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Learning objectives for this issue:

1. Describe the evidence for pharmacological interventions in child and adolescent bipolar disorder.
2. Articulate some of the skeptical and critical views of child and adolescent bipolar disorder.
3. Explain the use of amber lenses in patients with bipolar disorder.
4. Distinguish between severe mood dysregulation and bipolar disorder.
5. Discuss the role of brain function in bipolar disorder.

Pharmacologic Treatment of Youth with Bipolar Disorder: Where to Next?

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Dr. Goldstein has disclosed that he has received an investigator-initiated grant from Pfizer and has served on a speakers' bureau for Purdue Pharma. Dr. Fisher has reviewed this article and found no evidence of bias in this educational activity.

Bipolar disorder presents unique pharmacologic challenges. Depending on the phase of illness a patient is in, the focus may be on acute manic or mixed episodes, acute depressive episodes, maintenance treatment (ie, prevention of recurrent episodes), and/or treatment of comorbidities, such as anxiety, ADHD, and substance abuse. Those treating children or adolescents with bipolar disorder face the additional challenge of having far less information to inform their treatment decisions.

Our field has learned from the failure of tricyclic antidepressants for youth depression that it is not as simple as just extrapolating from adult studies. We need studies specifically focusing on youth to best understand the efficacy and tolerability of these medications.

As recently as a decade ago, there

was almost no information available to guide pharmacologic treatment decisions for youth with bipolar disorder. Fortunately, a lot has happened in the past 10 years. In this article we'll summarize some important findings. (For a more detailed overview, see Pfeifer et al, *CNS Drugs* 2010;24(7):575-593, and Goldstein et al, *Child Adolesc Psychiatric Clin North Amer* 2012;21:911-939, which contains a full listing of citations for studies referred to here.)

What Have We Learned?

Treatment of Acute Manic and Mixed Episodes

Most studies about the pharmacologic treatment of bipolar disorder among youth have focused on acute manic or mixed episodes. This makes good sense, as mania is the most distinctive aspect of bipolar disorder, manic/mixed episodes often present significant risks, and using psychosocial treatment alone is not advisable. When faced with a youth who is manic, the main question is *which* medicine to use rather than *whether* to use a medication. This scenario differs from unipolar depression or anxiety disorders, for which psychotherapy alone is often a reasonable option.

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Letter from the Editors

The diagnosis, treatment, and very existence of pediatric bipolar disorder is one of the most contentious debates in our field. While the controversy rages on, we can most agree that our goal remains providing the most efficacious and compassionate treatment to our patients, using a combination of experience, research-driven data, and common sense. We created this issue of *CCPR* with that

goal in mind. Some of these articles on bipolar disorder may seem to directly contradict each other. Our objective is to provide you with information from many viewpoints and leave the rest up to you. We hope you enjoy it.

As always, feel free to share your thoughts at info@thecarlatchildreport.com. Happy New Year from the editors of *CCPR*.

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Multiple large-scale studies of second-generation antipsychotics (SGAs) show clearly that this class of medications works very well for youth with manic/mixed episodes. In each of these large studies, SGAs have clearly and convincingly outperformed placebo. Although there have not been large head-to-head studies of one SGA against another, it appears that they are relatively similar in terms of anti-manic benefits. Where they differ is in side effect profiles, particularly weight gain and metabolic abnormalities. Correll and colleagues examined these changes among treatment-naïve youth receiving SGAs for a variety of conditions (Correll et al, *JAMA* 2009;302:1765–1773). Similar patterns of findings have been observed in bipolar disorder specifically.

Despite the fact that lithium is arguably the leading medication for the treatment of bipolar disorder in adults, so far there are no published placebo-controlled trials of lithium for acute

manic/mixed episodes among youth. An unpublished study found no significant advantage for lithium (41%) versus placebo (30%).

Regarding divalproex (Depakote), although some early open-label studies suggested possible benefits, with response rates in the 50% to 75% range, a large randomized controlled trial for youth found a low response rate (24%) that did not beat placebo (23%) (Wagner et al, *J Am Acad Child Adolesc Psych* 2009;48:519–532). There was some thought that this study may have been negative because of suboptimal divalproex levels. There are some potentially promising signals from studies of carbamazepine (Tegretol), oxcarbazepine (Trileptal), lamotrigine (Lamictal), and topiramate (Topamax); however there are no positive randomized controlled trials for any of these medications in the treatment of acute episodes of mania among youth.

Recently, the large, multi-site Treatment of Early Age Mania (TEAM) study compared lithium, divalproex, and risperidone (Risperdal) (Geller et al, *Arch Gen Psychiatry* 2012;59:515–528). The response rate for risperidone (68%) was significantly higher than for lithium (36%) or divalproex (24%), which did not differ significantly from one another. However, in some sites, risperidone was vastly superior to lithium, whereas in other sites there was a minimal difference between the two medications. Could it be that the efficacy of lithium depends in part on clinician characteristics (eg, familiarity with lithium) or patient characteristics (eg, family history)? Clearly, lithium is far too important an option, and the evidence base is far too limited, to prematurely conclude at this point that it does not work for mania among youth.

