

Bipolar Disorder in 10–17 Year Old Patients: Treatment Options and Cautions

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Abstract: In recent years, bipolar disorder (BD) has been diagnosed with increasing frequency in the pediatric population. BD requires a multimodal treatment plan to address complex symptoms and the associated comorbidities. Pharmacological intervention assists the core symptoms of the illness and psychotherapeutic intervention may be beneficial as an adjunctive treatment. Controlled studies corroborate the comparable short-term efficacy of several second generation antipsychotics and mood stabilizers for treating mania, but major dissimilarities exist with respect to the kind and severity of side effects. The selected treatment option is determined by the tolerance and safety. In addition, data suggests that youth may be more vulnerable to the adverse effects of psychotropic medications than adults. More clinical trials, that focus on risk-benefit ratios of these medications and that clarify assessment and management of their comorbidities are needed to find safer and more effective treatment options for long-term treatment.

Keywords: bipolar disorder, children and adolescents, treatment, second generation antipsychotics

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Introduction

In recent years, the diagnoses of bipolar disorder (BD) in children and adolescents has significantly increased.^{1,2} This increase in diagnosis may be due to several factors such as i) greater standardization of diagnostic criteria, ii) the controversy about the phenomenology of BD in youth by including children with severe mood dysregulation and behavioural problems^{3,4} and iii) to the increasing use of illicit drugs and prescription psychotropic medications that may induce a first episode of mania.⁵

BD in children and adolescents has different characteristics compared to adults. The main studies on pediatric BD published to date have agreed upon the following:^{6–8} i) higher rates of elevated, elated or expansive moods; ii) higher rates of psychotic symptoms; iii) important irritability; iv) episodic course; v) rapid cycling; vi) manic or hypomanic symptoms interspersed with depressive symptoms; and vii) higher rates of comorbidity with ADHD and anxiety disorders in children and adolescents.^{6,9} Substance use disorders and suicide attempts also characterize pediatric BD.^{10,11}

Early diagnosis and treatment are needed to decrease later functional impairment.^{12,13} This fact has caused an increase in the use of second generation antipsychotics (SGAs)^{14,15} and mood stabilizers (MSs), such as lithium and anticonvulsants in this population. However, insufficient high quality published studies are available for the efficacy and safety data for SGAs and MSs in children and adolescents. Some of the data have been extrapolated to children from clinical trials in adults.¹⁶ In general, the main side effects of SGAs include extrapyramidal symptoms (EPS) like akathisia or tardive dyskinesia (TD), increase in prolactin levels, weight gain and metabolic abnormalities that increase the risk of obesity, metabolic syndrome, cardiovascular comorbidity and hypertension as well as other pathologies in adulthood.¹⁷ MSs can also produce significant weight gain, somnolence, reduced cognition, polycystic ovarian syndrome (PCOS) and the development of essential tremors.¹⁸ Data suggests that youth may be more vulnerable to side effects of psychotropic medications than adults.¹⁷ For example, a recent study, has shown that SGA-related weight gain and somnolence was significantly greater in youth than adults.¹⁶ In addition, at the time of prescribing

a psychotropic agent in youth, one should consider that it is being done in a brain which is in a process of biological, psychological and social maturation changes.¹⁶

Recently new controlled clinical trials have demonstrated the efficacy of SGAs for the treatment of acute manic or mixed episodes in BD in youth. These studies have supported the FDA approval for risperidone, aripiprazol, quetiapine to treat manic and mixed episodes in BD aged 10–17 years, and olanzapine in adolescents aged 13–17 years.¹⁹ At the same time, several review paper about pharmacological treatments in pediatric bipolar disorder have emerged in the last 2 years.^{16,19–25} This paper aims to review recent literature for the pharmaceutical treatment options for pediatric BD with the intent of drawing a clinical profile of safety and efficacy considering the pharmacokinetic and pharmacodynamic peculiarities of this population. Also, we will briefly review emerging psychosocial treatment options for youths with BD.

Mechanism of Action, Metabolism and Pharmacokinetic Profile

When prescribing psychopharmacologic agents in youth, it is important consider the development-dependent variables of pharmacokinetics and pharmacodynamics.^{26,27}

Pharmacokinetics is the process by which a drug is absorbed, distributed, metabolized, and eliminated by the body and plays a significant role when deciding which drug to select and how frequently it is administered. Knowledge of pharmacokinetics can prevent drug interactions and help interpret correctly therapeutic drug levels.²⁸

In psychiatry, drugs are mainly administered orally or as intramuscular injections. The difference lies in the ability to predict the final bioavailability of the drug. First-pass metabolism plays a significant role in the absorption process. This term refers to the process by which drugs absorbed through the gastrointestinal (GI) tract are carried first to the liver via the portal circulation. For this reason, although oral administration is the most frequent, it is also the most unpredictable in terms of bioavailability. In pediatric population, there are certain peculiarities that could modulate the absorption of a drug when it is administered by oral route, such as an elevated



gastric pH, lesser variety of intestinal flora and prolonged gastric emptying time. As a result of reduced motility, the rate of absorption of drugs with limited water solubility such as carbamazepine can be significantly altered.²⁹ Therefore, it could be expected that in children, the absorption of drugs orally would be slower and thus, the time to achieve maximum plasma concentrations is prolonged.²⁹

After it is absorbed, it is distributed to the intravascular and extravascular spaces. The distribution depends on: total body water and lipid stores, regional blood flow, binding of drugs to plasma proteins, permeability of cell membranes and acid-base balance. All of these parameters vary with evolutionary changes.^{26,27,30} For example, children and adolescents have a lesser proportion of body fat than adults and many neuroleptics and antidepressants are lipid soluble, so when they are administered in children, they are found in higher plasma levels. Also, there exists a higher proportion of extra-cellular water in children than adults, so there is a higher plasma level of hydrophilic drugs.²⁹

The next phase is metabolism that refers to the biotransformation of drugs to different forms. Phase I reactions involve oxidation, reduction or hydrolysis and are mediated by cytochrome P450 (CYP450). The products of this phase are called metabolites and they can be more or less active and toxic than the initial component. The drugs that increase the CYP450 activity are inducers and those that reduce it are inhibitors. As a result, it may produce interactions by drugs metabolized by the same cytochrome, especially, when there is a unique common metabolism way. The specific CYP450 isoforms responsible for the majority of human drug metabolism are represented by CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.^{28,29} The isoenzyme CYP2D6 is of special interest to pediatric psychiatrists because it is involved in the metabolism of numerous psychotropic medications such as nortriptyline, paroxetine, fluoxetine, trazadone, venlafaxine, risperidone, perphenazine, haloperidol and others.³¹ The cytochrome enzymes are more efficient during childhood, beginning their decline after puberty. As the hepatic metabolic capacity in children is superior, it leads to a shorter half-life of drugs and a necessity to increase doses and/or shorten dose intervals in comparison to the usual adult dose to get equivalent

plasmatic levels.²⁷ The inter-individual variation in plasma concentrations of psychotropic drugs can be explained by genetic variation in drug metabolism. The CYP2D6 gene locus is highly polymorphic with more than 75 allelic variants identified. Among those are fully functional, reduced function and non-functional alleles, which convey a wide range of activity from none to ultrarapid metabolism. In clinical practice it is important to remember that 5%–10% of Caucasians are poor metabolizers of CYP2D6 in whom even low doses of CYP2D6 substrates may not be tolerated.²⁹

