

**Pediatric Bipolar Disorder: Medication Algorithm**  
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**Introduction**

Pediatric bipolar disorder (PBD) causes severe mood instability, affects school function and interpersonal relationships. Overall functioning is disrupted by irritability, aggressive and/or impulsive behavior, and psychosis (Geller et al., 2002; 2004; Pavuluri et al., 2005a) that lead these patients to seek help. The aim of this article is to (1) Systematically incorporate up-to-date knowledge from clinical trials into a pragmatic pharmacological treatment algorithm; and (2) Provide a systematic clinical approach to the multiple clinical challenges confronting the clinician. Enhanced treatment compliance is estimated to be an inevitable outcome of this model.

**Medication Algorithm**

**Basic Principles of this algorithm model** consist of (1) Prescription Hygiene, (2) Mood Stabilization, (3) Overcoming the obstacles in mood stabilization by addressing break-through symptoms, and (4) Problem Solving, for example, addressing treatment of comorbid conditions and/or adverse events of medications.

**(1) Prescription hygiene: In establishing a pharmacotherapeutic plan for mood stabilization,** four things are important to consider. **First,** a history should be obtained of which medications worsened the patient's clinical status in the past, which were ineffective, and which were transiently useful or helpful. **Second,** rapidly wean off all ineffective medications. **Third,** discontinue selective serotonin reuptake inhibitors (SSRIs). Despite compelling data in pediatric population of SSRIs worsening the symptoms either by switching or worsening mania (Beiderman et al, 2000), several

families bring children on substantial doses of SSRIs. PBD generally presents with mixed or dysphoric states, and many physicians tune into depressive symptoms at the cost of worsening the clinical state. **Fourth**, stimulants should be discontinued. Mood stabilization is the primary treatment objective and should be attained prior to controlling symptoms of ADHD. But, given the equivocal data (Carlson and Kelly, 1998; Carlson et al., 2000; Scheffer et al., 2005) and the negative influence of stimulants (DelBello et al., 2001; Mota-Castillo et al., 2001; Soutullo et al., 2002), if parents report that they have been singularly helpful and showed a pattern of response independent of affect dysregulation, the practitioner may elect to continue stimulants at the lowest possible doses and in preferably in long acting form.

**(2) Mood Stabilization:** The first treatment of choice continues to be a mood stabilizer such as lithium or divalproex sodium due to established track record of preventive properties (mainly based on studies of adult bipolar disorder). Lithium or divalproex sodium may not always be effective in PBD and/or slow in the onset of action. Consequently, second generation antipsychotics (SGA) are rapidly finding their place either as monotherapy (in emergency situations where stabilizing mania is a priority) (Frazier et al, 2001; DelBello et al., 2006) or in combination with a mood stabilizer (DelBello et al, 2002; Kowatch et al, 2003; Pavuluri et al, 2004 a, b,c, 2005b). The SGAs alone may be effective when irritability is prominent and demands a faster response not possible with first-line mood stabilizers (Pavuluri et al, 2000a). Combination therapy of SGA plus lithium or divalproex is an effective strategy as first line for severe cases, especially those with psychotic features (Kafantaris et al, 2001a, b). This strategy has the advantage of needing lower doses of SGAs compared to the doses potentially required for

monotherapy, resulting in far less severe adverse events. While the practitioner excludes those medications that failed to be effective, he or she can choose the next best option in the list either as an alternative monotherapeutic agent or for the combination regime (in severe cases or if monotherapy fails).

We propose a sequence of medications choices in each group with some general rationale in the **Tables 1** and **2**. While these tables provide a basic guideline, the clinician needs to use his or her discretion in individual cases. The levels of evidence dictated the order. General pros and cons of each medication are listed, as well as a rough estimate of relative efficacy. Some medications are better studied because of better funding based on the strategic plan of drug companies resulting in more and/or better data. Other medications were considered as safe and effective based on studies in adult bipolar disorder. There is a paucity of head to head comparison trials that have been done in PBD. Furthermore, as medications in these categories often take a long time to obtain pediatric indications. Therefore it is difficult to make broad statements about efficacy comparisons. **Prescribing information** of all the medications is beyond the scope of this article and is summarized in the “Handbook of Pharmacotherapy, A Life Span Approach” (Pavuluri and Janicak, 2008).

