

# Bipolar Network News

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Updates from the 2012 Meeting of the American Academy of Child and Adolescent Psychiatry

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## Heading Off Early Symptoms of Bipolar Disorder in Children at High Risk

At the American Academy of Child and Adolescent Psychiatry (AACAP) annual meeting in Toronto in October 2011, there was a symposium on risk and resilience factors in the onset of bipolar disorder in children who have a parent with the disorder.

### Family Focused Therapy Highly Encouraged

Amy Garrett reported that family focused therapy (FFT) in those at risk for bipolar disorder was effective in ameliorating symptomatology compared to treatment as usual. Family focused therapy, pioneered by David Miklowitz of UCLA involves three components. The first component is education about the illness and methods of self-management. The second is enhancement of communication in the family with practice and rehearsal of new modes of conversation. The third component is assistance with problem solving.

In Garrett's study, 50 children aged 7 to 17 were randomized to family focused treatment or treatment as usual. These children were not only at high risk for bipolar disorder, they were already prodromal, meaning they were already diagnosable with bipolar not otherwise specified (BP-NOS), cyclothymia, or major depressive disorder, and had also shown concurrent depressive and/or manic symptoms in the two weeks prior to the study. At baseline, compared to controls, these children at high risk for full-blown bipolar disorder by virtue of a parental history of the illness showed

increased activation of the amygdala and decreased activation of the prefrontal cortex. Most interestingly, after improvement with the family focused therapy (FFT), amygdala reactivity to emotional faces became less prominent and dorsolateral prefrontal cortical activity increased in proportion to the degree of the patient's improvement.

**The discussant for the symposium, Kiki Chang of Stanford University, indicated that the results of this study of family focused therapy were already sufficient to convince him that FFT was a useful therapeutic procedure in children at high risk for bipolar disorder by virtue of having a parent with a history of bipolar illness.** Chang is now employing the therapy routinely in all of his high-risk patients.

*Editors Note: This is an extremely important recommendation as it gives families a specific therapeutic process in which to engage children and others in the family when affective behavior begins to become abnormal, even if it does not meet full criteria for a bipolar I or bipolar II disorder.*

*FFT also meets all the important criteria needed for putting it into widespread clinical practice. Family focused therapy has repeatedly been shown to be effective in adults and adolescents with bipolar illness and now also in these children who are prodromal. The psychoeducational part of FFT is common sense, and dealing with communication difficulties and assisting with problem solving are also useful for stress reduction. Finally, this treatment intervention appears to be not only safe but also highly effective in a variety of different prodromal presentations of affect*

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*disorders even if children do not meet full criteria for bipolar disorder. Since the few studies of early intervention with psychopharmacological agents have not yet identified efficacious medications for the prodromes of bipolar disorder, and in particular medications with a high degree of safety, options such as family focused therapy are ideal as early interventions.*

*This editor concurs with Dr. Chang's assessment. **Family focused therapy (FFT) should be offered to all children at high risk who have begun to be symptomatic.** Early onset of unipolar depressive disorder or of bipolar disorder carries a more adverse prognosis than the adult-onset variety and thus should not be ignored. If more serious illness is headed off early, it even raises the prospects that the full-blown illness will not develop at all.*

There are a variety of risk factors that children with bipolar illness face.

### Gray Matter Volume Abnormalities May Coincide with Bipolar Risk

Tomas Hajek of Dalhousie University in Halifax presented data indicating

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## Risk Factors For Youth Onset Bipolar Disorder

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that in children at high risk for bipolar disorder, gray matter volume in the right inferior frontal gyrus is increased. While the left inferior frontal gyrus is important for language, the right side of the inferior frontal gyrus deals with response inhibition, autobiographical memory, mirror neurons, and empathy.

Interestingly, while children at high risk show increased volume in this area, already ill patients exhibit decreased volume in the same area. Other findings in the literature indicate that a duration of illness longer than 10 years

is associated with decreases in gray matter volume in this area of the brain. Hajek also found that lithium treatment could lessen the degree of prefrontal cortical volume loss over time.

*Editors Note: The findings raise the interesting conundrum that in those at high risk but unaffected by bipolar disorder, this area of brain is larger than normal, but in those who become ill, the volume of this area is slightly smaller, and the volume decreases as the illness continues. The mechanism of these effects is unknown, but these findings (which were replicated in two independent samples) suggest the possibility that increased volume in the inferior frontal cortex could be a marker of vulnerability to bipolar disorder in those at high risk but not yet ill.*

### Bipolar Network News

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The *BNN* is published four times a year by investigators working with patients with bipolar disorder to better understand the long-term course of illness. The newsletter is available free of charge to all who request it.

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## News From The “TEAM” Study: Risperidone Superior To Valproate And Lithium In Childhood Mania

A symposium at the Annual Meeting of the American Association of Child and Adolescent Psychiatry discussed the Treatment of Early Age Mania (TEAM) study. **This randomized partially blinded study compared risperidone, valproate, and lithium for the treatment of children with bipolar I mania.**

The study was held at five different sites in Pittsburgh, Washington DC, Baltimore, St. Louis, and Cleveland. Participants were all severely ill with a Clinical Global Assessment of Severity (C-GAS) score of less than 60 (the mean was 39, indicating that the children were substantially impaired). More than three quarters had psychosis (i.e. hallucinations or delusions) and 99% had dramatic mood shifts within a day (ultradian cycling). All of the participating children had the cardinal symptom of elevated mood.