Phase II can occur in nearly any organ, and it consists of the conjugation of resultant metabolites from phase I with UDP-glucuronic acid, sulphate and others making their urinary excretion easier. Some medications go straight to phase II, such as escitalopram, lorazepam so they would be the first option for treatment in case of hepatic insufficiency since their conjugation does not depend on the liver exclusively.^{28,30}

Renal excretion is also responsible for eliminating drugs and their metabolites from the body. Agents excreted as active metabolites or Non-metabolized agents, such as lithium, topiramate or gabapentin, need to be dose adjusted for patients who have impaired renal function. Children have greater glomerular filtration so they usually eliminate drugs faster than adults which results in a shorter half-life of drugs. One practical implication of this pharmacokinetic difference is that in order to achieve therapeutic serum levels for some drugs, children may require higher weight-adjusted (mg/kg) dosages than adults.^{28,32}

Pharmacodynamic principles are concerned with the biochemical and physiological effects of drugs at their effect sites, with their specific mechanism of action. It has been observed that pharmacodynamic differences exist between children and adults³³ since the neurotransmitter systems in developing brain have functions and characteristics that differ from the adult brain.³⁴ For example, during childhood and adolescence one is less susceptible to the anticholinergic effects of some medications because of decreased density of muscarinic receptors. In the same way, the lack of efficacy of tricyclic antidepressant may be due to the relative immaturity of the noradrenergic system in children.³⁵ However there is a higher density of dopamine receptors so



the extrapyramidal effects are more frequent than adults with antipsychotic administration.³⁶

Pharmacotherapy for Children and Adolescents with Bipolar Disorder

As indicated by the practice parameters and treatment guidelines that appeared in the American Academy of Child and Adolescent Psychiatry (AACAP),^{18,37} the optimal first-line agents for treatment of acute mania include monotherapy with the traditional MSs such as lithium, divalproex (DVP) and carbamazepine, and SGAs such as olanzapine, risperidone and quetiapine, or in combination in those who had a no response or a partial one to monotherapy. The FDA has recently granted indications to four SGAs, risperidone, aripiprazole, quetiapine and olanzapine, for the treatment of manic episodes in bipolar youth. Aripiprazole also received an indication for maintenance treatment in bipolar youth aged ≥ 10 years, although there have been no maintenance studies of aripiprazole in BD children and adolescents.¹⁹

Mood stabilizers

MSs are now understood to target pathways and mechanisms that are implicated in bipolar disorder. The following is a review of the available studies on MSs used to treat BD in youth (as resumed in Table 1).

Lithium

Lithium (Li) was approved by the FDA for the treatment of acute manic episodes and maintenance therapy in youth ≥ 12 years old. This indication was based on results from adult studies.^{38,39}

The exact mechanisms of Li's therapeutic effects are not fully known, even though it has been used for decades. Li acts on serotonin, norepinephrine and dopamine systems among others, with growing evidence about its neuroprotective and neurotrophic actions through different mechanisms of action described elsewhere.⁴⁰ Li is absorbed completely in the GI tract. Its initial half-life is 6 to 12 hours but when taken over long periods its half-life increases to 24 hours. Li is not metabolized, but is eliminated almost entirely by the kidney. Its half-life elimination is lower in children as its total renal clearance is higher.⁴¹ Recurrent follow-up during initial titration is necessary to ensure that blood concentrations are within a therapeutic and safe range, because of

Li's narrow therapeutic index. The recommended levels are 0.8–1.2 mEq/L for maintenance therapy and 1.0–1.5 mEq/L for an acute manic episode, even though these levels are based on studies of adults with BD.⁴¹ For instance, one study found that using Li-7 magnetic resonance spectroscopy, children and adolescents had lower serum to brain concentrations than adults, suggesting that children and adolescents may need higher serum Li levels to ensure that brain Li concentrations reach therapeutic levels.⁴²

Regarding its efficacy in the treatment of BD in children and adolescents, there are several case reports, chart reviews and a small number of prospective studies. The first double blind placebo controlled trial of Li as monotherapy in adolescents with BD was carried out by Geller and colleagues in 1998.⁴³ 25 subjects (aged 16.3 ± 1.2 years) with a history of BD I or II or major depressive disorder with one predictor of future BD, and comorbid substance dependency disorder were randomized to 6 weeks of treatment with either Li or placebo. Li was associated with improved Children's Global Assessment Scale (CGAS) scores (46.2% Li group vs. 8.3% placebo group) and decreased substance use. Kafantaris and colleagues⁴⁴ reported the results of a large open trial with 100 youths (mean age = 15.23 years) treated with Li for 4 weeks. In this trial, 46 subjects with comorbid psychosis or severe aggression received concomitant antipsychotic medication. Response rate to Li was reported to be 55%, using a reduction of $\geq 50\%$ in baseline Young Mania Rating Scale (YMRS) score as response criteria, and a remission rate, defined as a YMRS score ≤ 6 , was of 26%. The effect size for the change in manic symptoms was 1.48, but the use of adjunctive antipsychotic agents makes it difficult to assess the efficacy of Li alone. This study has been used as the lead-in study to a randomized placebo-controlled discontinuation trial for 2 weeks that involved 40 participants who had previously responded to open-label Li treatment.⁴⁵ The rates of relapse into mania were not significantly different between treatment groups, so they concluded that Li monotherapy may not be adequate to maintain remission in youth with bipolar disorder. However, 2 weeks was probably not enough time to detect a difference between the groups.⁴⁶ The authors also suggest several explanations for the high exacerbation rates in the Li group, such as the use of subjective reporting of deterioration,

**Table I.** Mood stabilizers commonly used for the treatment of children and adolescents with bipolar disorder.

Medication	FDA approval	Half life (h)	Recommended dosing	Side effects	Cautions
Lithium	Acute manic episodes and maintenance therapy in those aged ≥ 12 y	6–12 ^a 24 ^b	0.8–1.2 mEq/L for maintenance therapy 1.0–1.5 mEq/L for an acute manic episode	Nausea, headache, tremor, thyroid dysfunction, acne, weight gain, diabetes insipidus	Renal clearance is sole route of elimination. Toxicity may appear below therapeutic range
Divalproex sodium	No	11–20	Target dose 10–20 mg/kg Therapeutic range 50–100 mg/L.	Weight gain, nausea, increased appetite, sedation, headache, GI symptoms, alopecia, hyperammonemia, pancreatitis, hepatotoxicity, thrombocytopenia, polycystic ovary syndrome.	Delayed onset of action. Drug interactions. Inhibits hepatic enzymes and increases other drug levels
Carbamazepine	No	25–65 ^a 12–17 ^b	Target dose 10–20 mg/kg/d, Serum levels 4–14 ug/mL.	Dizziness, diplopia, headache, GI symptoms, skin rash, SIADH, neutropenia, agranulocytosis	Delayed onset of action. Drug interactions. Enhances CYP450 activity and decreases other drug levels
Oxcarbamazepine	No	2	To start at 8 to 10 mg/kg/day, divided into two doses. Dosage titration should be done over a 2 week period. To a maximum dose level of 900–2400 mg/d	Dizziness, nausea, somnolence, fatigue, rash, diplopia.	Little evidence to support his use in child and adolescents with BD.
Lamotrigine	No	7–66	To start with 25 mg/day titrating 25 mg every 2 weeks. For subjects taking DVP starting dose and titration should be halved	Rash (rarely Stevens-Johnson syndrome), headache, fatigue and nausea	Prolonged half life. Appearance of rash calls for immediate cessation.
Topiramate	No	21	Starting dose 50 mg/d. Target dose from 200–400 mg/d depending on weight	Cognitive disturbance, GI symptoms, sedation, decreased appetite, and paresthesias.	Little evidence to support its use in children and adolescents with BD. Studies suggest that topiramate is not effective in adults with BD

Notes: ^aInitial; ^bAfter several weeks of administration.

a short stabilization period, low threshold for measuring exacerbation of symptoms that may have been only transient in nature, and psychosocial stressors.⁴⁵

Poor or partial Li response has also been associated with the age of illness onset, mixed status and comorbid

presence of ADHD or psychosis in some,^{47,48} but not all studies.^{44,49}

Results of an open-label study suggest that Li may be useful for acute bipolar depression in adolescents.⁵⁰ Patel and colleagues reported a 6-week trial involving



27 adolescents. The authors reported a response rate of 48% using a $\geq 50\%$ reduction in baseline Child Depression Rating Scale Revised (CDRS-R) scores and a remission rate of 30% using a CDRS-R score ≤ 28 and a CGI-BP improvement score of 1 or 2.