### **(3) Addressing Break-Through Symptoms**

PBD presents a multitude of clinical challenges beyond acute mood stabilization that must be factored into both the acute and maintenance phases of treatment.

**Depression:** If there are prominent symptoms of depression, lithium or lamotrigine (Bowden et al, 2002; Calabrese et al, 2000) are chosen as primary mood stabilizers either alone or as adjuvant to other partially effective agent; Second choice would be a

combination of lithium plus lamotrigine; Third choice is a small dose of SSRI (in desperate circumstances of severe depression). Any SSRI in small doses of 2.5 to 5 mg in time limited manner and under close supervision and psychoeducation often is effective alongside a mood stabilizer (Wilens et al, 2003). It is important to balance the risks versus benefits, given the black box warning associated with SSRI use in children.

**Psychosis:** SGAs (if not on board already), must be added working down the list as indicated in TABLE 2 (Pavuluri et al, 2004 a,b,c).

**Persistent Aggression:** The tactic in this context is switching to SGA monotherapy if mild aggression is present. In moderate to severe presentations, combination of mood stabilizer and SGA is used, working down the list of choices (cf. Table 1 and 2) after excluding ineffective medications and adequate trial of chosen medications. Clonidine can be used to subdue rage attacks when things are out of control (Prince et al 1996; Pliszka et al., 2000). However, in our experience children can become disinhibited or become more aroused after persistent use, although this particular observation needs to be further examined.

**Treatment Resistance:** Chronic unremitting symptoms must be treated by using (1) alternative monotherapy, (2) at least two trials of combination regimes of mood stabilizers plus SGA, and then (3) moving on to triple therapy addressing comorbid conditions (for example, of additional stimulant for comorbid ADHD).

**Sleep Difficulties:** Primarily it is customary for the clinician to take advantage of increasing the PM dose of sedating mood stabilizer. Beyond that, melatonin 1- 3 mg (Smits et al, 2003), or trazodone 25-50mg (Saletu-Zyhlarz et al., 2001, 2003; Balon, 1994) can be administered to establish sleep routine that is critical in PBD. While these

compounds were not empirically supported by research in PBD youth for sleep in specific, these compounds were known to be sedative, safe in pediatric population, and interfere minimally with REM sleep. In subjects with abuse potential, benzodiazepines may be misused and medications such as trazodone may be effective alternatives (Rush et al., 1999).

#### **(4) Problem solving**

##### **(4.a) Comorbid Diagnoses and Management**

**ADHD:** While ADHD is a distinct disorder separate from PBD, it is not understood if the ADHD-like symptoms in PBD warrant additional treatment beyond mood stabilization. In our study, several subjects continued to show symptoms of inattention post mood-stabilization that warranted stimulant medication (Pavuluri et al, 2004a). Cognitive difficulties such as shifting attention and executive function seen in both ADHD and PBD can potentially be addressed by stimulants. Stimulants are almost always given in long acting form unless an additional after-school dose is required to sustain the benefits. Among psychostimulants, long-acting methylphenidate or mixed amphetamine salts are equally effective (Brown et al 2005). Atomoxetine is factored into algorithm as an alternative treatment if stimulants have been ineffective or not tolerated. There are no data establishing the safety or efficacy of atomoxetine in treating youth with co-morbid ADHD and PBD. Atomoxetine is a selective norepinephrine reuptake inhibitor with potential antidepressant effects and could theoretically trigger or exacerbate symptoms of mania in patients with PBD. Atomoxetine should be used with great care in youth with PBD.