Among the 290 participants, there was a high incidence of Axis I comorbidities, with 98% of patients having a disruptive behavioral disorder, 77.3% an anxiety disorder, 31% some form of sleep disturbance, and 17% an elimination disorder, of which 15% had enuresis (bedwetting). Nightmares were present in 25.9% of the sample, sleepwalking in 7.2%, and night terrors in 4.8%.

For the purposes of the study, a rating of 1 (not ill) or 2 (minimally ill) on the Clinical Global Impressions scale modified for bipolar illness (CGI-BP) was considered a significant response.

The children (age 6 to 15 with a mean age of 11) were randomized to

### Poor Cognitive Control in Children at High Risk

Pilyoung Kim of the National Institute of Mental Health (NIMH) reports that young children at high risk for bipolar disorder have difficulties with cognitive control, especially with more difficult tasks. Interestingly, the ventrolateral prefrontal cortex, which is near the inferior frontal cortex, showed increased activity in association with difficulties in working memory on a “two-back” test (where children view a series of symbols and must remember the symbol they viewed not one symbol back, but two back.)

### Decreased Neuronal Connectivity in Children at High Risk

Cecile Lana DeLuca reports that in healthy young people there are high levels of neuronal connectivity between two parts of the brain, the dorsolateral prefrontal cortex and the amygdala, but in well children at high risk for bipolar disorder by virtue of having a parent with the illness, there is decreased connectivity between these two important regions.

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## Risperidone Superior To Valproate And Lithium In Childhood Mania

treatment for 8 weeks with lithium, valproate, or risperidone. Lithium treatment reached blood levels of 1.1 to 1.3mEq/L, valproate reached levels of 111 – 225µg/ML, and risperidone doses reached 3mg per day. Children who were taking psychomotor stimulants for treatment of ADHD remained on the stimulants after randomization to one of the three drugs. While the treating physicians and clinicians were not blind, blind ratings were performed at week 8.

**With a response rate of 68.5%, risperidone was superior to lithium (35.6%) and valproate (24%) based on CGI-BP scores.** The mean dose of risperidone was 2.6mg +/- 1.2 per day. The mean blood level at week 8 for lithium was 1.1mEq/L and for valproate was 114µg/ML.

The number of children who improved sufficiently for their C-GAS scores to rise above 60 was also greater for risperidone at 48.3% compared to lithium at 26.7% and valproate at 17.0%.

*Editor's Note: These are among the first controlled data in children with mania*

*below the age of 10 (which is the minimum age for most FDA-approved studies of second-generation antipsychotic drugs). The findings were highly consistent with data in older children and adolescents.*

*As illustrated in the graph below showing results of several similar studies, response to extended release valproate (24%) did not significantly exceed that of placebo (23%) in a randomized industry-sponsored study in older children with mania. These numbers resemble the 24% response rate to immediate-release valproate in the TEAM study of younger children. In a meta-analysis by Correll in 2010 that analyzed data from 5 industry-sponsored studies of second-generation atypical antipsychotics, the rate of placebo response for bipolar mania was 29%, while the response to a second-generation atypical antipsychotic averaged 58% (approaching the 69% response to risperidone observed in the TEAM study).*

*There were differences in the apparent magnitude of response to both lithium and valproate in this TEAM study compared to open randomized data from 2000, in which Kowatch et al. showed that response to*

*valproate, lithium, and carbamazepine were comparable in children with acute mania. In that study, the response to valproate was about 50% and slightly but not significantly higher than the response to lithium and carbamazepine. Response to each of the three drugs was in a range similar to that of risperidone in the current study. Thus these discrepancies remain to be clarified.*

The TEAM researchers used statistical analyses to determine which variables might be associated with clinical response. A univariate analysis showed that older age and being African-American predicted a more favorable response, while having comorbid ADHD was associated with worse response. In a multivariate analysis, conduct disorder emerged as a predictor of poor response, and there were significant differences in response across the five different sites used in this study.

The Pittsburgh and Washington, DC sites had much higher response rates to lithium and valproate (similar to risperidone) than the other three sites in St. Louis, Cleveland, and Baltimore, which showed the same pattern of response noted in the overall group, i.e. lithium and valproate were inferior to risperidone. The reasons for these differences across sites was not clear, although the sites with better response to lithium and valproate also had the lowest dropout rate.

Interestingly, the dropout rate was higher on lithium and on valproate than on risperidone (32.2% for lithium, 26.0% for valproate, and 15.7% for risperidone). Dropouts for worsening of clinical symptoms were also significantly higher on lithium (13.8%) and valproate (11.5%); there were no dropouts for worsening of symptomatology on risperidone. Dropouts for side effects were not significantly different across the three drugs.

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### Atypical Antipsychotics More Efficacious Graph

## Results from the TEAM Study Favor Risperidone

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There were differences in side effects. Weight gain was greater on risperidone (averaging 3.3kg compared to 1.42kg on lithium and 1.67kg on valproate). Prolactin increases were substantially greater on risperidone (37.6 units) compared to negligible increases on lithium and valproate. Low-density lipoproteins (LDL cholesterol, the “bad” kind) increased on risperidone, but decreased on valproate. Thyroid stimulating hormone (TSH) increased on lithium, and platelets decreased on valproate. Gastrointestinal distress was more prominent on lithium as was increased urination, dry mouth, and thirst. Difficulty arousing in the morning was reported at baseline in 28.9% of those randomized to valproate, and this increased to 63.9% by the end of 8 weeks of treatment. All three drugs were associated with reductions in suicidal ideation.