Currently, the ongoing Collaborative Lithium Trial⁵¹ is an important study that may provide important data about the pharmacokinetics, safety, short and long term effectiveness of Li in children and adolescents with BD. Results of this study are still pending (clinicaltrials.org NCT00442039).

Li is usually well tolerated. Common difficulties found in most studies include: nausea, headache, tremor, thyroid dysfunction, acne, weight gain, and diabetes insipidus.⁵² Nevertheless, side effects of neurological origin appear to be more frequent in young children.⁵³ One study with children younger than 13 treated for aggressive behavior with low doses of Li showed significant side effects such as enuresis, asthenia and ataxia.⁵⁴ Li is teratogenic and its prescription is not recommended especially during the first trimester of pregnancy, due to increased risk of Ebstein's anomaly,⁵⁵ a congenital defect of the tricuspid valve. Recommendations for laboratory monitoring of Li include complete blood counts, thyroid panels, blood urea nitrogen, creatine, serum calcium, urinalysis and pregnancy screening at baseline and every 3–6 months thereafter.⁵⁶

Divalproex sodium

Divalproex sodium (DVP) has been approved by FDA as monotherapy for treatment of acute manic episode in adults, but not in pediatric BD.

Its pharmacological effects include decreased dopamine turnover, decreased N-methyl D-aspartate currents and increased GABA levels. DVP exercises its antimanic power through the inhibitory effect of GABA in the brain.²⁸ The active molecule is the ion valproate which has an elimination half-life from 11 to 20 h. Inter and intraindividual variability of the plasma levels is frequent. DVP has a complex metabolism mechanism, mostly by beta-oxidation or conjugation via glucuronidation. To a lesser degree it is also metabolized through CYP450 activity. DVP is an inhibitor on the CYP and UDP-glucuronosyltransferases (UGTs).³² Numerous drug interactions may modify its plasma concentrations.⁵⁷ For DVP

the recommended target dose is 10–20 mg/kg with a therapeutic range from 50 to 100 mg/L.⁵⁸

Guidelines for the treatment of type I BD in children and adolescents recommend using DVP alone or in combination with an atypical antipsychotic.¹⁸ However, most open-label and randomised trials of DVP in BD youth have only evaluated a modest number of subjects.⁵⁹ In addition, to date, there is only one published randomized, placebo-controlled study with negative results for DVP as monotherapy for the treatment of mania or mixed episodes in pediatric BD type I.⁶⁰ Wagner and colleagues,⁶¹ conducted an open-label trial for 2-to-8 week in 40 bipolar youth followed by a double-blind, placebo-controlled, discontinuation phase for the 17 responders. The authors found a response rate of 61%, using a $\geq 50\%$ decline in YMRS scores from baseline. In the open trial significant reductions were also reported for the CGI-Severity scale, Brief Psychiatric Rating Scale (BPRS), and Hamilton Rating Scale for Depression (HDRS), although 53% of participants required adjunctive medications. Moreover 58% of subjects discontinued the open-label portion of the study prematurely, because of ineffectiveness, non-compliance and drug intolerance. 14 of 17 participants also discontinued the double-blind portion prematurely. The limited sample size affected the statistical power to analyse the double-blind phase of the study. Recently a multicenter double-blind, randomized, placebo-control trial of extended-release (ER) DVP was published. It was conducted for 4 weeks in 150 bipolar subjects (aged 10–17 years) presenting a manic or mixed episode.⁶⁰ There was no statistically significant difference between DVP ER and placebo in the YMRS total score means change and other secondary efficacy measures. Authors reported a response rate (reduction $\geq 50\%$ in YMRS scores from baseline to final evaluation) of 24% in the DVP-ER group and 23% in the placebo group. These response rates are lower than those reported in other studies.⁶² A possible explanation is the outpatient setting of the study as compared to the inpatient setting in studies showing higher response rates.

Kowatch and colleagues⁴⁹ in a randomized trial compared the effectiveness of Li, DVP and CBZ, reporting a 53% response rate in the DVP group,



where response was defined as a $\geq 50\%$ decline in YMRS total score. They concluded that DVP may be as effective as Li or CBZ as acute monotherapy for bipolar youth. Findling and colleagues⁶³ led a double-blind, 18-month controlled trial comparing the long term effectiveness of DVP with Li in youth (aged 5–17 years) with BD. They reported that neither was superior to the other when utilized as a maintenance treatment. Subjects in both groups did not differ with respect to CDRS-R, YMRS or CGAS scores, or for time to mood relapse, and neither medication was particularly effective. Recent data suggest that DVP may be less effective than atypical antipsychotics in the acute treatment of pediatric BD.^{62,64}

In summary, there is some evidence that suggests that DVP may be useful for the treatment of acute mixed and manic episodes, and maintenance therapy in pediatric population. However the only placebo-control randomised control trial (RCT), has failed in showing efficacy of DVP as compared to placebo in acute mixed and manic episodes. DVP may be particularly useful in combination therapy with Li⁶⁵ and for patients whose symptoms have not been responsive to Li or DVP in monotherapy.^{63,66}

In a recent study, the most common side effects in children and adolescents with BD treated with DVP were weight gain (16%), nausea (9%) and increased appetite (8%). Other side effects were sedation, headache, GI symptoms and increases in mean plasma ammonia level.⁶⁷ DVP has also been associated with pancreatitis, hepatotoxicity, alopecia, thrombocytopenia, hyperammonemia and PCOS. Due to its side effects related to PCOS and teratogenic effects (neural tube defects), clinicians should be cautioned when prescribing DVP in adolescents females.⁶⁸

Recommendations for laboratory monitoring include obtaining complete blood counts, liver function tests and pregnancy screening at baseline and every 6 months thereafter, as well as careful monitoring of menstrual cycles in girls.⁶⁹

Carbamazepine

Carbamazepine (CBZ) has FDA treatment indications for acute mixed and manic episodes in adults with BD. Nevertheless, there is very limited evidence from

methodologically stringent studies to support its use in the treatment of youths.

