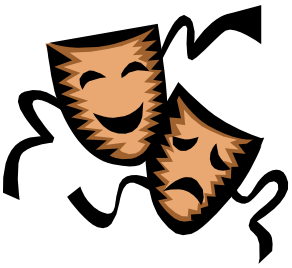
Revised Nov 9, 2009



Bipolar Disorder in Youth: Medication Guide for Primary Care Physicians

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Disclaimer

Where to Get this Handout

This handout is available from http://www.drcheng.ca in the Mental Health Information section. Any comments and suggestions are welcome and will help ensure this handout is helpful.

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Making the Diagnosis of Youth Bipolar

The diagnosis of youth bipolar is controversial. Mood swings are common in youth, and at what point does the severity constitute a psychiatric condition, and at what point does it constitute bipolar? Experts continue to debate the criteria for pediatric bipolar, and there are both “narrow” criteria (for youth that meet DSM criteria for Bipolar I, II or cyclothymia), and “broad” criteria for youth who have affect instability, but who do not necessarily meet DSM criteria for Bipolar I, II, or cyclothymia. Some have suggested using Bipolar NOS to describe atypical forms, which are most common in younger children.

Peak onset of bipolar (all ages) is generally 15-25, and generally it is accepted that adult criteria can be used in teenagers to make the diagnosis.

Definitions in Bipolar Disorder

Bipolar Disorder – a condition classically characterized by alternating, episodic highs and lows in energy. High phases (mania or hypomania) are classically characterized by increased energy, coincident with decreased need for sleep, pressure of speech, and increased goal-directed activities. Mood can be high (euphoric) or irritable (dysphoric). Low phases are classically characterized by low energy, coincident with increased need for sleep with depressed mood.

Rapid cycling—defined in DSM-IV-TR as four or more depressive, manic, hypomanic, or mixed episodes in the previous 12 months—is considered a longitudinal course specifier for bipolar I or II disorder. Episodes must be demarcated by: 1) full or partial remission lasting at least 2 months, or 2) or a switch to a mood state of opposite polarity.

Cycling variations include ultra-rapid (1 day to 1 week), ultra-ultra rapid or ultradian (<24 hours), and continuous (no euthymic periods between mood episodes). Rapid cycling occurs in an estimated 15% to 25% of patients with bipolar disorder, though psychiatrists in specialty and tertiary referral centers see higher percentages because of the illness’ refractory nature.

Rating Scales for Bipolar

The Child Mania Rating Scale-Parent version (CMRS-P) is the first rating scale designed and tested specifically to screen for PBD (Pavuluri et al., 2004b). It has 21 developmentally specific

items corresponding to DSM-IV-TR symptoms. A score of >15 (out of 63) reportedly indicates a 92% chance of having the diagnosis, but note that it is a screening and **not** a diagnostic tool.

Laboratory Investigations in Bipolar

Generally recommended baseline laboratory investigations (Chang, 2005) include:

- Thyroid screen, since hyperthyroidism may mimic mania, and hypothyroidism may cause depression or worsen rapid cycling of mood
- With any first-break psychosis or manic episode → consider neuroimaging (e.g. CT) to rule out mass lesion
- Consider EEG if any neurologic findings (e.g. focal findings), or evidence suggesting seizure – e.g. signs of possible seizure focus (abrupt onset of behavior change, repeated mannerisms, staring spells, change of consciousness, or symptoms consist with post-ictal state after rage episodes); temporal lobe epilepsy may occasionally present with anger outburst episodes that may resemble mania

Management of Bipolar Disorder

- Wean off all ineffective medications, e.g. such as antidepressants
  - Evidence suggests that SSRIs worsen symptoms by switching to or worsening mania (Biederman et al., 2000)

- In general, discontinue stimulants
  - However, if parents report stimulants have been helpful, then continue them but at lowest possible doses, and in long-acting forms ALONG with mood stabilizer

Treatment Guidelines for Bipolar

As of 2009, Kowatch has proposed the following algorithm

- First-line: antitypical antipsychotics such as aripiprazole, quetiapine, risperidone, ziprasidone
- Second-line: lithium, valproate, or olanzapine

Older practice guidelines for children and adolescents with bipolar disorder:
- Treatment Guidelines for Children and Adolescents with Bipolar Disorder, by the Child Psychiatric Workgroup on Bipolar Disorder;
- AACAP's Practice Parameters for the Assessment and Treatment of Children and Adolescents with Bipolar Disorder.