**Anxiety:** Anxiety disorders, including generalized anxiety disorder and separation anxiety disorder, are relatively common, especially in BD type 1. Psychotherapeutic interventions, such as CBT, remain the first choice of treatment in children and adolescents with co-morbid PBD and anxiety disorder. Small dose of SSRIs such as escitalopram XR as adjuvant medication may be effective if mania was stabilized, though there are no controlled trials for anxiety comorbid with bipolar disorder. SSRIs are the only medications consistently shown to be effective in controlled trials for childhood anxiety disorders (Birmaher et al., 2003; RUPP group, 2002; Black and Uhde, 1994). This treatment intervention requires educating the family about the risk of a manic switch and close monitoring of the treatment response is necessary. Guanfacine may be considered if vigilance and autonomic hyperarousal are prominent (Newcorn et al 1998). Benzodiazepines (Graae et al, 1994; Simeon et al., 1992; Bernstein et al., 1990) and buspirone follow as alternative choices. Risk for developing dependence needs to be considered for long-term use of benzodiazepines in adolescents. Buspirone may not be effective in all cases. Propranolol may be considered in cases of performance anxiety. Medication is often utilized in small doses, to reduce risks of exacerbating bipolar disorder and to enable patients to benefit from psychotherapeutic interventions.

**(4.b) Management of selected common side-effects:**

Low doses and slow titration are two fundamental principles that one may utilize to minimize the occurrence of treatment-emergent side-effects. If problems still continue, Switching to an alternative medication may be necessary. For persistent side-effects in the context of a child who has responded well to treatment, consideration should be given

to trying a lower dose of the medication prior to switching medications or employing pharmacological management strategies, as many side-effects are dose-related. When a risk-benefit analysis indicates that the offending drug needs to be retained at the desirable dose, strategies must be implemented to manage them. Some of the common challenges that require specific attention are listed below:

**Weight gain:** Despite several antidotes for weight loss, the single most important intervention is diet and exercise. If possible, consultation with a dietician is helpful. In our experience, simple weight management programs ( i.e. Weight Watchers®), have been successful when followed along with a parent, but should only be done after consultation with a knowledgeable health professional.. Timely meals and wise food choices cut down excessive calories. Weight gain from atypical antipsychotics and some antiepileptic agents often results from an increased appetite secondary to some pharmacological properties of these medications. Counseling parents that this may occur may help them to limit access to high calorie foods that may exacerbate this problem. Weight gain from lithium may partially be due to increased consumption of high calorie soft drinks or juice to compensate for the increased thirst caused by this medication. Limiting fluid intake to low calorie drinks is an easy way to prevent unnecessary weight gain.

**Extra pyramidal symptoms:** Benztropine 0.5-2 mg every other day to once a day is effective in combating extrapyramidal symptoms. Akathisia in patients treated with SGA is often missed and often responds to low doses of propranolol.

**Sedation:** Night- time dosing decreases problems with sedation. In the event of residual morning somnolence, the evening dose may be moved earlier in the evening.

**Gastrointestinal (GI) symptoms:** GI upset from divalproex is dose related.

Administering the medication with food and/or using a long acting preparation of divalproex sodium may decrease GI upset. Taking a SGA with a small snack 30 minutes-one hour before bed may decrease GI upset. GI upset from lithium is dose related and management strategy depends on whether the intolerance is specific to the upper or lower GI. Upper GI effects from lithium tend to be associated with high doses that directly irritate the stomach mucosa as well as high peak serum levels.. Switching to a sustained release formulation or dividing doses BID-TID and/or administering the medication with food will reduce GI upset. Lower GI effects such as diarrhea are correlated with high doses and high serum levels. This also may occur secondary to residual lithium left in the large intestine, which may create an osmotic effect, drawing excess water into the lower GI, resulting in diarrhea. Lower GI effects may be managed by reducing the overall dose, switching from sustained release formulations to immediate release tablets/capsules or liquid formulations. Dividing high QD doses of immediate release formulations to BID-TID may also help.

