI in 103 children and adolescents receiving olanzapine ($n = 50$, 13.9 ± 7.3 mg/day) or quetiapine ($n = 153$, 510.9 ± 250.3 mg) for at least 2 weeks. The olanzapine group gained an average of 3.8 kg and the quetiapine group 0.03 kg. In the olanzapine group, BMI increased by an average of 1.3 kg/m^2; in the quetiapine group, BMI decreased by 0.2 kg/m^2. These findings in weight and BMI change were significant even after controlling for baseline differences.

Another large naturalistic, short-term study (10.5–11.2 weeks) compared quetiapine and other SGAs in terms of cardio-metabolic effects [48]. Mean weight increases were 8.5 kg with olanzapine ($n = 45$), 6.1 kg with quetiapine ($n = 36$), 5.3 kg with risperidone ($n = 135$), 4.4 kg with aripiprazole ($n = 41$), and 0.2 kg in the untreated comparison group ($n = 15$). With olanzapine and quetiapine, respectively, mean levels of total cholesterol increased significantly by 15.6 mg/dL ($p < 0.001$) and 9.1 mg/dL ($p = 0.046$), triglycerides by 24.3 mg/dL (p = 0.002) and 37.0 mg/dL ($p = 0.01$), non-HDL cholesterol by 16.8 mg/dL ($p < 0.001$) and 9.9 mg/dL ($p = 0.03$), and ratio of triglycerides to HDL cholesterol by 0.6 ($p = 0.002$) and 1.2 ($p = 0.004$). With risperidone, triglycerides increased significantly by 9.7 mg/dL ($p = 0.04$). Metabolic baseline-to-endpoint changes were not significant with aripiprazole or in the untreated comparison group.

Cohen et al. [42] reviewed 41 short-term (3- to 12-week) controlled studies that evaluated SGA adverse effects in youths, in terms of odds ratios (ORs) or mean average effects: aripiprazole (10 studies, $n = 671$); olanzapine (14 studies, $n = 413$); quetiapine (ten studies, $n = 446$); risperidone (25 studies, $n = 1{,}040$); ziprasidone (four studies, $n = 228$); clozapine (five studies, $n = 79$, assessed only for weight gain and somnolence); and placebo/untreated (23 studies, $n = 1{,}138$). Compared with placebo, significant treatment-related increases were observed for weight gain with olanzapine (3.99 ± 0.42 kg), clozapine (2.38 ± 1.13 kg), risperidone (2.02 ± 0.32 kg), quetiapine (1.74 ± 0.38 kg), and aripiprazole (0.89 ± 0.32 kg). Glucose levels increased only with risperidone (3.7 ± 1.36 mg/dL) and olanzapine (2.09 ± 1.08 mg/dL). Cholesterol levels increased with quetiapine (10.77 ± 2.14 mg/dL) and olanzapine (4.46 ± 1.65 mg/dL). Triglyceride levels increased with olanzapine (20.18 ± 5.26 mg/dL) and quetiapine (19.5 ± 3.92 mg/dL). Hyperprolactinemia occurred only with risperidone (OR 38.63), olanzapine (OR 15.6), and ziprasidone (OR 9.35). EPS occurred with ziprasidone (OR 20.56), olanzapine (OR 6.36), aripiprazole (OR 3.79), and risperidone (OR 3.71). All SGAs increased the risk of somnolence/sedation.

More recently, a large prospective study described metabolic effects of diverse antipsychotics in drug-naive patients [49]. As expected, children and adolescents on antipsychotics experienced weight gain; quetiapine showed a lower weight gain than olanzapine and risperidone, and this gain did not further increase after 3 months of treatment. At a 6-month follow-up, treatment with quetiapine was not associated with increases in other metabolic parameters (whereas both risperidone and olanzapine were), and did not impact systolic blood pressure (as any other antipsychotic studied).