*Editor’s Note: In summary, risperidone was superior to lithium and valproate in very young children (aged 6 to 15) with BP I mania, but it had more side effects, including weight gain and increases in prolactin and LDL cholesterol. Data from this study and on the efficacy of risperidone were published by Barbara Geller et al. in the Archives of General Psychiatry in 2012.*

## Risperidone Trumps Valproate and Placebo for Treatment of Very Young Children with Mania

At another symposium at the annual meeting of the American Academy of Child and Adolescent Psychiatry, Bob Kowatch of Ohio State University discussed a controlled trial of valproate, risperidone, and placebo in children 3 to 7 years of age (average age 5.5) with a diagnosis of bipolar I disorder and a Young Mania Rating Scale score (YMRS) greater than 20 at baseline. All of the children were severely ill with an average Clinical Global Assessment of Severity (CGAS) score of 44. Seventy-six percent had comorbid attention deficit hyperactivity disorder (ADHD) and 15% had an anxiety disorder. Valproate doses started at 10mg/kg and were increased after 4 days to achieve blood levels of 80 to 100µg/ml. The average dose of valproate was 300mg/day and the average blood level was 88 µg/ml. Risperidone was started at 0.25mg and increased as needed. The average dose of risperidone was 0.5mg per day.

On the main outcome measure of decrease in the YMRS score, **risperidone was substantially more effective than placebo, while valproate showed only marginal nonsignificant effects.** However on the Clinical Global Impressions (CGI) scale for improvement in illness, risperidone showed 87% response, valproate 75% response, and placebo no response. Fifty percent reduction in YMRS score occurred in 88% on risperidone, 50% on valproate, and 15% on placebo.

Weight gain was mild on valproate and substantially more on risperidone. Risperidone was also associated with increases in insulin and prolactin.

The effect size (the size of the change the drug brought about in this study, which is calculated by dividing the mean difference between the experimental group and the control group by the standard deviation) for risperidone was extraordinarily large (3.58); very large for valproate (1.66), and moderate for placebo (0.56). The odds of getting well were 5 times greater than placebo for risperidone and 1.9 times greater than placebo for valproate.

*Editors note: These data in very young children (aged 3 to 7) resemble other controlled data in the literature about the treatment of older children and adolescents, indicating a superiority of atypical antipsychotics over placebo and a greater magnitude of effect achieved with atypicals than with valproate.*

## Kowatch’s Revised Treatment Algorithm

Based on these new data and the Federal Drug Administration (FDA) approval of several atypical antipsychotics for children with bipolar illness from ages 10 to 17, Dr. Kowatch recommended a new treatment algorithm for childhood onset bipolar disorder.

In a consensus statement on treatment guidelines for children published by Kowatch et al. in the *Journal of the American Academy of Child and Adolescent Psychiatry* in 2005, the authors suggested starting treatment with either an atypical antipsychotic, a mood stabilizing anticonvulsant, or lithium.

Here are Kowatch’s updated treatment recommendations for children with bipolar illness.

In Stage 1 of treatment, Kowatch recommends beginning with one of two strategies.

A. In a very young child with manic illness, Kowatch now recommends starting treatment with one of the atypical antipsychotics, such as quetiapine, aripiprazole, or risperidone.

B. An alternative to treatment with quetiapine, aripiprazole, or risperidone would begin with lithium or valproate. The atypical antipsychotics olanzapine and ziprasidone are also included as alternatives rather than first choices because the former carries a risk of weight gain and the latter is not FDA-approved for children and adolescents.

In Stage II Kowatch recommends adding the type of drug not used in

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# A Treatment Algorithm for Bipolar Disorder in Children and Adolescents

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Stage I (lithium or an anticonvulsant added to the initial atypical, or an atypical added to initial treatment with lithium or an anticonvulsant).

In Stage III one more medication is added so that the regimen consists of two mood stabilizers and an atypical or two atypicals and a mood stabilizer.

*Editors Note: This sequencing of treatments reflects the consensus of many clinicians that childhood onset bipolar disorder is difficult to treat and is associated with severe symptomatology that often dramatically impairs a patient's social, family, and academic life. In addition to multiple medications, psychotherapy and psycho-education are also typically required in order to achieve optimal mood stabilization.*

*There is some rationale for starting some severely ill children on the combination of lithium and valproate, based on a study by Findling et al. at Case Western Reserve University. They found that while almost one half of the children with bipolar disorder who were able to be stabilized on the combination of lithium and valproate, two thirds of these children relapsed upon randomization to either lithium or valproate monotherapy. However, most re-responded when the combination of the two drugs was re-instituted. These data provide strong controlled evidence that a majority of children with bipolar disorder in the US will not respond adequately to monotherapy with lithium or valproate, and will require the combination.*

*Even in the TEAM study we described in the article beginning on page 3, most*

*patients required combination treatment. Not only was risperidone superior to lithium or valproate in that study, but patients also did better in the second phase of the study when risperidone was added to one of the treatments as opposed to the combination of lithium and valproate. Given the superiority of one of the atypicals (risperidone), it can be assumed that there is a class effect and that all of the atypical antipsychotics would be as good or better than lithium or valproate.*

*If this is the case, then the choice of an atypical with which to begin treatment or to use adjunctively would depend on its side effects profile and long-term tolerability. A highly preliminary assessment of these factors is presented in the table below, which was updated in early 2012.*