Medication Recommendations for Bipolar for Children and Adolescents

Medications for Bipolar Disorder:

A. "Simple" Bipolar

According to Wagner, 2005:

- For youth presenting with bipolar without psychosis, first-line treatment is
  - Monotherapy with traditional mood stabiliziers (1st line lithium, divalproex and 2nd/3rd line carbamazepine) **or**

- Atypical antipsychotics (olanzapine, quetiapine, and risperidone).

- For youth presenting with bipolar with psychosis, first-line treatment is combination of

  - Traditional mood stabilizer (1st line lithium, divalproex or 2nd/3rd line carbamazepine) **plus**

  - Atypical antipsychotic.

Duration of Treatment -- If patient has achieved remission for 12-24 consecutive months, consider medication tapering or discontinuation.

B. Bipolar with Comorbid Depression

There is a shortage of data for children and adolescents. However, the adult data suggests that if there are prominent symptoms of depression, then options for primary mood stabilizers (either alone or added to another agent) include (Bowden, 2002; Calabrese et al., 2000):

- First choice
  - Lithium or
  - Lamotrigine (Lamictal)

- Second choice
  - Combination of lithium plus lamotrigine.

- Third choice is a small dose of SSRI (in severe depression). A long-acting medication and psychoeducation are often effective (Wilens et al., 2003).

C. Bipolar with Persistent Aggression

Adult data suggests the following:

If mild aggression:
- Switch to second generation antipsychotic monotherapy if mild aggression is present.

If moderate to severe aggression:
- Use a combination of mood stabilizer and second generation antipsychotic is used (see Table 1 and Table 2).
- Anti-adrenergics (e.g. Clonidine (Catapres) or Guanfacine) may be tried for rage attacks (Prince et al., 1996).

Treatment Resistance

If symptoms fail to respond, then options include:

1) alternative monotherapy;
2) at least two trials of combination regimes of mood stabilizers plus SGA; and
3) triple therapy addressing comorbid conditions.

Atypical Antipsychotics – Dosing in Children and Adolescents

Kowatch (Kowatch, 2009) recommends that the atypical antipsychotics be considered as **first-line** therapy

Table from http://www.currentpsychiatry.com/pdf/0811/0811CP_Article2.pdf

Medication	Starting dosage (mg)	Target Dosage (mg/day)	Precautions
Aripiprazole	2.5-5 mg QHS	10-30	Monitor for CYP3A4, 3D6 interactions, weight, BMI, cholesterol, lipids, glucose
Olanzapine (Zyprexa)	2.5 mg bid	10-20	Monitor for CYP2D6 interactions, weight, BMI, cholesterol, lipids, glucose, prolactin
Quetiapine (Seroquel)	50 mg bid	400-1,200	Monitor for weight, BMI, cholesterol, lipids, glucose
Risperidone	0.25 bid	1-2.5	Monitor for EPS, hyperprolactinemia (and sexual side fx, including galactorrhea), weight, BMI, cholesterol, lipids, glucose, prolactin
Ziprasidone	20 mg bid	80-160	Check baseline ECG and as dose increases or if indicated; monitor prolactin