A number of serious cardiovascular safety concerns related to the use of atypical antipsychotics, including quetiapine, have emerged, namely the corrected QT (QTc) interval prolongation. Jensen et al. [50] evaluated the effect of antipsychotics on QTc interval in youth receiving antipsychotics, meta-analyzing the results of 55 randomized or open clinical trials in 5,423 youth <18 years with QTc data. According to this meta-analysis, the risk of pathological QTc prolongation seems low, as aripiprazole significantly decreased the QTc interval (−1.44 ms, 95 % CI

−2.63 to −0.26, $p = 0.017$), while risperidone (+1.68, 95 % CI +0.67 to +2.70, $p = 0.001$) and even more ziprasidone (+8.74, 95 % CI +5.19 to +12.30, $p < 0.001$) significantly increased QTc. Compared with pooled placebo arms, aripiprazole decreased QTc ($p = 0.007$), whereas ziprasidone increased QTc ($p < 0.001$). Quetiapine was not significantly associated with QTc changes from baseline to last assessment greater than 60 ms, or QTc prolongations greater than 500 ms.

Specific effect of quetiapine on ECG has been reviewed in the available literature [51], and 12 case reports of QTc interval prolongation have been found (only one patient was younger than 18 years). Among these 12 case reports, risk factors included female sex (nine cases), co-administration of a drug associated with QTc interval prolongation (eight cases), hypokalemia or hypomagnesemia (six cases), quetiapine overdose (five cases), cardiac problems (four cases), and co-administration of cytochrome P450 3A4 inhibitors (two cases). No significant correlation resulted between QTc interval and quetiapine dose.

All patients (or the family) must be informed of this potential risk when prescribing quetiapine, namely when other co-occurring risk factors would amplify the risk, such as congenital QTc prolongation, supratherapeutic doses, co-administration of other drugs associated with QTc prolongation, factors that increase drug levels, and presence of electrolyte derangements associated with arrhythmias.

In summary, available data suggest that although quetiapine has a fairly good tolerability profile, as expressed by the relatively low rate of discontinuation [27], most of the data are undermined by the short duration of follow-ups, as the median study duration of 8 weeks is insufficient to assess the full impact of these outcomes, i.e., in terms of risk of diabetes and cardiovascular diseases. Furthermore, findings are not totally consistent among studies, as in several studies weight gain is not a reason of concern, while in others, it is greater than for risperidone. Similarly, some studies report a favorable profile of metabolic effects, while in other trials, quetiapine was associated with higher risk of low levels of HDL cholesterol, potentially clinically significant high triglyceride levels, and increased total cholesterol levels. Weight gain and alterations in lipid profile, as well as thyroid function, need to be closely monitored. Hyper-prolactinemia and EPS are consistently low among studies, while sedation can be impairing in the first weeks, namely when the titration is more rapid. Guidelines and evidence-based recommendations for the monitoring of metabolic and neurologic complications associated with the chronic use of SGAs, as well as which adverse events should be routinely monitored in children, are available [52], as such negative events may have greater long-term impact in children.

12 Titration Strategy

Although it is generally assumed that younger patients require lower doses of antipsychotics than adults, adolescents may require rapid titration to the same dose level as, or even higher levels than, adults for optimal clinical response [53]. There is some controversy about the best strategy to titrate quetiapine. A low titration (i.e., 25–50 mg increases every 1–3 days, according to age and weight) may be recommended when clinical condition allows it, minimizing first sedative effects and improving compliance, with a first assessment at 150–200 mg/day and further increments and assessments at 400, 600, and 750 mg/day. A more rapid titration has been recently proposed in a 9-day fixed titration phase with a final quetiapine XR dose of 600 mg/day, with 50 mg for the first 2 days, 100 mg for the third and fourth days, 200 mg for the fifth and sixth days, 400 mg for the seventh and eight days, 600 mg on the ninth day, and possibly 800 mg when clinical response is poor [54].

A rapid loading has been proposed as a safe strategy when severity of symptomatology requires a prompt action. On the basis of a review of published findings, Arango and Bobes [55] proposed that a rapid initiation schedule (e.g., 400 mg by day 2, increasing to 600 mg/day by day 3 and often up to 800 mg/day by day 4, or in severe cases, 300 mg on day 1, 600 mg on day 2 and 900 mg on day 3) can be used to provide safe, effective treatment in hospitalized adolescent and adult patients with acute schizophrenia.