One recent study examined the efficacy and tolerability of mood-stabilizing medications for manic/mixed episodes among adults and youth. Among youth, but not among adults, SGAs were more efficacious than other mood-stabilizers. Similarly, among youth, but not among adults, SGAs were associated with substantially greater weight

gain than other mood stabilizers.

Treatment of Acute Bipolar Depression

A handful of small open-label studies have looked at the impact of mood stabilizing medications on the depressed phase of bipolar disorder among youth. Response rates in studies of lithium and lamotrigine have been good, around 50% to 60%. Only one placebo-controlled study (N=32 adolescents) has been published so far, comparing quetiapine (Seroquel) with placebo. Enthusiasm about the high response rate for quetiapine (71%) was tempered by the equally high response rate for placebo (67%). Since quetiapine is the leading option for bipolar depression among adults, future larger studies among youth are likely. Treatment guidelines discourage the use of antidepressants as monotherapy, but acknowledge a potential role when used in combination with a mood-stabilizing medication. Unlike the adult data, there are no rigorous placebo-controlled studies of antidepressants for bipolar depression among youth, so caution is warranted.

Comorbidity and Treatment

ADHD is one of the most common comorbid conditions among youth with bipolar disorder. It seems that youth with comorbid ADHD have less robust response to mood stabilizing medication. In addition, there is the concern that stimulants could potentially destabilize mood among youth with bipolar disorder. Fortunately, studies have shown that once mood is adequately stabilized with mood stabilizing medications, youth with comorbid ADHD can often be safely and effectively treated with adjunctive stimulants. Although anxiety is very common among youth with bipolar disorder, and is associated with greater overall clinical severity, no treatment studies to date have specifically endeavored to improve comorbid anxiety among youth with bipolar disorder. There is support from a small placebo-controlled trial that lithium may help to reduce substance use and improve

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All editorial content is peer reviewed by the editorial board. Dr. Fisher, Dr. Parry, Dr. Preston, Dr. Shatkin, Dr. Stubbe, and Dr. Zuckerman have disclosed that they have no relevant financial or other interests in any commercial companies pertaining to this educational activity.

This CME/CE activity is intended for psychiatrists, psychiatric nurses, psychologists and other health care professionals with an interest in the diagnosis and treatment of psychiatric disorders.

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How We Got Here: The Psychodynamics of Juvenile Bipolar Disorder and the Clinician

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Dr. Harris has disclosed that she has no relevant relationships for commercial interests in any companies related to this educational activity.

The studies have been done and the consensus is in. Juvenile bipolar disorder (JBD) has probably been overdiagnosed recently, and the DSM-5 will describe a narrower phenotype to qualify for the diagnosis. The 40-fold increase in the diagnosis from 1994/1995 to 2002/2003 (Moreno C et al, *Arch Gen Psychiatry* 2007;64(9):1032–1039) was an overreaction that will likely be reined in. At this point, it is worth thinking about how we got here, and what it means for clinicians as a cautionary tale for the future.

First, there is a lot to be said about external pressures that have contributed to this increase in diagnosis. The rise of pharmaceutical companies' economic might and direct-to-consumer advertising have been pointed to as possible culprits, as the explosion in advertising has somewhat destigmatized the use of psychiatric medications. Some have pointed to prominent researchers' financial relationships with these companies. Congressional investigations into high-profile academic researchers receiving payments from pharmaceutical companies directly related to their research has

been damaging to the field's image.

The fiscal constraints on the mental health care system in general have clearly also played a role. Psychiatrists are pushed into seeing patients in ever-shorter visits, insurance requires diagnoses sooner in the process, and environmental supports like parent partners, well-trained foster parents, small classrooms, quality after school programs, and intermediate level treatment are scarce, favoring pharmaceutical over human intervention. Further, diagnostic labels like JBD may make accessing services like individual education plans easier.

Aside from these bigger questions, there is the question of how and why individual, well-meaning, caring, concerned clinicians were apparently eager to embrace this diagnosis before the science was in. The decision to give a child a label of a serious mental illness is not made lightly, nor out of conscious self-interest. There may be emotional, counter-transference reasons why this happens that are worth exploring.

It is important to emphasize that the children who have been being diagnosed with juvenile bipolar disorder are as a group very impaired. Indeed, when Dr. Joseph Biederman was caught in the crosshairs of the congressional conflict of interest investigation, the chiefs of child and adult psychiatry at Massachusetts General Hospital wrote a letter to the editor supporting him entitled,

"Heroes in Mental Health" pointing out how much these children and families struggle, and how much credit he deserves for being willing and able to offer help and hope to them.

Believing that you know what is happening, giving it a label, and having something to offer is tremendously liberating for both the family and the doctor. However, the drive to feel helpful, and the fear of being powerless, has a downside. Our discomfort with sitting with uncertainty and despair understandably leads us to reach for whatever we can offer.