Mood Stabilizers: Dosing in Children and Adolescents

Agent • **Canadian Brand Name**	**Dosing and Comments**
Lithium • Lithium carbonate: Duralith, Carbolith, tabs 150, 300, 600 mg) • Lithium citrate: syrup 300 mg/5 mL)	Lithium is the only medication approved by the FDA for children with bipolar disorder (as of Oct 13, 2003) For acute phase, start at 15-30 mg/kg/day or 0.5-1.5 g/m^2 Maintenance dosing estimate: 10-30 mg/kg/day Dosage schedule: doses may be divided throughout the day, but <u>once daily dosing</u> is preferred with serum-lithium concentration is stabilized Maintenance target: • Acute mania 1.0-1.3 mmol/L (or mEq/L) • Maintenance 0.5-1.0 mmol/L (or mEq/L) Monitoring • Baseline weight, CBC, lytes, creatinine, BUN, glucose, Ca, P, TSH, β-HCG, urine R & M, ECG if >40 y/o or cardiac Hx • Lithium blood level after 5 d and 12-h post last dose; repeat until steady state in therapeutic range (i.e. until dosage and serum level have remained constant for 4-weeks) • Repeat Li levels q 3-6 mos, or if concerns about toxicity, or if potential for levels to be changed (e.g. drug interaction, or changing from one lithium preparation to another) • Repeat Ca, TSH, creatinine, BUN q 6-12 mos.
Divalproex sodium • Epival (tabs 125, 250, 500 mg, elixir available	Start 5-15 mg/kg/day (adults: 250 mg tid) Increase 5-10 mg / kg per week If the total dose a day is greater than 250 mg, may divide by bid dosing if better tolerated. Maintenance target: • Serum level 350-800 mmol/L • Dosage 15-60 mg/kg/day Maximum dosage 60 mg/kg/day (adults: 1000-1500 mg/day) **Screening recommendations for women of reproductive age taking VPA** • History to include FHx of PCOS, obesity, gestational diabetes, baseline menstrual history (to assess for oligomenorrhea and/or sub-fertility) • Labs: consider baseline androgens • Consider folic acid supplementation for patients considering pregnancy • If suspicion of PCOS emerges, consider referral to endocrinology **Baseline** • Baseline weight, CBC, lytes, creatinine, BUN, LFT (AST, ALT), coagulation (PT, PTT), β-HCG, urine R & M **Monitoring** • Valproate blood levels after 3 d and 12 hr post last dose); repeat until steady state • Repeat levels and baseline bloodwork at q 3-6 mos (if stable q 12 mos). • Re-do CBC, coagulation tests (PT/PTT) in event of spontaneous bruising, bleeding • Watch for the rare VPA-induced carnitine deficiency • Treatment is carnitine supplementation, with 50-100 mg/kg/day

	• Carnitine dosage 50-100 mg/kg/day
	• Tablets supplied 330 mg
	• Carnitine Dosage
	  • Adults: 990 mg bid-tid (i.e. 1-3 g/day)
	  • Infants/children: start at 50 mg/kg/day, and titrate up to 50-100 mg/kg/day with maximum of 3 g/day