A possible strategy of a rapid loading of quetiapine has been explored in pediatric bipolar disorder by Scheffer et al. [21]. Quetiapine was started at 100 mg/day, and increased to 400 mg/day by day 5, with a high rate of responders. Regarding the side effects with this strategy of titration, sedation was reported by 50 % of subjects during the first week, but this rate dropped in the following weeks, while neither abnormalities in blood pressure nor EPS occurred during the study.

13 Conclusions

While literature about use of quetiapine in youth is increasing in different pediatric psychiatric disorders, some caveats should be considered. The great majority of the trials were funded by industry, which may present a potential risk for bias, and an urgent need for independent studies emerges from this review. The side effect profile, at least in the short term, seems relatively favorable, although youth may be particularly sensitive to weight gain and metabolic changes [49, 56]. Tolerability should be balanced with the expected efficacy, based on available

research. Data from the literature indicate that quetiapine may be an effective agent in EOS, and in bipolar disorder with (hypo)manic episodes, but not with depressive episodes [57], contrarily to studies in adult patients [58]. However, some findings suggest that risperidone and olanzapine may be more effective in these disorders, albeit less tolerated. Less evidence supports quetiapine efficacy in CD symptoms, pure or associated with bipolar disorders, or in BPD. Quetiapine cannot be considered among the first options in patients with ASD or TS. Furthermore, quetiapine is sometimes used for indications scarcely supported by empirical evidence (i.e., anxiety disorders, depression, insomnia) [59, 60], but data are not available in pediatric populations. Finally, an emerging concern has been reported about case reports of potential misuse/abuse, a phenomenon unseen with other atypical antipsychotics [61, 62].

Prescribing practices have been under ongoing scrutiny because of the marked increase in on-label and off-label use, concerns regarding medication safety, and the comparative efficacy of available medications. There is a need for high-quality trials that focus on comparisons that reflect everyday clinical practice decisions [63]. This includes more head-to-head comparisons of different antipsychotics and different doses to define clear parameters on the efficacy, safety, and tolerability of this pharmacotherapy for children and adolescents. From this perspective, placebo comparisons are likely to have less impact on clinical practice.

One of the greatest priorities for future research is the systematic evaluation of adverse events given that such events may have greater long-term impact in children. Future studies should evaluate patient-important outcomes, including health-related quality of life, school performance, cognitive functioning, and developmental outcomes.

Conflict of interest Dr. Masi was on the advisory boards for Eli Lilly, Shire and Angelini, has received research grants from Eli Lilly and Shire, and has been a speaker for Eli Lilly, Shire, Lundbeck and Otsuka. Dr. Pfanner has received research grants from Eli Lilly and Shire and has been a speaker for Eli Lilly and Shire. Drs. Milone, Veltri, Iuliano and Pisano do not have any conflicts of interest to declare.