**Provisional Status of Efficacy, Tolerability, and Utility of Treatments for Pediatric Mania\***  
(where utility is a rough subjective integration of efficacy, practicality, and long-term tolerability)

\*2/2012 To be modified as further data become available

Drug	Evidence in: ADULTS				CHILDREN			
	Acute		Prophylactic		Mania	Problems	Tolerability	Utility
	Mania	Depression	Mania	Depression				
<b>Mood stabilizers</b>								
Valproate	+++A	+	++	++	(++)	Weight gain, Polycystic ovarian syndrome	B+	B+
Lithium	+++A	++	+++A	+++	++A	Weight, DI, Thyroid, Acne, Requires blood levels	B	B+
Carbamazepine	+++A	++	++	++	(++)	Rash, Rare bone marrow suppression	C+	B
Oxcarbazepine	++	+	?	?	(+)	Hyponatremia, Sedation	B	B
Lamotrigine	0	(++)	++A	+++A	(+/-)	Rare severe rash (1/2500)	B-	C
<b>Atypical Antipsychotics</b>								
Aripiprazole	+++A	+/- **UP	+++A	+/-	+++A	Akathisia, Weight gain +, GI upset	A-	A
Clozapine	+++	++	+++	++	+++	Seizures, Drooling, Weight gain +, Requires white blood cell monitoring	C	C
Olanzapine	+++A	++*A	+++A	++	+++A	Weight gain +, sedation	B-	B-
Quetiapine	+++A	+++A ++*UP	+++*A	+++*A*	+++A	Weight gain ++, sedation	B	A-
Risperidone	+++A	+/-	+++A	+	+++A	Prolactin increases, Weight gain ++	B	B+
Ziprasidone	+++A	?	+++A	?	+++	Weight gain, Increases QTC interval (but not clinically problematic)	A-	A

A	FDA approved, FDA approval pending	( )	Ambiguous data	*	Adjunctive	A	Excellent
+++	Strong evidence, placebo controlled RCT	+	Some evidence of likely effectiveness	?	Unknown effect	B	Good
++	Substantial evidence, multiple series	+/-	Minimal evidence	0	No effect	C	Fair
						D	Poor

## Treating Bipolar Depression in Youth Despite the Lack of Good Data

At the Ryan Licht Sang pediatric bipolar conference, researcher Karen Dineen Wagner summarized the controlled data on treatment of bipolar depression in children. Almost none exist, with the exception of one study in which quetiapine (Seroquel) was not found to be more effective than placebo.

Unlike mania, for which there are several approved treatments for children aged 10 to 17, **there are no FDA-approved treatments for bipolar depression in children.**

In adults, quetiapine is the only approved monotherapy for bipolar depression, and the only other approved treatment is the combination of fluoxetine and olanzapine. Despite the frequency with which conventional antidepressants (SSRIs, SNRIs, bupropion, and tricyclic antidepressants) are prescribed for bipolar depression, the data on their efficacy is mostly negative, based on a 2010 meta-analysis by researchers Sidor and MacQueen.

Given that there is little data available even for adults, Wagner reviewed the open (uncontrolled) studies on depression in children with bipolar disorder. Some evidence of good response to lithium or lamotrigine can be found in case series and chart reviews. In studies of atypical antipsychotics for mania in children, the mania rating scales used contain items about depression, and these often show some improvement.

Wagner concluded that one option is to use monotherapy with atypicals, lithium, or lamotrigine in children with bipolar depression.

Wagner created a revised Mood Disorder Questionnaire for Adolescents (MDQ-A), which focuses on a possible diagnosis of bipolar disorder instead of unipolar depression. This was published in the *Journal of Clinical Psychiatry* in 2006 and is reproduced below. Dr.

Wagner indicated that the instrument is more valid when the answers are supplied by a parent than by the adolescent.

*Editor's Note: The lack of research on the treatment of children with bipolar disorder is a public health problem.*

### Factors Making the Lack of Good Data Troublesome

1. Epidemiological data published by Merikangas et al. in 2010 indicate that 2.7% of children and adolescents in the US have bipolar disorder. The illness began with a depressive episode in at least half of those children. This means we lack good information for the treatment of more than a million children in the US.

2. Depression is associated with considerable dysfunction and disability.

3. Roughly two-thirds of the weeks of follow up after an episode of mania in children are associated with symptomatic depression or mania.

4. Depression is a major cause of suicide, and suicide rates have increased in recent studies of adolescents.

5. Among adults in the Bipolar Collaborative Network (where this editor is an investigator) and in the STEP-BD study, onset of illness in childhood was associated with a poorer outcome in adulthood.

6. Duration of time from illness onset to first treatment of depression or mania is an independent risk factor for a poor outcome in adulthood, resulting in more time depressed and greater severity of depression, more episodes, and less time euthymic.

*Given these immediate and long-term problems related to childhood onset bipolar depression and the relative absence of good data on treatment (from randomized, double-blind, placebo-controlled clinical trials), how should parents, physicians, and clinicians proceed? A number of important principles may form useful guidelines.*

#### Mood Disorder Questionnaire for Parents of Adolescents

(Wagner et al., *Journal of Clinical Psychiatry* 2006, 67(5): 827-30.)