**Lithium related high thyroid stimulating hormone (TSH):** Elevations in thyroid stimulating hormone (TSH) occur in approximately 15% of patients. This usually occurs within the first four weeks of therapy and may normalize after transient elevation. Usually new elevations are not evident after four years. In accordance with standard lithium monitoring guidelines, baseline monitoring of free T4 and TSH and then follow-up at one month, six months, then yearly until year four is recommended. Additional monitoring may be needed after substantial dose increases. If hyperthyroidism occurs and

lithium needs to be continued, this may be effectively treated with levothyroxine titrated based on levels of TSH on follow up.

### **Updating Chicago Medication Algorithm Project for PBD (C-MAP for PBD):**

Since the commencement of our algorithm project and the subsequent publication of our feasibility study (Pavuluri et al, 2004a) we have continued to update our strategies and tactics based on new information. Aripiprazole is added to the list of SGAs. The role of lamotrigine has been elevated as specified in the scheme above. Atomoxetine was added as a second line medication after trying stimulants for comorbid ADHD. In our experience, clonidine has been shown to cause worsening of symptoms in a subgroup of patients with PBD despite excellent short-term response for autonomic arousal. We are closely monitoring this phenomenon. Consequently, we are currently choosing Guanfacine (given the longer half-life compared to clonidine) or propranolol as an alternative for extreme hyperarousal that does not respond to mood stabilization. Given the recent review presenting equivocal evidence of trazodone's efficacy as sleep medication (James and Mendelson, 2004), it was placed lower on the list after medications such as melatonin that had better data to support its safety and efficacy in idiopathic insomnia ( Smits et al, 2003), although not tested for sleep problems directly in PBD.

### **Conclusion**

PBD affects cognitive, behavioral and affective domains of a child's being. Affect dysregulation is the central feature of this disorder. It is not clear that the juvenile onset version of PBD is contiguous with the adult variant of bipolar disorder. The primary goal of pharmacotherapy is mood stabilization while including the problem solving

approach to deal with complex comorbid, residual, breakthrough and/or associated symptoms. It is imperative that any medication management be coupled with a meaningful holistic therapeutic approach that is practical and tailored to the PBD.

## References\*

1. Balon R (1994), Sleep terror disorder and insomnia treated with trazodone: a case report. *Ann Clin Psychiatry*. 6(3): 161-163.
2. Biederman J, Mick E, Spencer T, Wilens TE, Faraone SV (2000), Therapeutic dilemmas in the pharmacotherapy of bipolar depression in the young. *J Child Adolesc Psychopharmacol* 10:185-192.
3. Biederman J, Mick E, Wozniak J, Aleardi M, Spencer T, Faraone SV (2005), Open label study of risperidone in children with bipolar disorder. *J Child Adolesc Psychopharmacol* 15:311-7.
4. Bernstein GA, Garfinkle BD, Borchardt CM (1990), Comparative studies of pharmacotherapy for school refusal. *J Am Acad Child Adolesc Psychiatry* 29(5):773-81.
5. Birmaher B, Axelson DA, Monk K, Kalas C, Clark DB, Ehmann M, Bridge J, Heo J, Brent Da (2003), Fluoxetine for the treatment of childhood anxiety disorders. *J Am Acad Child Adolesc Psychiatry* 42(4):415-23.
6. Black B, Uhde TW (1994), Treatment of elective mutism with fluoxetine: a double-blind, placebo-controlled study. *J Am Acad Child Adolesc Psychiatry* 33(7):1000-6.
7. Bowden CL (2002), Lamotrigine in the treatment of bipolar disorder. *Expert Opin Pharmacother*. 3(10):1513-9. Review.
8. Brown RT, Amler RQ, Freeman WS, et al. (2005), Treatment of attention-deficit/hyperactivity disorder: overview of the evidence. *Pediatrics*. 115:749-57.