References

1. Sikich L, Fraziet JA, McClellan J, Findling RL, Vitiello B, Ambler D, Puglia M, Maloney AE, Michael E, DeJong S, Slifka K, Noyes N, Hlastala S, Pierson L, McNamara NK, DelPorto-Bedoya D, Anderson R, Hamer RM, Lieberman JA. Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizoaffective disorders: findings from the Treatment of Early-Onset Schizophrenia Spectrum Disorders (TEOSS) study. Am J Psychiatry. 2008;165:1420–31.
2. Baeza I, de la Serna E, Calvo-Escalona R, Morer A, Merchán-Naranjo J, Tapia C, Martínez-Cantarero MC, Andrés P, Alda JA, Sánchez B, Arango C, Castro-Fornieles J. Antipsychotic use in children and adolescents: a 1-year follow-up study. J Clin Psychopharmacol. 2014;34:613–9.
3. Findling RL. Use of quetiapine in children and adolescents. J Clin Psychiatry. 2002;63(suppl 13):27–31.
4. Winter HR, Earley WR, Hamer-Maansson JE, Davis PC, Smith MA. Steady-state pharmacokinetic, safety, and tolerability profiles of quetiapine, norquetiapine, and other quetiapine metabolites in pediatric and adult patients with psychotic disorders. J Child Adolesc Psychopharmacol. 2008;18:81–98.
5. McConville BJ, Arvanitis LA, Thyrun PT, Yeh C, Wilkinson LA, Chaney RO, Foster KD, Sorter MT, Friedman LM, Brown KL, Heubi JE. Pharmacokinetics, tolerability, and clinical effectiveness of quetiapine fumarate: an open-label trial in adolescents with psychotic disorders. J Clin Psychiatry. 2000;61:252–60.
6. Findling RL, Reed MD, O'Riordan MA, Demeter CA, Stansbrey RJ, McNamara NK. Effectiveness, safety, and pharmacokinetics of quetiapine in aggressive children with conduct disorder. J Am Acad Child Adolesc Psychiatry. 2006;45:792–800.
7. Johnson TN, Zhou D, Bui KH. Development of physiologically-based pharmacokinetic model to evaluate the relative systemic exposure to quetiapine after administration of IR and XR formulations to adults, children and adolescents. Biopharm Drug Dispos. 2014;35:341–52.
8. Shaw JA, Lewis JE, Pascal S, Sharma RK, Rodriguez RA, Guillen R, Pupo-Guillen M. A study of quetiapine: efficacy and tolerability in psychotic adolescents. J Child Adolesc Psychopharmacol. 2001;11:415–24.
9. Schimmelmann BG, Mehler-Wex C, Lambert M, Schulze-zur-Wiesch C, Koch E, Flechtner HH, Gierow B, Maier J, Meyer E, Schulte-Markwort M. A prospective 12-week study of quetiapine in adolescents with schizophrenia spectrum disorders. J Child Adolesc Psychopharmacol. 2007;17:768–78.
10. Findling RL, McKenna K, Earley WR, Stankowski J, Pathak S. Efficacy and safety of quetiapine in adolescents with schizophrenia investigated in a 6-week, double-blind, placebo-controlled trial. J Child Adolesc Psychopharmacol. 2012;22:327–42.
11. Jensen JB, Kumra S, Leitten W, Oberstar J, Anjum A, White T, Wozniak J, Lee SS, Schulz SC. A comparative pilot study of second-generation antipsychotics in children and adolescents with schizophrenia-spectrum disorders. J Child Adolesc Psychopharmacol. 2008;18:317–26.
12. Arango C, Robles O, Parellada M, Fraguas D, Ruiz-Sancho A, Medina O, Zabala A, Bombín I, Moreno D. Olanzapine compared to quetiapine in adolescents with a first psychotic episode. Eur Child Adolesc Psychiatr. 2009;18:418–28.
13. Castro-Fornieles J, Parellada M, Soutullo CA, Baeza I, Gonzalez-Pinto A, Graell M, Paya B, Moreno D, de la Serna E, Arango C. Antipsychotic treatment in child and adolescent first-episode psychosis: a longitudinal naturalistic approach. J Child Adolesc Psychopharmacol. 2008;18:327–36.
14. Swadi HS, Craig BJ, Pirwani NZ, Black VC, Buchan JC, Bobier CM. A trial of quetiapine compared with risperidone in the treatment of first onset psychosis among 15- to 18-year-old adolescents. Int Clin Psychopharmacol. 2010;25:1–6.
15. Robles O, Zabala A, Bombín I, Parellada M, Moreno D, Ruiz-Sancho A, Arango C. Cognitive efficacy of quetiapine and olanzapine in early-onset first-episode psychosis. Schizophr Bull. 2011;37:406–15.
16. Pathak S, Findling RL, Earley WR, Acevedo LD, Stankowski J, DelBello MP. Efficacy and safety of quetiapine in children and adolescents with mania associated with bipolar I disorder: a 3-week, double-blind, placebo-controlled trial. J Clin Psychiatry. 2013;74:100–9.