Pharmacological effects of CBZ include increased sodium influx, the release of glutamate, inhibition of adenosine A1 and dopaminergic activity. Its target dose is 10–20 mg/kg/d, with serum levels of 4–14 ug/mL. CBZ is an inducer of liver metabolism and therefore decreases plasma levels of others compounds such as DVP.²⁸

Published data in children and adolescents with acute mixed and manic states consist basically of case reports, retrospective chart reviews^{70–72} and several open trials.^{49,73,74} Davanzo and colleagues⁷¹ reported a retrospective review suggesting that by week 2 of hospitalization both Li and DVP may be more efficacious than CBZ in bipolar pre-adolescents. On the other hand, in the previously discussed study led by Kowatch and colleagues⁴⁹ in which Li, DVPX and CBZ were compared, CBZ was shown to be efficacious with a response rate of 38% similar to Li and DVP. After finishing this trial with a single mood stabiliser, subjects were recruited for an extended phase lasting for another 16 weeks.⁷⁴ In this extended phase, 35 subjects were openly treated with their acute phase mood stabiliser (Li, CBZ or DVP), or a second psychotropic medication was added based on response, such as MS, stimulants, antidepressants or antipsychotics. 60% of the participants received a second treatment over the 6 month duration of the study. The therapeutic response rate was 80% according to the YMRS. These results showed that the association of a MS with another psychotropic drug was superior to monotherapy with a MS.

Recently, an 8-week open-label prospective trial of CBZ-ER monotherapy in pediatric BD (aged 6–12 y/o) has been published. 27 subjects were enrolled, but only 16 (59%) completed the trial. There was a modest antimanic effect, and a significant improvement in the severity of depression, psychosis and ADHD symptoms.⁷³

Common adverse effects associated with CBZ include dizziness, diplopia, headache, GI complaints, transient leukopenia and skin rash with severe side effects including SIADH, neutropenia and agranulocytosis.⁷⁵ In addition, CBZ carries a risk of Stevens-Johnson syndrome in subjects of Asian ancestry who had the HLA-B*1502 allele.⁷⁶



Lamotrigine

In 2003 Lamotrigine (LMG) was approved by the FDA for the maintenance treatment of BD type I in adults. Several trials in adults suggest that its use is beneficial principally for the treatment of depressive symptoms.^{77,78}

Studies of the use of LMG in youths are scarce. One open-label study,⁷⁹ suggests that LMG may be beneficial for adolescents with bipolar depression. In 20 adolescents with BD who were experiencing a depressive episode, LMG was used for 8 weeks either as monotherapy ($n = 13$) or adjunct therapy to other medications ($n = 7$), including mood stabilizers, antipsychotics and stimulants. The primary effectiveness measure was a CGI-I ≤ 2 , and the secondary criterion was a decrease of 50% in the CDRS. 84% of the subjects reported to have a positive response to LMG according to the CGI-I and 68% had a decrease of at least 50% in the CDRS. Pavuluri and colleagues⁸⁰ published a 14-week open trial with 46 BD type I or II in a manic/mixed or hypomanic episode aged 8–18. During the first 8 weeks, subjects received a SGA to stabilize the acute symptoms associated to LMG. In the following 6 weeks, LMG was used as monotherapy. The authors reported a response rate on manic symptoms of 72% (YMRS < 12), on depressive symptoms of 82%, (CDRS-R < 40), and a remission rate of 56% (CGI ≤ 2) at the 14-week end point. Authors concluded that LMG appears to be effective in maintaining symptom control in bipolar youths. In a third, 12-week open-label trial study in 39 children and adolescents with BD spectrum, authors also reported improvement in mood symptoms (mania and depression) as well as ADHD and psychotic symptoms.⁸¹

Despite promising results in these open-label clinical trials with LMG, randomized placebo-control studies are necessary to confirm the efficacy of LMG in youth with BD.

At the start of this medication is necessary to be careful since rapid titration has been associated with Stevens-Johnson syndrome. Furthermore, it occurs more frequently in youths than in adults.⁸²

The pharmacokinetics of LMG are linear, and most of it is conjugated by the UGT's.³² It is important to remember that if LMG is taken with DVP the risk for rash may increase because DVP inhibits glucuronidation increasing plasma levels of LMG.

The recommendation is to start at 25 mg/day titrating 25 mg every 2 weeks. For subjects taking DVP doses should be halved. Other commonly reported side effects are headache, fatigue and nausea.^{79,80} Skin-rash has also been reported and usually resolves after discontinuation of treatment.⁸¹

Oxcarbazepine

Oxcarbazepine (OXC) is an antiepileptic drug with a chemical structure similar to CBZ, but with a different metabolism mechanism. OXC has no FDA indication for treatment in either adult or pediatric BD.

OXC is quickly absorbed after oral administration, exhibits linear pharmaco-kinetics and no auto-induction occurs. Shorter elimination half-lives have been reported in children as compared to adults. The potential interaction of OXC is relatively low. However, OXC appears to decrease the plasmatic level of topiramate and LMG.⁸³

There is little evidence to support the use of OXC in the treatment of acute mixed and manic episodes in children and adolescents. Wagner and colleagues⁸⁴ reported the results of a 7-week multicenter randomized double-blind, placebo-controlled trial of OXC in 116 youth with BD type I. Using the YMRS as the primary outcome measure, there was no statistically significant difference between both groups (OXC vs. Placebo). Furthermore, results suggest that potentially OXC may worsen symptoms in BD youth. Adverse effects included dizziness, nausea, somnolence, fatigue, rash and diplopia.

Topiramate

Topiramate, like OXC, has no FDA indication for treatment of either adult or pediatric BD. Topiramate is a glutamate release antagonist and a GABA reuptake inhibitor.²⁸

Studies suggest that topiramate is not effective for the treatment of acute mixed or manic mood states in adults with BD.⁸⁵ DelBello and colleagues⁸⁶ published a retrospective chart review of topiramate as adjunctive treatment of bipolar youths. They reported response rates of 73% and 62%, using CGI ≤ 2 as improvement criteria, for mania and overall illness, respectively. The same work group⁸⁷ led a multicenter 4-week, prospective, double-blind, placebo-controlled trial evaluating the effectiveness of topiramate in children and adolescents with BD. This study was



initially designed to enrol approximately 230 subjects but the study was prematurely discontinued because of negative results of topiramate for adults with BD and only 56 subjects were recruited. Preliminary analysis of this sample showed that topiramate-treated youths had a double reduction in mean total YMRS scores compared to placebo group. Results were inconclusive since the limited sample size affected the statistical power to detect significant differences.

The most common adverse effects associated with topiramate are cognitive disturbance, GI symptoms, sedation, decreased appetite, and paresthesias. As topiramate has been associated with weight loss, it has been used to offset weight gain associated with SGAs.⁸⁸ Wozniak and colleagues⁸⁹ published an open label trial with pediatric bipolar comparing olanzapine as monotherapy and topiramate plus olanzapine. They concluded that combination treatment of olanzapine with topiramate induced a reduced weight gain but did not lead to greater reduction in symptoms of mania as compared to olanzapine alone.

Second generation antipsychotics (SGAs)

Atypical antipsychotics appear to have mood-stabilizing properties. It has been hypothesized that their antimanic effect is related to dopamine receptor blockade, while their anti-depressant effect is related to the blockade of serotonin 5-HT₂ receptors. However, no hypotheses exist for the mechanism of action of SGAs in preventing recurrences of BD in the long-term.⁹⁰ A recent review has analyzed the efficacy of the treatment of SGAs in BD youth with manic or mixed episodes, using the concept of the number of subjects needed to treat (NNT) and the risk for the adverse effects using the number needed to harm (NNH).¹⁹ The NNT is the number of subjects who need to be treated with a specific treatment to yield one additional good outcome compared with placebo. The lower the NNT the more effective is the treatment. Single-digit NNT figures show at least 10% superiority over placebo, and demonstrate efficacy in the treatment of disease. On the other hand, the NNH indicates the number of subjects that need to be exposed to a risk factor to cause harm in one patient. The higher the NNH, the less likely are adverse effects to occur. Typically, double digit NNHs are accepted, as they show no

more than a 10% increase in risk when compared to placebo. We will briefly comment on the NNT and NNH when reviewing each SGAs (Table 2).