1. Has there ever been a time for a week or more when your adolescent was not his/her usual self and...

- |   |                                     |
|---|-------------------------------------|
| felt too good or excited?   | felt he/she could do anything?      |
| needed much less sleep?   | was so easily distracted by things? |
| spent too much money?   | used more alcohol or drugs?         |
| was so irritable that he/she started fights or arguments with people?   |                                     |
| couldn't slow his/her mind down or thoughts raced through his/her head? |                                     |
| had much more energy than usual?  |                                     |
| was much more active or did more things than usual?                     |                                     |
| had many boyfriends or girlfriends at the same time?                    |                                     |
| was more interested in sex than usual?                                  |                                     |
| did many things that were foolish or risky?                             |                                     |

2. If you checked YES to more than one of the above, have several of these ever happened to your adolescent during the same period of time?

3. How much of problems did any of these cause your adolescent--like school problems, failing grades, problems with family and friends, legal troubles?

No problem    Minor problem    Moderate problem    Serious problem

**If you checked 5 or more of the 13 behaviors on Question 1, Yes on Question 2, and Moderate or Serious on question 3, investigate a diagnosis of bipolar disorder.**

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# Options for Treating Bipolar Depression in Children and Adolescents

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## Guidelines for Treating BP Depression in Youth

1. Engage the child and family in treatment, since not treating this illness will likely convey serious harm.

2. Use the safest and best tolerated treatments first.

3. Since there are no FDA-approved treatments for bipolar depression in childhood, use non-FDA-approved treatments.

4. Accurate diagnosis and longitudinal follow up are essential.

5. Careful monitoring and follow up will facilitate evaluation of the treatments undertaken and allow the development of optimal approaches for a given child.

6. Educate families about the illness, giving honest information about the current paucity of controlled studies and gaining informed consent.

7. Encourage family education and therapy. This can include:

a. Family psychoeducation about illness recognition and management.

b. The family focused treatment pioneered by David Miklowitz.

c. The multi-family psychoeducational psychotherapy developed by Mary Fristad.

d. Cognitive behavioral therapy (CBT), dialectical behavior therapy (DBT), and Interpersonal and Social Rhythm Therapy (IPSRT) for older children and adolescents.

8. Parents, with the help of their own physicians, should optimize their own treatment (if they have an affective illness) and/or look after their own wellbeing with as much support as they can acquire from family, friends, and social and advocacy groups.

9. Recognize that many potential psychopharmacological options are available, though current recommendations and treatment sequences may change dramatically as more information becomes available.

*Accordingly, clinicians and parents should view the following ideas from this editor as highly preliminary. Please*

*remember that BNN editors cannot take medical responsibility for any preliminary ideas, strategies, suggestions, and direct or implied recommendations published here, which must be affirmed and authorized by the appropriate treating physician who bears the medical responsibility for any treatments undertaken and who must assess treatments by reviewing the available literature as it evolves and the child's progress. The preliminary and perhaps idiosyncratic views of the editor cannot be taken as recommendations for any given individual, as the application of these views to a given individual in the absence of a detailed review of their history and condition may be entirely inappropriate.*

## Possible Treatment Options for Bipolar Depression in Children and Adolescents in Absence of Good Evidence-Based Data

(To be reviewed and revised as new information becomes available)

If my child were depressed after an episode of mania (i.e. had bipolar depression), I would consider doing some of the following:

1. Get good education about the illness and monitor the child's mood and behavior on the daily prospective Life Chart (NIMH-LCM). This is available on our website, bipolarnews.org.

2. Get the child evaluated by an expert and begin some form of psychotherapy for them and for the family.

3. Encourage a good diet and as much exercise as possible.

4. Include in the diet omega-3 fatty acids, which may have some antidepressant efficacy and are probably good for him/her anyway.

5. Check for low Vitamin D levels and treat accordingly.

6. Consider N-acetylcysteine (NAC), which has been found to have antidepressant effects in adults and anti-irritability effects in children aged 8 to 17 with autism.

7. Consider NAC more strongly if the patient begins to experiment with alcohol or marijuana, as NAC may help with substance avoidance.

8. Avoid the usual antidepressants for unipolar depression, since early age of onset of depression is a risk factor for switching into mania after taking antidepressants. Kiki Chang of Stanford University and Joe Biederman of Massachusetts General Hospital have reported that they see lots of activation and/or switching in children with bipolar disorder treated with antidepressants.

9. Consider starting lamotrigine at very low doses (12.5mg/day with very slow upward titration to limit the risks of serious rash, which occurs in 1/5000 adults and about 1/2500 children).

10. Consider folic acid (folate), which can potentiate effects of antidepressants. There is some evidence that lamotrigine can interfere with folate metabolism.

11. If needed, add an atypical antipsychotic with low weight gain potential, such as the partial dopamine agonist aripiprazole (Abilify, starting at 1mg/day or lower) or lurasidone (Latuda). There are two instances of positive data on lurasidone in adult bipolar depression, and the drug has a good profile of weight and metabolic neutrality so far in adults. Or consider quetiapine (Seroquel), especially if anxiety and insomnia are present (although a trial in children and adolescents with bipolar depression was not positive).

12. If needed, augment treatment of an older child with lithium.

13. If the child is still depressed, add very, very short-term treatment with minute doses of a selective serotonin reuptake inhibitor (SSRI) or bupropion under the cover of one or more mood stabilizers above.

14. If the child is still depressed, consider a trial of repetitive transcranial magnetic stimulation (rTMS), the effectiveness of which in adolescents has been reported by Chris Wall at the Mayo Clinic.