9. Calabrese JR, Suppes T, Bowden CL, Sachs GS, Swann AC, McElroy SL, Kusumaker V, Ascher JA, Earl NL, Greene PL, Monaghan ET (2000), A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. Lamictal 614 Study Group. *J Clin Psychiatry* 61(11):841-850.
10. Carlson GA, Kelly KL (1998), Manic symptoms in psychiatrically hospitalized children-what do they mean? *J Affect Disord* 51:123-135.
11. Carlson GA, Bromet EJ, Sievers S (2000), Phenomenology and outcome of subjects with early- and adult-onset psychotic mania. *Am J Psychiatry* 157:213-219.
12. Cheng-Shannon J, McGough JJ, Pataki C, McCracken (2004), Second-generation antipsychotic medications in children and adolescents. *J Child Adolesc Psychopharmacol* 14:372-394.
13. DelBello MP, Soutullo CA, Hendricks W, Niemeier RT, McElroy SL, Strakowski (2001), Prior stimulant treatment in adolescents with bipolar disorder: association with age at onset. *Bipolar Disord* 3:53-57.
14. DelBello MP, Schwiers ML, Rosenberg HL, Strakowski SM (2002), A double-blind, randomized, placebo-controlled study of quetiapine adjunctive treatment for adolescent mania. *J Am Acad Child Adolesc Psychiatry* 41:1216-1223.
15. DelBello MP, Carlson GA, Tohen M, Bromet EJ, Schwiers M, Strakowski SM (2003), Rates and predictors of developing a manic or hypomanic episode 1 to 2 years following a first hospitalization for major depression with psychotic features. *J Child Adolesc Psychopharmacol* 13:173-185.

16. DelBello M, Kowatch R, Adler C, Stanford KE, Welge JA, Barzman GH, Nelson E, Strakowski S (2006), A double-blind randomized pilot study comparing quetiapine and divalproex for adolescent mania. *Am Acad Child Adol Psychiatry*. 45:305-313.
17. Delbello MP, Findling R, Kushner S, Wang D, Olson W, Capece J, Fazzino L, Rosenthal N (2005), A pilot controlled trial of topiramate treatment for mania in children and adolescents with bipolar disorder. *Am J Psychiatry*. 44:539-47.
18. Faraone SV, Glatt SJ, Tsuang MT (2003), The genetics of pediatric-onset bipolar disorder. *Biol Psychiatry* 53(11):970-977.
19. Frazier JA, Meyer MC, Biederman J, Wozniak J, Wilens TE, Spencer TJ (1999), Risperidone treatment for juvenile bipolar disorder: A retrospective chart review. *J Am Acad Child Adolesc Psychiatry* 38:960-965.
20. Frazier JA, Biederman J, Tohen M, Feldman PD, Jacobs TG, Toma V (2001), A prospective open-label treatment trial of olanzapine monotherapy in children and adolescents with bipolar disorder. *J Child Adolesc Psychopharmacol* 11: 239-250.
21. Geller B, Cooper TB, Sun K, Zimmerman B, Frazier J, Williams M (1998), Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. *J Am Acad Child Adolesc Psychiatry* 37:171-178.
22. Geller B, Tillman R, Craney JL, Bolhofner K (2004), Four-year prospective outcome and natural history of mania in children with a prepubertal and early adolescent bipolar disorder phenotype. *Arch Gen Psychiatry* 61(5):459-467.