Risperidone

Risperidone was the first SGA approved by the FDA to treat acute mania or mixed BD episodes in youths (≥ 10 years) as monotherapy in 2007.¹⁹ Risperidone is an antagonist of serotonin 5-HT₂ and dopamine D₂ receptors, as well as alpha-1 receptors, and is available as tablets, dissolvable tablets, oral solution and depot intramuscular injections. It is metabolized by CYP2D6 and its mean half-life when administered orally is >20 h.⁹¹ The recommended dose in children and adolescents with acute manic or mixed episodes is to start with 0.25 mg/day increasing to 0.5–1 mg daily, with a target dose of 2.5 mg/day once, twice or three times daily.¹⁹

Several studies report that risperidone is effective in treatment of child and adolescent mania.^{64,92–96} Frazier and colleagues⁹⁴ conducted a retrospective chart review with 28 bipolar youths that received risperidone during 6–8 months. 82% of the subjects presented improvement in manic symptoms using the CGI-I score < 2 . Also, Biederman and colleagues⁹³ in a 8 week open-label, prospective study with risperidone in 30 BD, aged 6–17 years showed that 70% of the sample had a decrease in manic symptomatology as defined by a CGI-I score < 2 .

In another open-label trial, 37 subjects with BD type I, aged 5–18 years were randomized to receive risperidone (0.75 ± 0.75 mg/day) in combination with DVP or Li during 6 months. The YMRS and CGI-Severity scores improved significantly over time in both groups. There were no statistically significant differences between groups.⁹⁶

Haas and colleagues⁹⁵ reported a 3 week multicenter, randomized, double-blind, placebo-controlled 3-arm trial in 169 BD subjects aged 10–17 years experiencing a manic or mixed episode. Subjects were randomized to placebo, risperidone 0.5–2.5 mg/day, or risperidone 3–6 mg/day. Authors reported a greater decrease of mean YMRS total score in the risperidone groups compared to the placebo group. No differences in response rates were reported between both risperidone groups. The combined risperidone group had a response rate of 61% vs. 28% in the placebo group. EPS and

**Table 2.** Second generation antipsychotics commonly used for the treatment of children and adolescents with BD.

Medication	FDA approval	Half life	Recommended dosing	Side effects	Young mania rating scale response rate (NNT)	≥7% weight gain (NNH)
Risperidone	Yes Acute manic or mixed episodes in youths aged ≥10 years as monotherapy	20–24 h	To start with 0.25 mg/day increasing to 0.5–1 mg daily Target dose of 2.5 mg/day once, twice or three times daily	EPS, weight gain and hyperprolactinemia. Somnolence, headache, GI symptoms and fatigue	3	11
Olanzapine	Yes Acute manic or mixed episodes in adolescents aged 13–17 years	21–54 h	To start with 2.5 mg/day Target dose of 5–20 mg once or twice daily	Weight gain, metabolic syndrome, hepatic enzyme levels, hyperprolactinemia, appetite, sedation and to a lesser degree EPS.	4	2.5
Quetiapine	Yes Acute manic or mixed episodes in youth aged 10–17 years as monotherapy or in combination with Li or DVP	3 h	To start with 50 mg/day taken at bedtime Target dose of 300–600 mg once or twice daily.	Orthostatic hypotension, somnolence, sedation, dizziness, weight gain and headache.	4.2	8.2
Aripiprazole	Yes Acute manic or mixed episodes as monotherapy in youth aged 10–17 years Maintenance treatment	75 h	To start with 2 mg/day. Target dose of 10–30 mg once or twice daily.	Sedation and somnolence, fatigue, akathisia and EPS, salivary hypersecretion and GI symptoms.	3.6	28
Ziprasidone	No	4 h	To start with 20 mg twice daily. Target dose of 80–160 mg once or twice daily.	QTc prolongation. Sedation, somnolence, headache, nausea, fatigue and dizziness.	3.7	33
Clozapine	No	12 h	To start with 25 mg daily. Target dose of 150–400 mg once or twice daily	Agranulocytosis, orthostatic hypotension, sedation, sialorrhoea, constipation, weight gain, metabolic abnormalities, seizures, myocarditis	N/A	N/A

Abbreviations: EPS, Extrapyramidal symptoms; GI, Gastrointestinal; NNT, number needed to treat; NNH, Number needed to harm.

prolactin levels were significantly greater in the high-dosage risperidone group. Therefore, results indicate that risperidone 0.5–2.5 mg has a better risk–benefit profile than risperidone 3–6 mg. These results yield a NNT = 3 for risperidone as compared to placebo.¹⁹

Pavuluri and colleagues⁶⁴ reported a 6-week, double-blind, randomized, clinical trial in 66 youth aged 8–18 year with mania. Subjects were randomly assigned to either risperidone (0.5–2 mg/day) or DVP (60–120 µg/ml). The response and remission rate on YMRS were greater for risperidone than for



DVP (78.1% vs. 45.5% and 62.5% vs. 33.3%). The drop-out rate was greater in the DVP group (48%) than in the risperidone group (24%), with increased irritability being the most common reason for drop-out in the DVP group. These results suggest a greater and quicker improvement of manic symptoms with risperidone than with DVP.

There are no studies with risperidone for bipolar depression and long-term maintenance treatment.

The most frequent and problematic adverse effects described with risperidone are EPS (especially at high doses), weight gain and hyperprolactinemia. Other adverse effects are somnolence, headache, GI symptoms and fatigue.⁹¹ Weight gain with risperidone is greater in children and adolescents as compared to adults (16). Defining clinically significant weight gain as a $\geq 7\%$ increase in weight from baseline to endpoint, the NNH with risperidone is 11 as compared with placebo. Also the NNH for hyperprolactinemia in subjects receiving risperidone as compared with placebo was 1.3.¹⁹

Olanzapine

Olanzapine was approved by the FDA in 2009 to treat manic or mixed episodes of BD type I in adolescents aged 13 through 17 years.¹⁹ Olanzapine is an antagonist of serotonin 5-HT_{2A}, 5HT_{2C}, 5-HT₃ and D₂ receptors and weakly binds to the beta-adrenergic, benzodiazepine, GABA-A and muscarinic receptors. Its absorption is not affected by food in clinical trials of adults and has a long half-life (21–54h). In pharmacokinetic studies of youth, an increased concentration-to-dose ratio has been observed. It is metabolized by CYP1A2 and 2D6 and therefore, special care should be taken when simultaneously prescribing an antidepressant, such as fluoxetine that is also metabolized by CYP2D6.⁹⁷ Olanzapine is available in tablets, orally disintegrating tablets and injectable formulation. It may be initiated at 2.5 mg/day and titrated to a target dose of 5–20 mg once or twice daily.⁹⁷

Several case series,^{98,99} open-label prospective studies^{100,101} and a double-blind placebo-controlled study¹⁰² indicate that olanzapine may be useful for the treatment of mania. Frazier and colleagues¹⁰¹ conducted the only trial of olanzapine-treatment including BD subjects <10 years old. They reported an 8-week open-label prospective trial of olanzapine monotherapy (dose range: 2.5–20 mg/d) in 23 BD aged 5–14 years.