## Obesity and Bipolar Disorder in Children and Teens May Be Linked

The annual meeting of the American Academy of Child and Adolescent Psychiatry in Toronto in October 2011 featured a symposium on the impact of obesity on the course of childhood onset bipolar illness.

### Typical Treatment of Bipolar Disorder in Youth

At the symposium, researcher David Axelson described the typical outcome of bipolar illness and the medications used during naturalistic treatment. The data came from the large collaborative study Course and Outcome of Bipolar Illness among Youth (COBY), in which he and his colleagues followed 255 patients with bipolar I disorder, 30 patients with bipolar II, and 153 patients with bipolar not otherwise specified for a mean of 5 years. He discussed only bipolar I at the symposium.

The study initially followed 270 children with bipolar I for a mean of 582 weeks and observed how their illness was treated. The children ranged in age from 7 to 17 years (average 14.4 years). Ninety-three percent of the children were treated with one or more anti-manic agents. These included atypical antipsychotics in 77%, valproate or carbamazepine in 44%, and lithium in 47%. Antidepressants were used in 46% of the children, stimulants in 43%, and benzodiazepines in 21%. Sixty percent of the children were treated with two classes of anti-manic medications concurrently at some point.

A univariate analysis showed that older children received smaller amounts of antipsychotics and more anticonvulsants and lithium. Variables associated with better response, that is, a rating of either much or very much improved on the Clinical Global Impressions scale for bipolar disorder (CGI-BP), included older age and treatment with atypical antipsychotics. Those who had comorbid attention deficit hyperactivity disorder (ADHD) or

psychosis at baseline did more poorly. Mean symptom scores were better when the children received any anti-manic treatment including an atypical or lithium, but worse when they received valproate or carbamazepine.

These data are similar to those from other prospective treatment outcome studies in childhood-onset bipolar I illness that suggest **the illness is difficult to treat and stabilize even when multiple medicines are used in combination.**

### Obesity and Mood Disorders in Youth

Ben Goldstein, another researcher who spoke at the symposium, indicated that in the scientific literature, obesity has been associated with a higher number of depressive episodes and longer length of depression, more recurrences of depression, more anxiety disorders, more hospitalizations, more suicide attempts, and worse functional outcomes. In the same group of patients discussed by Axelson above, 42% were overweight or obese, compared to 34% of the general population of children in this age range.

Factors associated with overweight in Goldstein's research included substance abuse, a history of physical abuse, prior hospitalization, and being on 2 or more medications. Those patients who were overweight or obese spent more time ill in a manic or depressive episode.

**This is one of the first prospective studies to show that obesity in children is associated with increases in episodes, symptoms, and increased severity of illness, but the mechanisms of this effect remain to be clarified.**

Goldstein cited the data of Bond et al. published in *Biological Psychiatry* in 2011, which showed that in young adults admitted to the hospital for a first episode of mania, those with an increased body mass index (BMI) had

less white matter volume in the brain and less volume in their temporal lobe. These data suggest that obesity may interact with changes in the brain, either driving them or resulting from them.

### Obesity, Diabetes, and Bipolar Disorder

Researcher Roger McIntyre summarized the literature on obesity in adults with bipolar disorder and suggested that **bipolar disorder should be categorized as a metabolic syndrome type II because of the high incidence of overweight and obesity in adults with the illness and their high risk for premature mortality via cardiovascular disease.** (The metabolic syndrome is diagnosed when any three of five problems occur: high blood sugar, increases in cholesterol, increases in triglycerides, high blood pressure, or overweight/increased waist circumference.)

McIntyre noted that some factors overlap in patients with mood disorders and diabetes. These include abnormalities in insulin, pro-inflammatory cytokines, reactive oxygen species, glucose dysregulation, and abnormal levels of neurotrophic factors. He cited data by Kim et al. published in *European Psychiatry* in 2011 that obesity was associated with decreases in attention, processing speed, and verbal fluency.

Other data indicate that adults with diabetes have neurocognitive alterations. These data may be related to findings that people with diabetes have decreased volume in the hippocampus and amygdala. McIntyre reported his own preliminary findings that 40 IU of insulin administered intranasally 4 times a day led to improvement in cognition. He cited the need for studies of the effect of exercise on outcome and cognition in bipolar disorder, as well as the need to study

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## How to Treat Obesity and Bipolar Disorder in Children and Adolescents

*Continued from Page 8*

bariatric surgery (in which a portion of the stomach is tied off to encourage weight loss) and the potential effects of a ketogenic diet, a high-fat low-carbohydrate diet that produces ketones, which the brain can use for energy. Ketogenic diets decrease oxidative stress and increase insulin sensitivity.

McIntyre cited findings that metformin, a drug used for diabetes, was often associated with small amounts of weight loss, as were the anticonvulsants topiramate and zonisamide. However, he noted that **in his own experience, the combination of naltrexone at 50mg/day plus bupropion at 300mg/day is associated with more substantial weight loss**, and he uses this treatment regimen as a first-line pharmacological intervention in both unipolar and bipolar patients with overweight or obesity.

### Addressing Behavior to Treat Youth Obesity

Researcher Tina Goldstein discussed behavioral prevention of obesity in pediatric bipolar disorder. She indicated that being overweight (with a body mass index (BMI) greater than 25) or obese (with a BMI greater than 30) was associated with a variety of poorer outcomes, including more severe bipolar illness, more hospitalizations and suicide attempts, poorer quality of life, and more substance use in children with bipolar disorder. She emphasized that systematic intervention is required to address the rapid onset in weight gain that often occurs in the first 12 weeks of treatment with atypical antipsychotics.