17. DelBello MP, Schwiers ML, Rosenberg HL, Strakowski SM. A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. J Am Acad Child Adolesc Psychiatry. 2002;41:1216–23.
18. DelBello MP, Kowatch RA, Adler CM, Stanford KE, Welge JA, Barzman DH, Nelson E, Strakowski SM. A double-blind randomized pilot study comparing quetiapine and divalproex for adolescent mania. J Am Acad Child Adolesc Psychiatry. 2006;45:305–13.
19. DelBello MP, Adler CM, Whitsel RM, Stanford KE, Strakowski SM. A 12-week single-blind trial of quetiapine for the treatment of mood symptoms in adolescents at high risk for developing bipolar I disorder. J Clin Psychiatry. 2007;68:789–95.
20. Joshi G, Petty C, Wozniak J, Faraone SV, Doyle R, Georgiopoulos A, Hammerness P, Walls S, Glaeser B, Brethel K, Yorks D, Biederman J. A prospective open-label trial of quetiapine monotherapy in preschool and school age children with bipolar spectrum disorder. J Affect Disord. 2012;136:1143–53.
21. Scheffer RE, Tripathi A, Kirkpatrick FG, Schultz T. Rapid quetiapine loading in youths with bipolar disorder. J Child Adolesc Psychopharmacol. 2010;20:441–5.
22. DelBello MP, Chang K, Welge JA, Adler CM, Rana M, Howe M, Bryan H, Vogel D, Sampang S, Delgado SV, Sorter M, Strakowski SM. A double-blind, placebo-controlled pilot study of quetiapine for depressed adolescents with bipolar disorder. Bipolar Disord. 2009;11:483–93.
23. Findling RL, Pathak S, Earley WR, Liu S, DelBello MP. Efficacy and safety of extended-release quetiapine fumarate in youth with bipolar depression: an 8-week, double-blind, placebo-controlled trial. J Child Adolesc Psychopharmacol. 2014;24:325–35.
24. Barzman DH, DelBello MP, Adler CM, Stanford KE, Strakowski SM. The efficacy and tolerability of quetiapine versus divalproex for the treatment of impulsivity and reactive aggression in adolescents with co-occurring bipolar disorder and disruptive behavior disorder(s). J Child Adolesc Psychopharmacol. 2006;16:665–70.
25. Masi G, Pisano S, Milone A, Pfanner C, Manfredi A. Quetiapine monotherapy in adolescents with bipolar disorder comorbid with conduct disorder. J Child Adolesc Psychopharmacol. 2013;23:568–71.
26. Connor DF, McLaughlin TJ, Jeffers-Terry M. Randomized controlled pilot study of quetiapine in the treatment of adolescent conduct disorder. J Child Adolesc Psychopharmacol. 2008;18:140–56.
27. Findling RL, Reed MD, O'Riordan MA, Demeter CA, Stansbrey RJ, McNamara NK. A 26-week open-label study of quetiapine in children with conduct disorder. J Child Adolesc Psychopharmacol. 2007;17:1–9.
28. Kronenberger WG, Giauque AL, Lafata DE, Bohnstedt BN, Maxey LE, Dunn DW. Quetiapine addition in methylphenidate treatment-resistant adolescents with comorbid attention-deficit/hyperactivity disorder, conduct/oppositional-defiant disorder, and aggression: a prospective, open-label study. J Child Adolesc Psychopharmacol. 2007;17:334–47.
29. Findling RL, McNamara NK, Gracious BL, O'Riordan MA, Reed MD, Demeter C, Blumer JL. Quetiapine in nine youths with autistic disorder. J Child Adolesc Psychopharmacol. 2004;14:287–94.
30. Hardan AY, Jou RJ, Handen BL. Retrospective study of quetiapine in children and adolescents with pervasive developmental disorders. J Autism Dev Disord. 2005;35:387–91.
31. Golubchik P, Sever J, Weizman A. Low-dose quetiapine for adolescents with autistic spectrum disorder and aggressive behavior: open-label trial. Clin Neuropharmacol. 2011;34:216–9.