In this trial response rate (defined as a >30% decrease in YMRS scores and CGI ≤ 3) was of 61%. Similarly, in a 4-week, open-label, prospective study of olanzapine monotherapy (dose range: 10–20 mg/day), in 20 BD type I inpatients aged 12–18 years, DelBello and colleagues, showed a response rate of 74% ($\geq 50\%$ decrease in YMRS scores) and a 59% remission rate at study endpoint.¹⁰⁰ Tohen and colleagues,¹⁰² reported a 3-week multicentre, double-blind, randomized placebo-controlled trial of olanzapine (n = 107) versus placebo (n = 54) in BD subjects aged 13–17 years in a manic or mixed episode. The primary outcome measure was the mean change from baseline-to-endpoint in the YMRS score, and was significantly greater for subjects receiving olanzapine compared to placebo. Furthermore, a greater proportion of olanzapine-treated subjects met response (49% vs. 22%) and remission (35% vs. 11%) criteria. These results yield a NNT = 4 for olanzapine as compared to placebo.¹⁹

Although there are no studies with olanzapine in long-term maintenance treatment in youth with BD, its use as a first line of treatment is limited due to its side-effects profile as discussed below. There are no studies for the treatment of bipolar depression with olanzapine in youth.

The most frequent and problematic adverse effects described with olanzapine are weight gain, metabolic effects such as increase in fasting glucose, total cholesterol and triglycerides, hyperprolactinemia and increased hepatic enzyme levels. Other side effects include increased appetite, sedation and to a lesser degree EPS.^{17,97,103} Based on a randomized placebo-control trial,¹⁰² the incidence of clinically significant weight gain ($\geq 7\%$) was 42% in the olanzapine group versus 2% in the placebo group, yielding a NNH = 2.5.¹⁹ The magnitude and incidence of weight gain is greater in adolescents than in adults.¹⁶ Some studies have reported that metformin could be effective in reducing associated weight gain with antipsychotics.^{104,105} Also combined treatment olanzapine plus topiramate has been suggested to reduce weight gain during treatment.⁸⁹

Quetiapine

In 2009 quetiapine was approved by the FDA for the acute treatment of manic episodes of BD in youth aged 10–17 years as monotherapy or in combination with Li or DVP.¹⁹ Quetiapine has a high affinity for



histaminergic H₁ and α_1 -adrenergic neuroreceptors. It also exhibits affinity for serotonin 5-HT₂ and 5-HT_{1A} and dopamine D₁ and D₂ receptors, showing a higher selectivity for 5-HT₂ relative to D₂ receptors. Quetiapine absorption is not affected by food.¹⁰⁶ It is metabolized by CYP3A4 and has an average half-life of 3 h in children.¹⁰⁷ The recommended starting dose is 50 mg/day taken at bedtime, increased to 100 mg/day after 2 days, and then increased to a target dose of 300–600 mg after 2 additional days once, twice or three times daily.¹⁹

DelBello and colleagues reported a 3-week, multi-center, double-blind, randomized, placebo-controlled trial, of 277 BD aged 10–17 years, in a manic/mixed episode receiving quetiapine (dose range 400–600 mg/d) versus placebo. The YMRS response rate was higher for those receiving quetiapine than for those receiving placebo (61% vs. 37%, NNT = 4.2).¹⁹ In a 6-week, randomize, double-blind, placebo-controlled study, 30 manic or mixed BD I adolescents (12–18 years) received an initial DVP dose of 20 mg/kg and were randomly assigned to combination therapy with quetiapine or placebo. Primary efficacy measures were change in YMRS score from baseline to endpoint and YMRS response rate. The DVP plus quetiapine group was significantly more effective in both measures than the group treated with DVP alone. However, mild or moderate sedation was more common in the DVP plus quetiapine group than DVP alone.¹⁰⁸ The same research group,⁶² in a 4-week, double blind, randomize study of quetiapine (400–600 mg/d) versus DVP (serum level 80–120 μ g/mL) for the treatment of adolescent mania found that quetiapine is at least as effective as DVP with a quicker response than DVP for the treatment of acute mania in adolescents with BD.

Quetiapine has been approved by FDA for the treatment of depressive episodes in adults with BD type I and II. In children and adolescents one study has evaluated the efficacy of quetiapine in the treatment of depressive episodes in BD type I.¹⁰⁹ The study consisted of an 8-week, double-blind controlled study in 32 adolescents aged 12–18 years comparing quetiapine (n = 17) versus placebo (n = 15). There was no statistically significant difference between both groups in change in the CDRS-R scores from baseline to endpoint. Additionally, there were no group differences in the secondary outcome measures or overall response and remission rates. High placebo response rates were also reported.

The most common side effects associated with quetiapine are somnolence, sedation, dizziness, and headache. Rates of clinically significant weight gain were 12.2% in quetiapine versus 0% in placebo yielding a NNH = 8.2.¹⁹ Other frequently reported adverse effects of quetiapine in younger populations include orthostatic hypotension¹⁰⁸ possibly related with quetiapine affinity for histaminic and α_1 -adrenergic receptors.

Aripiprazole

The FDA has approved aripiprazole to treat acute manic and mixed episodes as monotherapy in children and adolescents (≥ 10 years), and for maintenance treatment of BD, from data extrapolated from adult studies (110). Aripiprazole is a partial agonist of dopamine D₂ and serotonin 5-HT_{1A} receptors and an antagonist of serotonin 5-HT_{2A} receptors. Aripiprazole also has strong affinity for D₃ receptors, moderate affinity for D₄, 5-HT_{2C}, 5-HT₇, alpha-1 adrenergic, histamine H₁ receptors and the serotonin reuptake transporter, and no affinity for the cholinergic muscarinic receptor. Aripiprazole has got linear pharmacokinetics and a long half-life in serum (up to 75 hours in adults). It may be administered once daily, and food does not affect its absorption. Aripiprazole is a major substrate for both CYP2D6 and CYP3A4; although it has no inhibitory or inducing effects on these CYP systems it may interact with other drugs that are strong inhibitors (fluoxetine, paroxetine) or inducers (carbamazepine) of these CYP. It is available in tablet, dissolving tablet and oral solution forms. The recommended dosing of aripiprazole in children and adolescents with acute mania or mixed episodes is to begin with 2 mg/day. After 2 days, increase to 5 mg/day and increase to the target dose of 10 mg/day after 2 additional days. Subsequent dose increases should be administered in 5 mg/day increments to a target of 10–30 mg/day once or divided into twice daily.¹¹¹

In a 4-week multicenter randomize, double-blind, placebo-controlled trial, 296 BD type I aged 10–17 years with a manic or mixed episode, were randomized to placebo (n = 99), aripiprazole 10 mg/d (n = 98) or aripiprazole 30 mg/d (n = 99).¹¹² YMRS response rate was greater for both aripiprazole groups (45% 10 mg, 63% 30 mg) than placebo group (26%) yielding a NNT = 3.6.¹⁹ In an 8-week open-label prospective study with aripiprazole in 19 BD youth aged 6–17 years, results showed a YMRS response rate of 79%. No improvement was observed in depressive symptoms.¹¹³



Two other clinical trials have evaluated the efficacy of aripiprazole in youth with BD and ADHD comorbidity. Tramontina and colleagues, showed in an open clinical trial¹¹⁴ followed by a double blind placebo controlled trial¹¹⁵ that there was an improvement in affective symptoms, but not in ADHD symptoms.

To date, there are no published studies with aripiprazole for the treatment of bipolar depression and for the maintenance treatment of BD in children and adolescents.