**Goldstein developed a program of cognitive behavior therapy and motivational interviewing about healthy behaviors for overweight children with bipolar disorder.** Goals were good nutrition, physical activity,

and decreases in sedentary behavior. Her preliminary data showed that this treatment intervention brought about weight loss in a small number of children, and she suggests prospective controlled studies be undertaken.

Goldstein's motivational interviewing techniques have proven useful in diabetes, dental disease, reproductive health, and substance abuse.

Her training program in this case included three 45-minute sessions in person and 2 phone booster sessions. The four major components were: 1) expressing empathy for the difficulty of following a weight maintenance program, 2) clarifying discrepancies between the child's behavior and his or her goals, 3) accepting the child's resistance, and 4) supporting self-efficacy.

The program emphasizes five strategies. The first strategy is personalized feedback for the family about: a) the need for change, b) overview of mood, medications, and weight; and c) assessment and charting of BMI, particularly using a visual presentation of the percentile at which the child falls on the BMI chart.

The second strategy was dealing with the "big 5" factors. These are: 1) assessment of sweets in beverages, 2) favorite versus healthy foods, 3) physical activity, 4) number of family meals, and 5) media time, i.e. computers, TV, etc. Each of these was rated by the family in a typical week and feedback was given about where changes could be useful.

The third strategy was evaluating readiness for change and addressing the child's ambivalence. Goldstein suggested choosing just two goals on which to focus, based on their importance and the child's confidence that he or she could change that behavior.

The fourth strategy was developing a plan for change. This involved collaboration, considering attainable goals, and noting a menu of options for how to proceed.

The fifth strategy was evaluating the change plan, which included problem-solving, trouble-shooting, anticipating future challenges, and increasing motivation for sustaining behavioral changes.

As a case example, the research team identified a child who was waking up sedated and drinking five energy drinks in order to get to school. The plan agreed on by the child, family, and research team was that the child would decrease the morning drinks to three and increase physical activity by playing more basketball with his brother. The child was a collaborator and partner, and thus could develop his own goals and act on his own to accomplish them. In this example the child was able to lose weight despite staying on an atypical antipsychotic.

Goldstein's full article on this topic was published in the 2011 volume of *Child and Adolescent Psychopharmacology*.

### Systematic Treatment of Obesity

Christoph Correll was the discussant of the symposium. He emphasized the importance of developing a systematic treatment plan and personalized feedback for every child who struggles with obesity.

Correll suggests that patients be weighed at intake and at each psychiatric visit. In his clinic, he has reception staff help patients weigh themselves and measure their waist circumference at each visit. When staff became involved in this way, compliance increased from 27% to 90%.

Management of weight in children with bipolar disorder should be a priority with a focus on prevention, close monitoring, active psychoeducation and motivational interviewing, and the development of an individualized treatment plan.

# Bipolar Disorder and Its Comorbidities in Children and Adolescents

A symposium on bipolar disorder and its comorbidities in children and adolescents took place at the annual meeting of the American Academy of Child and Adolescent Psychiatry in 2011. The following findings were reported there.

## ADHD

Researcher Janet Wozniak discussed the relationship between bipolar illness and attention deficit hyperactivity disorder (ADHD).

Based on interviews with family members of children with bipolar illness alone, bipolar illness plus ADHD, ADHD alone, and controls, she concluded that bipolar illness occurred more often in families of children with bipolar illness with or without ADHD. Similarly, she showed that there was more ADHD in relatives of children with either ADHD alone or ADHD comorbid with bipolar illness.

Wozniak concluded that **the comorbidity of bipolar illness and ADHD is a unique subtype of bipolar disorder and requires further study.**

## Emotional Dysregulation and Substance Abuse

In another presentation, researcher Tim Wilens indicated that children with bipolar disorder and emotional dysregulation had an 8- to 20-fold increased risk of having a substance abuse comorbidity with their bipolar disorder.

## Substance Abuse Comorbidity

Researcher Ben Goldstein reported at the symposium that the onset of bipolar illness predates the onset of substance abuse in 60 to 83% of instances of comorbid illness. He emphasized the dramatic negative impact of comorbid substance use in children with bipolar disorder, in terms of legal entanglements, pregnancy,

academic failure, suicide, and lack of compliance with medication regimens.

Goldstein reported that in the multi-site, National Institute of Mental Health (NIMH)-funded Course and Outcome of Bipolar Illness in Youth (COBY) study, the largest longitudinal study to date of youth with bipolar disorder, the risk of new onset of substance abuse over the course of 4 years of follow-up was 32%.

Given that 15% of children in the study already had substance abuse at intake, it appears that **approximately half of the children with bipolar illness in this study had or acquired a substance abuse problem near the beginning of their illness.** Two-thirds of the children in the study had abused both alcohol and cannabis.

Predictors of having already been diagnosed with substance abuse at study intake included: experimental (casual) alcohol use, panic disorder, family history of substance abuse disorder, history of oppositional defiant disorder or conduct disorder, decreased family cohesion, and less exposure to antidepressants.

In those who developed substance abuse after entering the study, there was a gap of an average of 2.7 years prior to the initiation of substance abuse. This provides a window of opportunity for intervention. The predictor variables for acquiring substance abuse during follow-up included: less time euthymic, more time manic, increased incidence of panic disorder, and treatment with fewer medications.