32. Podobnik J, Foller Podobnik I, Grgic N, Marcinko D, Pivac N. The effect of add-on treatment with quetiapine on measures of depression, aggression, irritability and suicidal tendencies in children and adolescents. Psychopharmacology. 2012;20:639–41.
33. Mukaddes NM, Abali O. Quetiapine treatment in children and adolescents with Tourette's disorder. J Child Adolesc Psychopharmacol. 2003;13:295–9.
34. Copur M, Arpaci B, Demir T, Nacir H. Clinical effectiveness of quetiapine in children and adolescents with Tourette's syndrome: a retrospective case-note survey. Clin Drug Invest. 2007;27:123–30.
35. Copur M, Hergüner S, Arpaci B. Tolerability of quetiapine in children and adolescents with Tourette's syndrome. Int J Clin Pharmacol Ther. 2011;49:177–8.
36. Gilbert DL, Batterson JR, Sethuraman G, Sallee FR. Tic reduction with risperidone versus pimozide in a randomized, double blind cross-over trial. J Am Acad Child Adolesc Psychiatry. 2004;43:206–14.
37. Yoo HK, Joung YS, Lee JS, Song DH, Lee YS, Kim JW, Kim BN, Cho SC. A multicenter, randomized, double-blind, placebo controlled of aripiprazole in children and adolescents with Tourette's disorder. J Clin Psychiatry. 2013;74:e772–80.
38. Chang K, DelBello M, Chu WJ, Garrett A, Kelley R, Mills N, Howe M, Bryan H, Adler C, Eliassen J, Spielman D, Strakowski SM. Neurometabolite effects of response to quetiapine and placebo in adolescents with bipolar depression. J Child Adolesc Psychopharmacol. 2012;22:261–8.
39. Adler CM, DelBello MP, Weber WA, Jarvis KB, Welge J, Chu WJ, Rummelhoff E, Kim MJ, Lee JH, Strakowski SM. Neurochemical effects of quetiapine in patients with bipolar mania: a proton magnetic resonance spectroscopy study. J Clin Psychopharmacology. 2013;33:528–32.
40. Klasen M, Zvyagintsev M, Schwenzer M, Mathiak KA, Sarkheil P, Weber R, Mathiak K. Quetiapine modulates functional connectivity in brain aggression networks. Neuroimage. 2013;75:20–6.
41. Masi G, Liboni F. Management of schizophrenia in children and adolescents: focus on pharmacotherapy. Drugs. 2011;71:179–208.
42. Cohen D, Bonnot O, Bodeau N, Consoli A, Laurent C. Adverse effects of second-generation antipsychotics in children and adolescents: a Bayesian meta-analysis. J Clin Psychopharmacol. 2012;32:309–16.
43. McConville B, Carrero L, Sweitzer D, Potter L, Chaney R, Foster K, Sorter M, Friedman L, Browne K. Long-term safety, tolerability, and clinical efficacy of quetiapine in adolescents: an open-label extension trial. J Child Adolesc Psychopharmacol. 2003;13:75–82.
44. Findling RL, Pathak S, Earley WR, Liu S, DelBello MP. Safety, tolerability, and efficacy of quetiapine in youth with schizophrenia or bipolar I disorder: a 26-week, open-label, continuation study. J Child Adolesc Psychopharmacol. 2013;23:490–501.
45. Fraguas D, Merchán-Naranjo J, Laita P, Parellada M, Moreno D, Ruiz-Sancho A, Cifuentes A, Giráldez M, Arango C. Metabolic and hormonal side effects in children and adolescents treated with second-generation antipsychotics. J Clin Psychiatry. 2008;69:1166–75.
46. Noguera A, Ballesta P, Baeza I, Arango C, de la Serna E, González-Pinto A, Parellada M, Graell M, Moreno C, Otero S, Castro-Fornieles J. Twenty-four months of antipsychotic treatment in children and adolescents with first psychotic episode: discontinuation and tolerability. J Clin Psychopharmacol. 2013;33:463–71.
47. Patel NC, Kistler JS, James EB, Crismon ML. A retrospective analysis of the short-term effects of olanzapine and quetiapine on weight and body mass index in children and adolescents. Pharmacotherapy. 2004;24:824–30.
48. Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation

antipsychotic medications during first-time use in children and adolescents. JAMA. 2009;302:1765–73.
49. Arango C, Giráldez M, Merchán-Naranjo J, Baeza I, Castro-Fornieles J, Alda JA, Martínez-Cantarero C, Moreno C, de Andrés P, Cuerda C, de la Serna E, Correll CU, Fraguas D, Parellada M. Second-generation antipsychotic use in children and adolescents: a six-month prospective cohort study in drug-naïve patients. J Am Acad Child Adolesc Psychiatry. 2014;53:1179–90.
50. Jensen KG, Juul K, Fink-Jensen A, Correll CU, Pagsberg AK. Corrected QT changes during antipsychotic treatment of children and adolescents: a systematic review and meta-analysis of clinical trials. J Am Acad Child Adolesc Psychiatry. 2015;54(1):25–36.
51. Hasnain M, Vieweg WV, Howland RH, Kogut C, Breden Crouse EL, Koneru JN, Hancox JC, Digby GC, Baranchuk A, Deshmukh A, Pandurangi AK. Quetiapine, QTc interval prolongation, and torsade de pointes: a review of case reports. Ther Adv Psychopharmacol. 2014;4:130–8.
52. Pringsheim T, Panagiotopoulos C, Davidson J, Ho J, CAMESA guideline group. Evidence-based recommendations for monitoring safety of second generation antipsychotics in children and youth. J Can Acad Child Adolesc Psychiatry. 2011;20:218–33.
53. Arango C, Parellada M, Moreno DM. Clinical effectiveness of new generation antipsychotics in adolescent patients. Eur Neuropsychopharmacol. 2004;14:S471–9.
54. Pagsberg AK, Jeppesen P, Klauber DG, Jensen KG, Rudå D, Stentebjerg-Olesen M, Jantzen P, Rasmussen S, Saldeen EA, Lauritsen MB, Bilenberg N, Stenstrøm AD, Pedersen J, Nyvang L, Madsen S, Lauritsen MB, Vernal DL, Thomsen PH, Paludan J, Werge TM, Winge K, Juul K, Gluud C, Skoog M, Wetterslev J, Jepsen JR, Correll CU, Fink-Jensen A, Fagerlund B. Quetiapine versus aripiprazole in children and adolescents with psychosis—protocol for the randomised, blinded clinical tolerability and efficacy of antipsychotics (TEA) trial. BMC Psychiatry. 2014;14:199.
55. Arango C, Bobes J. Managing acute exacerbations of schizophrenia: focus on quetiapine. Curr Med Res Opin. 2004;20:619–26.
56. Correll CU, Penzner JB, Parikh UH, et al. Recognizing and monitoring adverse events of second-generation antipsychotics in children and adolescents. Child Adolesc Psychiatr Clin N Am. 2006;15:177–206.
57. Cosgrove VE, Roybal D, Chang KD. Bipolar depression in pediatric populations: epidemiology and management. Paediatr Drugs. 2013;15:83–91.
58. Young AH, Calabrese JR, Gustafsson U, Berk M, McElroy SL, Thase ME, Suppes T, Earley W. Quetiapine monotherapy in bipolar II depression: combined data from four large, randomized studies. Int J Bipolar Disord. 2013;1:10–7.
59. Panagiotopoulos C, Ronsley R, Elbe D, et al. First do no harm: promoting an evidence-based approach to atypical antipsychotic use in children and adolescents. J Can Acad Child Adolesc Psychiatry. 2010;19:124–37.
60. McKean A, Monasterio E. Off-label use of atypical antipsychotics: cause for concern? CNS Drugs. 2012;26:383–90.
61. Sansone RA, Sansone LA. Is seroquel developing an illicit reputation for misuse/abuse? Psychiatry. 2010;7:13–6.
62. Cha HJ, Lee HA, Ahn JI, Jeon SH, Kim EJ, Jeong HS. Dependence potential of quetiapine: behavioral pharmacology in rodents. Biomol Ther. 2013;21:307–12.
63. Seida JC, Schouten JR, Boylan K, Newton AS, Mousavi SS, Beaith A, Vandermeer B, Dryden DM, Carrey N. Antipsychotics for children and young adults: a comparative effectiveness review. Pediatrics. 2012;129:771–84.