The most common adverse effects associated with aripiprazole are sedation and somnolence, fatigue, akathisia and EPS, salivary hypersecretion and GI symptoms. Acute dystonia was reported in subjects receiving 30 mg/day. There is uncertainty regarding the development of tardive dyskinesia (TD) in this population. In adults cases of TD secondary to aripiprazole have been described, although cases of TD that improved with aripiprazole have also been described.^{111,112,116} Also aripiprazole may decrease plasma levels of prolactin.¹¹² When compared to placebo, there were no statistically significant changes in weight gain (NNH = 28),¹⁹ metabolic or cardiovascular parameters.

Ziprasidone

Ziprasidone was approved by the FDA for the treatment of acute manic episodes in adults,¹¹⁷ but not in pediatric mania.²⁵ Ziprasidone exhibits a high antagonist activity at dopamine D₂ and serotonin 5HT_{2A}, 5HT_{2C}, and 5HT_{1D} receptors and agonist activity at 5HT_{1A} receptors. It also binds to noradrenaline and serotonin transporters, and shows low affinity for histamine H₁, α_1 -adrenergic, and muscarinic M₁ receptors.^{118,119} Ziprasidone absorption increases by >50% when taken with food and it is important to inform patients and their families about this. Approximately 1/3 of ziprasidone is metabolized through CYP3A4 and 2/3 is cleared via reduction by aldehyde oxidase. It shows linear pharmacokinetics and a serum half-life of 4h approximately.^{118,120} Recommended dose for pediatric populations may be a starting dose of 20 mg twice daily, which may be titrated to 80–160 mg once or divided into twice daily.^{19,120}

Biederman and colleagues¹²¹ conducted an 8-week open-label trial of ziprasidone monotherapy in 21 BD youth aged 6–17 years showing a statistically significant improvement in mean YMRS scores and CGI. In a multicenter, 4-week, double-blind, placebo-controlled trial of ziprasidone in subjects

with BD I (manic or mixed) aged 10–17 years, 150 subjects were randomized to ziprasidone (flexible dose: 80–160 mg/d) and 88 to placebo. Results found that ziprasidone is an effective treatment for symptoms of bipolar mania with a safety profile in children similar to adults.¹²² To date, there are no studies of ziprasidone for treatment of bipolar depression or for long term maintenance treatment of BD.

The most common adverse effects are sedation, somnolence, headache, nausea, fatigue and dizziness. As compared with other SGAs, Ziprasidone has little effect on body weight gain, yielding a NNH = 33,¹⁹ or on metabolic parameters,¹¹⁸ and may be a more appropriate agent for subjects at high risk of developing metabolic syndrome. However, one of the most worrying adverse effects described with Ziprasidone is QTc prolongation via IKr blockade. QTc prolongation is not harmful in itself, but increases the risk of developing ventricular arrhythmia Torsades de Pointes.¹²³ Before starting treatment, it is recommended to rule out personal and family cardiac history, including sudden death. Additionally, electrocardiogram monitoring at baseline and following attainment of ziprasidone target dosage should be obtained.^{120,124,125}

Clozapine

Clozapine is the oldest of the atypical antipsychotics, but no randomized controlled trials for its use in bipolar youths exist. Therefore, clozapine has not been approved by the FDA. As in adults, its use is reserved for patients who have demonstrated resistance to other medication regimens.¹²⁶ Clozapine has a complex pharmacological profile. It shows low affinity to dopamine D₂ receptors and a more selective antagonism for D₄ receptors. It also shows antagonism for 5-HT_{2A} receptors, as well as adrenergic, cholinergic and histaminergic receptors.¹²⁷ Clozapine has a half-life of approximately 12 h. It is metabolized primarily by the CYP1A2, so smoking can cause induction of its metabolism, and somewhat later by CYP2D6 and 3A4. Clozapine should be started at a low dose (eg, 25 mg daily) and titrated slowly up to 150–400 mg once or twice daily depending on the patient's weight and pharmacological response.^{19,128}

Data of the efficacy of clozapine in youth with BD is limited to a few cases series and chart reviews that report significant improvement in mood symptoms,



aggression and functioning in youth with BD who did not respond to treatment with antipsychotics or mood stabilizers.^{129–131}

Clozapine has significant adverse effects that limited its use to non-responsive severe BD youth. Its use has been associated with agranulocytosis, and therefore requires repeated monitoring of blood plasma levels, seizures, myocarditis, and other adverse cardiovascular and respiratory effects. The most common adverse events associated with clozapine in youth include orthostatic hypotension, sedation, sialorrhoea, constipation, weight gain and metabolic abnormalities.^{19,127}

Paliperidone

Paliperidone is a metabolite of risperidone and one of the newer SGA. To date, there are no published studies of this agent in the pediatric BD population. Recently, two randomized placebo controlled trials in adults were published.^{132,133} At high doses it can induce EPS and hyperprolactinemia similar to risperidone.¹³⁴

Pharmacological Treatment of Bipolar Depression

Children and adolescents with BD present significant depressive symptoms as well as depressive episodes throughout their illness.⁷ Despite causing important functional impairment¹² and the increased risk for suicide,¹¹ there is limited data for treatment options in BD depression.

In adults, antidepressants have historically been the first option for treatment, but due to their propensity for inducing manic switching or cycle acceleration, this approach has been questioned.¹³⁵ The non-antidepressant medications considered as first-line treatments for adults, include Li, LMG, olanzapine-fluoxetine combination,¹³⁶ and quetiapine.¹³⁷ It is important to remember that youth, especially peripubertal children, may be more susceptible to pernicious effects of SSRIs than adults. SSRIs have been associated with increased suicidality in youth,¹³⁸ that finally led to the black-box warning on all antidepressants enforced by the FDA.¹³⁹

In a retrospective study of 52 children with BD who had been exposed to an antidepressant, 50% of the subjects experienced antidepressant induced mania in the 30 days after starting antidepressants and 25% of the subjects had new-onset suicidal ideation.¹⁴⁰ SSRIs should be used with caution in BD youth because of the

potential risk for mania or worsening mood instability, and the increased risk of suicidality.⁴⁶ AACAP's most recent guidelines for BD youth recommend that antidepressants should never be prescribed without the addition of at least one mood stabilizer.³⁷

As previously mentioned, two prospective open label trials have studied Li and LMG for bipolar depression in adolescents.^{50,79} These studies suggest that both medications may be useful for the treatment of bipolar depression. However, it is necessary to have larger, placebo-controlled trials to confirm these findings, especially knowing the increased rate of placebo response that has been shown in depression in youth.¹⁴¹ Despite studies showing efficacy in adults with bipolar depression, quetiapine monotherapy has failed to demonstrate efficacy in adolescents with bipolar depression in one randomized control trial.¹⁰⁹

Alternative treatments

Given some of the limitations of MSs and SGAs, attention of some clinicians has been turning to other possible treatments for BD, such as omega-3 fatty acids. There is some evidence in adults that dietary supplementation with omega-3 fatty acids may be beneficial in psychiatric conditions, including schizophrenia, mood disorders and borderline personality disorder.¹⁴² In an open label trial of omega-3 fatty acids, 20 youth with bipolar spectrum disorder, showed a modest improvement in manic symptoms.¹⁴³ In a 16-week, double-blind, placebo controlled trial of omega-3 fatty acids in 51 youth aged 6–17 years with symptomatic BD, no differences were found in reduction of mood symptoms. However in secondary analysis, serum omega-3 fatty acids levels were correlated with an improvement in overall illness and mania.¹⁴⁴ Other options, such as inositol, *Hypericum perforatum*, melatonin or acupuncture, have been tested for the treatment of BD with controversial results.¹⁴⁵ More double-blind, placebo-controlled trials are needed to determine the possible role of alternative treatments in youth with BD.