23. Gustavson LE, Boellner SW, Granneman GR, Qian JX, Guenther HJ, el-Shourbagy T, Sommerville KW (1997), A single-dose study to define tiagabine pharmacokinetics in pediatric patients with complex partial seizures. *Neurology* Apr;48(4):1032-7.
24. Graae F, Milner J, Rizzotto L, Klein RG (1994), Clonazepam in childhood anxiety disorders. *J Am Acad Child Adolesc Psychiatry*. 33(3):372-6.
25. James SP, Mendelson WB (2004), The use of trazodone as a hypnotic: a critical review. *J Clin Psychiatry* 65 (6): 752-5.
26. Janicak PG, Davis JM, Preskorn Sh, Ayd, FJ Jr (2006), *Principles and Practice of Psychopharmacotherapy*. Philadelphia: Lippincott Williams and Wilkins (4th edition).
27. Kafantaris V, Coletti DJ, Dicker R, Padula G, Pollack S (2001a), Adjunctive antipsychotic treatment of adolescents with bipolar psychosis. *J Am Acad Child Adolesc Psychiatry* 40:1448-1456.
28. Kafantaris V, Dicker R, Coletti D J, Kane JM (2001b), Adjunctive antipsychotic treatment is necessary for adolescents with psychotic mania. *J Child Adolesc Psychopharmacol* 11:409-413.
29. Kafantaris V, Coletti DJ, Dicker R, Padula G, Kane JM (2003), Lithium treatment of acute mania in adolescents: a large open trial. *J Am Acad Child Adolesc Psychiatry* 42:1038-45.
30. Kafantaris V, Coletti DJ, Dicker R, Padula G, Kane JM, Pleak RR, Alvir MJJ (2004), Lithium treatment of acute mania in adolescents: a placebo controlled discontinuation study. *J Am Acad Child Adolesc Psychiatry* 43:984-993.

31. Kowatch RA, Suppes T, Gilfillan SK, Fuentes RM, Bruce D. Grannemann, M.S, Emslie GJ (1995), Clozapine treatment of children and adolescents with bipolar disorder and schizophrenia: a clinical case series. *J of Child Adolesc Psychopharm* 5: 241-253.
32. Kowatch RA, Suppes T, Carmody TJ, Bucci JP, Hume JH, Kromelis M, Emslie GJ, Weinberg WA, Rush AJ (2000), Effect size of lithium, divalproex sodium, and carbamazepine in children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 39:713-20.
33. Kowatch RA, Sethuraman G, Hume JH, Kromelis M, Weinberg WA (2003), Combination pharmacotherapy in children and adolescents with bipolar disorder. *Biol Psychiatry* 53(11): 978-984 .
34. Mathias S, Wetter TC, Steiger A, Lancel M (2001), The GABA uptake inhibitor tiagabine promotes slow wave sleep in normal elderly subjects. *Neurobiol Aging*. 22(2):247-53.  
  
Mota-Castillo M, Torruella A, Engels B, Perez J, Dedrick C, Gluckman M (2001), Valproate in very young children: An open case series with a brief follow-up. *J Affect Disord* 67:193-197.
35. Newcorn JH, Schulz K, Harrison M, DeBellis MD, Udarbe JK, Halperin JM (1998), Alpha-2 agonists: neurochemistry, efficacy, and clinical guidelines for use in children. *Child Adol Psychopharmacology*. 45:1099-1122.
36. Pavuluri MN, Birmaher B., Naylor M. Pediatric Bipolar Disorder: Ten Year Review, *Journal of American Academy of Child and Adolescent Psychiatry* (2005a), 44 (9): 846-871

37. Pavuluri MN, Henry DB, Devineni B, Carbray JA, Naylor MW, Janicak PG (2004a), A pharmacotherapy algorithm for stabilization and maintenance of pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 43:859-867.
38. Pavuluri MN, Henry D, Naylor M, Sampson G, Carbray J, Janicak PG (2004b), Open-label prospective trial of risperidone in combination with lithium or divalproex sodium in pediatric mania. *J Affect Disord* 82 (Suppl 1):S103-11.
39. Pavuluri MN, Herbener ES, Sweeney AJ (2004c), Psychotic features in pediatric bipolar disorder. *J Affect Disord* 80:19-28.
40. Pavuluri M, Henry D, Carbray J, Sampson G, Naylor M, Janicak PG (2005b), Divalproex sodium in Pediatric Mixed Mania: a six month prospective trial, *Bipolar Disord* 7:266-73.
41. Pavuluri MN, Janicak PG (2008), *Handbook of Psychopharmacotherapy: Life Span Approach*. Philadelphia: Williams and Wilkins.
42. Pavuluri MN, Schenkel LS, Aryal S, Harral EM, Hill SK, Herbener ES, Sweeney JA (2006), Neurocognitive function in unmedicated manic and medicated euthymic pediatric bipolar patients, *Am J Psychiatry* 163:286-93.
43. Pliszka SR, Greenhill LL, Crismon ML, et al. (2000) The Texas Children's Medication Algorithm Project: Report of the Texas Consensus Conference Panel on Medication Treatment of Childhood Attention-Deficit/Hyperactivity Disorder. *J Amer Acad Child Adolesc Psychiatry* 39:908-919.
44. Prince JB, Wilens TE, Biederman J, Spencer TJ, Wozniak JR (1996) Clonidine for sleep disturbances associated with attention-deficit hyperactivity disorder: a