Goldstein emphasized that 1 in 3 children experienced onset of substance abuse within 3 or 4 years of follow-up, and **predictor variables included: increasing symptomatology, decreasing use of medications, recreational use of drugs, and a parent with a history of substance abuse (particularly active substance abuse).** He suggested that making sure a parent with substance

abuse is in treatment is one of the most important variables in preventing the new onset of substance abuse in their offspring with bipolar disorder. A second crucial factor is emphasizing medication adherence in order to decrease manic and anxious symptomatology, which are also independent predictors of new onset of substance abuse in children with bipolar disorder.

In the last presentation of the symposium, researcher Caleb Adler from the Lindner Center of HOPE in Cincinnati presented data indicating that those **children who experienced onset of bipolar illness before onset of substance abuse had a more difficult course of illness than those who first developed substance abuse and then bipolar disorder.** These data emphasize the importance of primary prevention of substance abuse acquisition in adolescents and young adults with bipolar disorder, who are at extraordinarily high risk for this comorbidity.

In Adler's research the most commonly abused substances were cannabis (used by 30% of participants), alcohol (27%), both cannabis and alcohol (18%), cocaine (4%), and opiates (3%).

Adler reported that 40% of bipolar adolescents who were well on entry to his study acquired substance abuse. He found that activity in three parts of the brain (the prefrontal cortex, insula, and anterior cingulate) was lower prior to the acquisition of substance abuse in those who went on to abuse substances than in those who did not begin abusing substances. This suggests that there may be alterations in the brain that convey a vulnerability to new onset of substance abuse. Surprisingly, he also found that some of the changes associated with marijuana abuse seemed to normalize brain abnormalities. Those changes could be positive and compensatory.

## The Explosive Combination of Bipolar Disorder and Substance Abuse

At the 2012 annual meeting on pediatric bipolar disorder sponsored by the Ryan Licht Sang Foundation and Massachusetts General Hospital, Timothy E. Wilens gave a plenary talk on "The Explosive Combination of Bipolar and Substance Abuse."

Wilens cited the statistic that 10% of -lation have at some time received a diagnosis of a substance abuse disorder. **The age of onset of substance abuse peaks between ages 15 and 20.**

Wilens said that in a recent survey, among substance users aged 12 or higher in the general population, about 50% had used marijuana in the previous month and about 50% had used prescription narcotics (often obtained from their parents' medicine chest).

The rate of mortality from substance abuse has risen dramatically since 1993 and now approximates that from automobile accidents. According to Wilens, rates of emergency room visits and fatalities have increased recently, and this has been linked to opiate overdoses.

**Adolescents with bipolar disorder are at greatly increased risk of substance abuse compared to the general population. Most substance abuse follows the onset of bipolar disorder, not vice versa.**

Wilens cited the data of researcher Ben Goldstein that on 8-year follow up, 32% of bipolar adolescents developed a substance use disorder. Those treated with antimanic agents were much less likely to develop a substance use disorder. MORAL: Treat bipolar disorder psychopathology in adolescents well and help them avoid substance abuse.

Children with persistent emotion dysregulation were: 1) more likely to develop a substance use disorder, 2) more likely to begin using substances earlier, and 3) more likely to have a more severe form of combined (multiple) substance use disorders.

### Treating Substance Use

Wilens suggested that a good interview is better than urine toxicology screens for assessing substance use. He suggested the following treatment paradigm:

1. Aggressive psychoeducation about substance use disorders for parents and children, starting before the child reaches age 12.

2. Close monitoring of the child's mood and substance use.

3. Use of groups, cognitive behavioral therapy (CBT), dialectical behavior therapy (DBT), and motivational enhancement. That is, increase discussion about what is not going well. Parents can engage with their child about how best to improve the child's life, e.g. asking, "Do you want to return to a sports team or receive permission to drive a car again? How can we help get you there?"

4. Working with parents even if their child does not come to initial sessions.

Some pharmacological approaches can be useful for substance abuse. Geller et al. published an article in 1998 showing that lithium helped decrease substance use. A 2011 article by DelBello et al. showed that quetiapine plus topiramate was more helpful in decreasing marijuana use than quetiapine plus placebo.

Editor's Note: Another option not mentioned by Wilens at the meeting is N-acetylcysteine (NAC), which is useful for a variety of substance use disorders and addictions including smoking, alcohol, marijuana, cocaine,

and heroin. (See our overview in BNN Volume 14, Issue 1 from 2010 for a discussion of possible mechanisms of these effects.) NAC's safety in children has been demonstrated in a study by Fung et al. in children with autism aged 8 to 17. Positive effects on depression have also been reported in adults with bipolar disorder, in whom NAC substantially beat placebo after about 3 months.

**Bipolar disorder in an adolescent is a medical emergency, and using multiple methods for treating the illness well and heading off the development of a substance use disorder may be life saving.** Psychoeducation is a must. Bipolar disorder and substance abuse in combination are like a metastatic malignancy; all the therapeutic stops must be pulled out in order to slow it or cure it.

Not incidentally, Wilens indicated that from a political/economic perspective, substance-related treatment is highly cost effective. He noted that for every dollar spent, 4 to 7 dollars are saved in reduced crime, legal costs, and theft alone. When health care savings are included, the savings are about \$12 for every \$1 spent.

**Contact Wilens' clinic at Massachusetts General Hospital at [armsmgh@partners.org](mailto:armsmgh@partners.org) or (617) 643-4699.**

**The Massachusetts General Hospital website on Addictions is <http://www.addictionanswers.com>.**

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