Valproic Acid • • Alti-Valproic • Depakene • Deproic • Dom-Valproic • Med Valproic, • Novo-Valproic • Nu-Valproic • Penta-Valproic • pms-Valproic Acid • pms-Valproic EC	Essentially same instructions as for Divalproex, but generally not used due to being more difficulties being tolerated. Divalproex and valproate sodium form valproic acid in the body
Zinc	Dosage: 100 mg (RDA 15 mg) Indicated for hair loss on valproate
Selenium	Dosage: 200 mcg (RDA 70 mcg) Indicated for hair loss on valproate
Lamotrigine • Lamictal (Tabs 25, 100, 150 mg)	Dosage for adults/adolescents <u>not on valproate</u> • Start: 25 mg/day x 2-weeks, then increase to 50 mg/day x 2-weeks, then to 100 mg/day then reassess • Usual target dose: 150-250 mg bid Dosage for adults/adolescents <u>on valproate</u> (which can double or triple serum lamotrigine levels), start with lower lamotrigine doses • Start: 12.5 mg/day x 2-weeks, then 25 mg/day x 2-weeks, then to 50 mg/day then reassess • Usual target dose: 50-100 mg bid (if taking valproate) Monitoring: • Baseline creatinine, BUN, LFT (PT, PTT, AST, ALT), β-HCG • No routine blood levels nor monitoring • Watch for Stevens-Johnson syndrome
Carbamazepine • Tegretol (Chewable 100 mg, Tabs 200 mg, Oral susp'n: 100 mg/5 mL, CR (slow release – bid)	Carbamazepine is 2nd or 3rd line due to risk of adverse effects (rash, agranulocytosis) Start at 100-200 mg daily Target: Serum level 4-12 Monitoring • Baseline weight, CBC, lytes, creatinine, BUN, LFT (AST, ALT, ALP, Bilirubin, PT, PTT), β-HCG • ECG if >40 y/o or cardiac history • Blood levels after 3 d (12-hr post last dose) • Repeat until steady state in therapeutic range (4-12 ng/mL; 17-50 µmol/L) • Watch for levels dropping over first 2-months due to induction • Repeat levels and baseline bloodwork at 6-wks and q 6 mos.
Gabapentin	Start at 100-200 mg daily

• Neurontin (tabs 100, 300, 400 mg)	5-12 years: 25-35 mg/kg/day >12 years: up to 2400 mg/day Monitoring: • Baseline creatinine, BUN, LFT (PT, PTT, AST, ALT), β-HCG, weight • No routine blood levels nor monitoring

Monitoring Recommendations Once Stabilized

With divalproex
- Serum valproate, CBC, AST and ALT every 6-months

With lithium
- Renal panel (since lithium is renally excreted) and TSH (to check for hypothyroidism) every 6-12 months)

With any mood stabilizers/antipsychotics
- Fasting glucose/lipid profile important every 6-12 months, or if weight gain occurs, in order to monitor for developing type II diabetes

Addressing Weight Gain

Usual strategies for medication-induced weight gain include:
- Diet/exercise strategies
- Changing medication
- Adding medication
  - Topiramate at 75-200 mg daily – however, monitor closely for cognitive side effects (e.g. word finding difficulties) at higher dosages

Psychosocial Recommendations

Pavluri and colleagues have come up with the RAINBOW mnemonic for helping caregivers and professionals to remembering key psychosocial strategies for bipolar disorder in youth:

- **R**outine: Establish a strict routine to allow stable circadian rhythm and sleep hygiene while cutting down distractions.
- **A**ffect regulation / anger control: Establish techniques to self-monitor mood using mood charts and education about the disorder.
- **I** can do it: Help the child to string together a positive self-story.
- **N**o negative thoughts: Restructure negative thinking and help parents to “live in the now.”
- **B**e a good friend / balanced lifestyle: Encourage parents to organize play dates, help children build positive ties, and focus on obtaining a blaanced lifestyle in caring for themselves.
- **O**h, how can we solve it? Engage families in collaborative problem-solving through interpersonal and situation methods.
- **W**ays to ask and get support: Encourage children to draw a support tree and write in all the people close to them on each branch.

References

- Altman LS, Schneck CD: Bipolar moving target: Draw a bead on rapid cycling with type-specific therapies, Current Psychiatry Online, Vol. 3, No. 11 / November 2004, Retrieved July 15, 2005 from http://www.currentpsychiatry.com/2004_11/1104_Altman.asp