Pharmacological treatment of comorbid conditions

As noted above, the high rates of comorbidity of ADHD (60%) and anxiety disorders in pediatric BD



(40%)^{6,146} are an important characteristic of the disease. Stimulants are the most common pharmacological class used in this illness¹⁴⁷ but they may induce manic symptoms. Interestingly, two studies reported that comorbidity with ADHD decreased the response level for Li in bipolar adolescents.^{47,148}

The main goal of treating BD in children and adolescents with comorbid ADHD is first to stabilize the mood symptoms with either a MSs or SGAs, and if ADHD symptoms persist add a stimulant, starting with low doses and slowly increasing.^{149–151} Three randomized placebo control trials have investigated the efficacy of stimulants in ADHD symptoms in BD youth after mood stabilization. Two studies^{149,150} demonstrated efficacy, and another¹⁵¹ failed to show superiority of stimulants as compared to placebo. In an 8 week open label trial, Chang and colleagues,¹⁵² studied the efficacy of adjunct atomoxetine in 12 euthymic youth with BD and comorbid ADHD. Results suggested that atomoxetine was effective in improving ADHD symptoms; there was no change in mood symptoms. Two subjects were discontinued early due to worsening of their mood symptoms.

Comorbid anxiety disorders are also frequent. The habitual treatment used for anxiety disorders are SSRIs and as discussed previously, they have the potential to exacerbate manic symptoms. In bipolar adults, it has been reported that olanzapine and quetiapine may reduce comorbid anxiety, so it could be a first line option treatment in youth with BD and comorbid anxiety disorder.¹⁵³ Other treatment options may be the use of a GABAergic agents such as gabapentine⁴⁶ or benzodiazepines.²⁴ Benzodiazepines may be useful for short-term treatment but careful monitoring of symptoms for disinhibition and potential creation of tolerance and dependence is required.

Disruptive behavioral disorders are also common among children and adolescents with BD and may have legal repercussions.¹⁵⁴ Luckily, SGA and the mood stabilizers appear to be effective in modulating aggressive behaviour and irritability.^{155,156}

Psychotherapeutic interventions

The development of BD during childhood or adolescence disrupts ongoing developmental processes, causing marked global, academic, and social dysfunction.^{12,37} Although psychopharmacology assists the core symptoms

of the illness, they may not address the associated functional impairments. Consequently a multimodal treatment that compounds psychopharmacology and adjunctive psychosocial therapies is practically always indicated for early onset BD. The psychosocial interventions are usually focused on creating awareness and understanding of the disorder (psychoeducation), sleep hygiene, medication adherence, mood monitoring, skill building (communication, problem solving, emotion regulation and impulse control), enhancement of relationships, relapse prevention and a safety plan.³⁷

Some controlled data on psychosocial interventions is starting to emerge for children and adolescents with BD. Fristad and colleagues developed the multi-family psychoeducation groups (MFPG) for children with mood disorder aged 8 to 12 years, showing improved outcome as compared with a wait-list control.¹⁵⁷ Miklowitz and colleagues adapted their family-focused therapy for adolescents and reported positive results in a 2-year randomized clinical trial. They demonstrated that adolescents who received family focused intervention showed overall improvement in depressive symptoms.¹⁵⁸ Other psychosocial interventions that have been adapted for youth with BD are showing promising results in their preliminary data. Dialectical Behaviour Therapy (DBT) for adolescents with BD was adapted by Goldstein and colleagues.¹⁵⁹ Preliminary outcomes are positives with decreased rates of suicidality, nonsuicidal self-injurious behavior, emotional dysregulation, and depression symptoms after the intervention. Pavuluri and colleagues¹⁶⁰ developed the child- and family focused cognitive-behavioural therapy (CFF-CBT), for children 8–12 years old with bipolar spectrum disorders and their families. Preliminary results showed overall improvement and feasibility of the intervention. Other psychosocial interventions adapted for adolescents with BD are the interpersonal and social rhythm therapy (IPSRT-A)¹⁶¹ and the cognitive behavioural therapy (CBT) for BD.¹⁶²

Conclusions

Despite the controversy surrounding the phenomenology of BD in youth, different studies have clarified that the DSM-IV classic criteria have more validity than other clinical presentations such as



chronic non episodic irritability, aggressive behavior and attention problems.^{7,163,164} Consequently, before starting pharmacological treatment the first critical step is undertaking a good clinical assessment ruling out other psychiatric disorders (severe ADHD with conduct disorders, major depression with anxiety, severe mood dysregulation, etc) as treatment options differ for these conditions.⁵ A good indicator of BD mood symptoms is their episodic character whereas other behavioral disorders present with more chronic symptoms such as irritability or aggression.

At the same time, new evidence about the pharmacological treatment of manic and mixed episodes in BD youths have led to the recent approval by the FDA for SGAs to treat mania. Reviewing several randomized placebo controlled trials all SGAs have shown a similar efficacy in treating manic or mixed episodes with a NNT around 3–4. Differences among SGAs were found in their adverse events profiles. For example olanzapine, followed by quetiapine and risperidone showed significant weight gain as compared to aripiprazole and ziprasidone. Also adverse events such as EPS, hyperprolactinaemia and sedation vary across agents. Thus recommendation for ideal treatment options should be made personalized depending on an individual patients symptoms and their tolerance to an agent while minimizing potential adverse effects.¹⁹ DVP and Li have not shown the same short-term efficacy in the treatment of manic or mixed episodes in BPI when compared to SGAs: however, increased adverse events such as weight gain, EPS or somnolence are more common with SGAs as compared to MSs.¹⁶

On the other hand, the data on how to treat depressive episodes in youth with BD is still inconclusive. Open label studies suggest that Li or lamotrigine may be more effective for the treatment of depressive episodes while SSRIs should be used with caution due to their risk for inducing mania or mood instability. As with unipolar depression, high placebo response rates have been shown for treatment of depressive episodes in BD youth. Psychosocial treatment, although in early stages, may play an important role in the specific treatment of depression in BD youth in the future, as pharmacological treatment seems to be insufficient and associated with multiple side effects (especially SSRIs).

For treatment maintenance, open label studies suggest that MS such as Lithium or DVP in monotherapy or combination therapy (both MS or a

MS and a SGAs) may be effective in mood episode prevention. Monitoring medication therapeutic levels and thyroid profiles is necessary when using Li and DVP. DVP may not be indicated as a first treatment choice for adolescent females due to risk of PCOS. Research towards safer and effective maintenance therapy treatment options is necessary.

BD is highly comorbid with other Axis I disorders such as ADHD and anxiety disorder and specific treatments to manage these conditions may be also required. In general the efficacy of the medical treatment for BD must be balanced with safety and tolerance to optimize individual treatment selection; it is therefore important to monitor for specific adverse events.

The global impairment induced by BD in youth occurs during a sensitive neurodevelopmental period. Thus, clinicians should weigh the risk-benefit profile of uncertain long-term side effects of pharmacological treatment compared with the side effects of untreated bipolar disease in the developing adolescent. Research in psychosocial therapies is crucial for the long-term management of the illness, and the role that they may play in the treatment of comorbid conditions while providing support to the patient and the family in the management of social, family and educational functioning.

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