systematic chart review of 62 cases. *J Am Acad Child Adolesc Psychiatry* 35:599-605.

45. Research Units on Pediatric Psychopharmacology Anxiety Study Group (2001), Fluvoxamine for the treatment of anxiety disorders in children and adolescents. *N Engl J Med* 344:1279-1285.
46. Rush CR, Baker RW, Wright K (1999), Acute behavioral effects and abuse potential of trazodone, zolpidem and triazolam in humans. *Psychopharmacology (Berl)* Jun; 144(3):220-33
47. Rynn MA, Siqueland L, Rickels K (2001), Placebo-controlled trial of sertraline in the treatment of children with generalized anxiety disorder. *Am J Psychiatry* 158(12):2008-2014.
48. Saletu-Zylarz GM, Abu-bakr MH, Anderer P, Semler B, Decker K, Parapatics S, Tschida U, Winkler A, Saletu B (2001) Insomnia related to dysthymia: polysomnographic and psychometric comparison with normal controls and acute therapeutic trials with trazodone. *Neuropsychobiology* 44(3):139-4.
49. Saletu-Zyhlarz GM, Anderer P, Arnold O, Saletu B (2003), Confirmation of the neurophysiologically predicted therapeutic effects of trazodone on its target symptoms depression, anxiety and insomnia by postmarketing clinical studies with a controlled release formulation in depressed outpatients. *Neuropsychobiology*. 48 (4): 194-208.
50. Cheng K, Howe M, Saxena K (2006), An open label study of lamotrigine adjunct or monotherapy for the treatment of children and adolescents with bipolar depression, *J Am Acad Child Adolesc Psychiatry* 45:298-304.

51. Scheffer R, Kowatch R, Carmody T, Rush J (2005), Randomized, placebo-controlled trial of mixed amphetamine salts for symptoms of comorbid ADHD in pediatric bipolar disorder after mood stabilization with divalproex sodium. *Am J Psychiatry* 162(1):58-64.
52. Simeon JG, Ferguson, HB, Knott V, Roberts N, gauthier B, Dubois C, Wiggins D (1992), Clinical, cognitive, and neuropsychological effects of alprazolam in children and adolescents with overanxious and avoidant disorders. *J Am Acad Child Adolesc Psychiatry* 31:29-33.
53. Smits MG, van Stel HF, van der Heijden K, Meijer AM, Coenen AM, Kerkhof GA (2003), Melatonin improves health status and sleep in children with idiopathic chronic sleep-onset insomnia: a randomized placebo controlled trial. *J Am Acad Child Adolesc Psychiatry* 42(11):1286-1293.
54. Soutullo CA, DelBello MP, Ochsner JE, McElroy SL, Taylor SA, Strakowski SM, Keck PE Jr. (2002), Severity of bipolarity in hospitalized manic adolescents with history of stimulant or antidepressant treatment. *J Affect Disord* 70:323-327.
55. Wilens TE, Biederman J, Kwon A, Chase R, Greenberg L, Mick E, Spencer T(2003), A systematic chart review of the nature of psychiatric adverse events in children and adolescents treated with selective serotonin reuptake inhibitors. *J Child Adolesc Psychopharmacol* 13:143-52.