- Biederman J, Mick E, Spencer T et al. (2000), Therapeutic dilemmas in the pharmacotherapy of bipolar depression in the young. J Child Adolesc Psychopharmacol 10(3):185-192.
- The BALANCE (Bipolar Affective Disorder Lithium/Anti-convulsant evaluation) trial retrieved Feb 15, 2004 from http://cebmh.warne.ox.ac.uk/balance/Shared/bloods.pdf
- Bostic et al, 2003, retrieved Oct 3, 2003 from www.psychiatrictimes.com/p030988.html
- Chang, K, Children and Bipolar Disorder: Recognizing Early Onset, April 28, 2005, Retrieved August 1, 2005 from http://www.medscape.com/viewprogram/4058_pnt.
- DelBello M, Kowatch R, Adler C, Strakowski S (2004), Controlled trial of quetiapine versus divalproex for the treatment of pediatric bipolar disorder. Presented at the 51st Annual Meeting of the American Academy of Child and Adolescent Psychiatry. Washington, D.C.; Oct. 22.
- DelBello MP, Schwiers ML, Rosenberg HL, Strakowski SM (2002), A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. J Am Acad Child Adolesc Psychiatry 41(10):1216-1223.
- DelBello MP, Soutullo CA, Hendricks W et al. (2001), Prior stimulant treatment in adolescents with bipolar disorder: association with age at onset. Bipolar Disord 3(2):53-57.
- James SP, Mendelson WB (2004), The use of trazodone as a hypnotic: a critical review. J Clin Psychiatry 65(6):752-755.
- Kafantaris V, Coletti DJ, Dicker R et al. (2001a), Adjunctive antipsychotic treatment of adolescents with bipolar psychosis. J Am Acad Child Adolesc Psychiatry 40(12):1448-1456.
- Kafantaris V, Dicker R, Coletti DJ, Kane JM (2001b), Adjunctive antipsychotic treatment is necessary for adolescents with psychotic mania. J Child Adolesc Psychopharmacol 11(4):409-413.
- Kowatch A, Strawn J, Sorter M. (2009). Clinical trials support new algorithm for treating pediatric bipolar mania. Current Psychiatry. 8(1):19- 34. Retrieved Nov 9, 2009 from http://www.currentpsychiatry.com/pdf/0811/0811CP_Article2.pdf
- Kowatch RA, Sethuraman G, Hume JH et al. (2003), Combination pharmacotherapy in children and adolescents with bipolar disorder. Biol Psychiatry 53(11):978-984.
- Pavuluri MN, Graczyk PA, Henry DB et al. (2004a), Child- and family-focused cognitive-behavioral therapy for pediatric bipolar disorder: development and preliminary results. J Am Acad Child Adolesc Psychiatry 43(5):528-537.
- Pavuluri MN, Henry DB, Carbray JA et al. (2004c), Open-label prospective trial of risperidone in combination with lithium or divalproex sodium in pediatric mania. J Affect Disord 82(suppl 1):S103-S111.
- Pavuluri MN, Henry DB, Carbray JA, Birmaher B (2004b), Child Mania Rating Scale (CMRS): development, reliability and validity. Biol Psychiatry 55(suppl):845S.
- Pavuluri MN, Henry DB, Devineni B et al. (2004d), A pharmacotherapy algorithm for stabilization and maintenance of pediatric bipolar disorder. J Am Acad Child Adolesc Psychiatry 43(7):859-867.
- Pavuluri MN, Herbener ES, Sweeney JA (2004e), Psychotic features in pediatric bipolar disorder. J Affect Disord 80(1):19-28.
- Pavuluri MN, Janicak PG (2004), Handbook of Psychopharmacotherapy: A Life Span Approach. Philadelphia: Lippincott, Williams & Wilkins.
- Pavuluri MN, Naylor MW: Multi-Modal Integrated Treatment for Youth With Bipolar Disorder, Psychiatric Times, May 2005, Vol. XXII, Issue 6. Retrieved July 7, 2005 from http://www.psychiatrictimes.com/showArticle.jhtml?articleId=164303314
- Ramshaw & Roberge, Psychiatric Medications, 2001 for guidelines on monitoring
- Wagner, Karen: Medication Treatment Guidelines for Children and Adolescents with Bipolar Disorder, Presented at the Annual Meeting of the American Academy of Child and Adolescent Psychiatry, Oct 2005, Toronto.