<p align="center"><b>TABLE 1. Lithium and Anti Epileptic Medications: Rationale Behind the Sequence*</b> (often referred to as mood stabilizers)</p>		
<b>Name</b>	<b>Pros</b>	<b>Cons</b>
Lithium (Geller et al, 1998; Kafantaris et al., 2003)	FDA approved in children for acute mania and maintenance (grand fathered in), well studied in adults, works well in classic presentation .	Slow onset of action, poor response to monotherapy, frequent urination and hypothyroidism often cause concerns.
Divalproex sodium (Kowatch et al., 2000; Pavuluri et al., 2005b)	Well studied in adult bipolar disorder. Effective when coupled with stimulants for comorbid Attention Deficit Hyperactivity Disorder (ADHD)	Poor response to Monotherapy in children. Poor tolerability secondary to excitability, gastro intestinal side effects, weight gain, sedation. Potential adverse effects on the liver and thrombocytopenia require regular laboratory monitoring.
Carbamazepine (Kowatch et al, 2000)	Long standing efficacy in adults	Efficacy in children not established. Substantial side effect profile. Large number of drug interactions. Substantial laboratory monitoring required.
Oxcarbazepine	Anecdotal evidence suggesting that it may decrease aggression in PBD	Efficacy not established
Lamotrigine (Cheng et al, 2006)	Accruing evidence on maintenance for adult bipolar disorder. Considered as a primary choice along side lithium, for depression subtype. Potentially useful in combination with Second Generation Antipsychotics or lithium for mixed or depressive episodes where depression is predominant.	Very slow titration over 6-8 weeks to avoid rash. Although serious rash is uncommon, benign rash, if occurs, is treatable with prednisone and may limit ability to re-challenge
Topiramate (DelBello et al, 2006)	May have some benefit in reducing weight.	Negative trial in adult bipolar disorder, cognitive dulling. Equivocal evidence

		available in PBD, including that for neutralizing weight gain as an adjuvant. Significant side effect profile.
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\*Janicak et al. (2006) offers comprehensive overview of the trials in adult bipolar disorder, currently being updated for fourth edition.

<b>TABLE 2. Second Generation Antipsychotics (SGAs): Rationale Behind the Sequence*</b>		
<b>Name**</b>	<b>Pros</b>	<b>Cons</b>
Risperidone (Frazier et al, 1999; Biederman et al, 2005)	Efficacy demonstrated in pediatric trials. It has a , predictable response profile and reduces aggressive behavior.	Weight gain is common. Extrapyramidal side effects (EPS) and symptoms from prolactin elevation (e.g. menstrual disturbances) sometime affect tolerability.
Quetiapine (DelBello et al, 2002; 2006)	Efficacy demonstrated in pediatric trials. Little/no extrapyramidal side effects	Sedation and weight gain are common.
Aripiprazole	Emerging data on adult bipolar disorder and pediatric disorders	EPS, nausea and vomiting, response is not always predictable with no knowledge on predictive factors,
Ziprasidone (Cheng-Shannon et al 2004)	Weight neutral in pediatric studies	EPS and less evidence for efficacy; Risk of prolonged QT interval requires cardiac monitoring
Olanzapine (Frazier et al., 2001)	Good data in adult bipolar disorder and emerging data in PBD	Severe weight gain limits tolerability and places children at risk for long-term sequelae.
Clozapine (Kowatch et al., 1995)	Potentially useful in treatment resistant cases	Regulatory blood draws to check white blood count presents logistical challenges. Significant side effect profile often limits tolerability in children and puts them at risk for long-term sequelae.

\*Janicak et al. (2006) provides information on adult trials using SGA in bipolar disorder.

\*\*With SGA use, one must consider the risk for metabolic syndrome (elevated lipids, high blood pressure and diabetes mellitus). Although the level of such risk in children and the life long consequences of their use are unknown, these parameters require close monitoring.