Sadly, what we feel comfortable offering has been shrinking. It has been clearly documented that the number of psychiatrists doing a significant amount of psychotherapy has been declining markedly (Mojtabai R & Olfson M, *Arch Gen Psychiatry* 2008;65(8):962–970), and the same study found that those who provide psychotherapy to all their patients prescribe medications less frequently than those who provide psychotherapy less often. As we do less therapy, the old adage, "when all you have is a hammer, everything looks like a nail" may apply. When we don't have the option to do therapy, or feel less comfortable doing it, we are much more pulled to believe that what we do have to offer—namely diagnostic labels and medications—are useful and meaningful.

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global functioning among youth with bipolar disorder and comorbid substance use disorders. A recent randomized trial examined topiramate or placebo in combination with quetiapine, for manic youth with comorbid cannabis use disorders. Topiramate was associated with reduced cannabis use, and was also associated with reduced appetite, lessening quetiapine-associated weight gain.

Maintenance Treatment

No large-scale, placebo-controlled

studies have been conducted on the topic of maintenance treatment among youth with bipolar disorder. One study examined youth with bipolar disorder who had stabilized on the combination of lithium and divalproex. Those youth were randomized to discontinue one of the two mood-stabilizers, and the findings suggested that in this context lithium and divalproex were equally effective at preventing/delaying mood episode recurrences. There is some evidence from prospective open-label or naturalistic studies that extended (>six

months) treatment with lithium and/or divalproex may help to reduce the burden of mood symptoms among youth with bipolar disorder. This includes prevention of recurrences and further reductions in subsyndromal symptoms.

Where to Next?

There is an important need for continued research regarding pharmacologic treatment of youth with bipolar disorder. Areas in obvious need of progress include combination treatment, maintenance treatment,

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Pediatric Bipolar Disorder (PBD): A Skeptical, Mainstream, Non-US Perspective

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Although practicing in Australia, I have followed the PBD phenomenon in the USA for several years. PBD had become the most common diagnosis in pre-pubertal children in US psychiatric inpatient units by 2004 (Blader JC, Carlson GA, *Biol Psychiatry* 2007;62(2):107–114). “The epidemic of childhood bipolar disorder” (as later described by Allen Frances in *Psychiatric Diagnosis Gone Wild: The “Epidemic” Of Childhood Bipolar Disorder*, *Psychiatric Times*, April 8, 2010) was of interest to colleagues here in Australia when we became aware of it. Many US phenomena disseminate globally and we wondered if PBD would too.

Glen Spielmans, PhD (who, among other jobs, is the research editor for this newsletter’s sister publication, *The Carlat Psychiatry Report*), and I researched pharmaceutical industry documents released post-litigation that tell a sorry tale (Spielmans G & Parry P, *J Bioethical Inquiry* 2010;7(1):13–29). Among these documents was evidence of pharmaceutical companies seeking broadened criteria for bipolar disorder. (You can see the documents at <http://bit.ly/UL9tJq>) Internal pharmaceutical company documents noted that patents for SSRIs were expiring, whereas most atypical antipsychotics were young in their patent lives. Increasing bipolar disorder diagnoses was key to maximizing sales for on-patent antipsychotics. As Frances, chair of the DSM-IV task force, remarked: “New diagnoses in psychiatry can be far more dangerous than new drugs” (Frances A. Diagnosing the D.S.M. *The New York Times*. May 11, 2012).

PBD Generally Not Diagnosed Outside USA

It is true that if similar epidemiological methodology to the US researchers’

method is used, then comparable rates of PBD can be found outside the USA (Van Meter AR et al, *J Clin Psychiatry* 2011;72(9):1250–1256). There are PBD research centers in Europe, notably Spain, and in South America that have links with US researchers. But 17 years after the first publication in the USA about the postulated PBD phenotypes, PBD has not been accepted in mainstream clinical practice in other countries.

I was part of a group that surveyed the Royal Australian & New Zealand College of Psychiatrists (RANZCP) faculty of child and adolescent psychiatry (CAP) and found majority skepticism: only 3.5% thought our US colleagues were not overdiagnosing bipolar disorder, 90% thought they were overdiagnosing, and 6% were unsure (Parry P et al, *Child Adolesc Mental Health* 2009;14(3):140–147).

A German survey of child psychiatrists (Meyer TD et al, *Bipolar Disord* 2004;6(5):426–431), gave even more conservative results than our survey, and the British *National Institute for Health and Clinical Excellence* (NICE) 2006 guidelines on bipolar disorder stipulated that the PBD phenotypes were for research and not for use in clinical practice (NICE Clinical Guidelines 2006; www.nice.org.uk/CG38). A more recent German survey of inpatient diagnoses found a slight rise in bipolar diagnoses in late adolescence but no rise under age 15. They noted the contrast with US data: “While Blader and Carlson reported ...73 children and 204 adolescents per 100,000 ...the rates in Germany ...are 0.14 and 5.22 per 100,000” (Holtman M et al, *Bipolar Disord* 2010;12(2):155–163).

The international discrepancy in PBD diagnoses was reflected in three main child and adolescent psychiatry (CAP) association meetings in 2009: at AACAP in Hawaii there were more than 40 oral PBD presentations, whereas at both the RANZCP meeting in New Zealand and the large European Society for Child and Adolescent Psychiatry (ESCAP) meeting in Hungary there were none. At the International Association for Child and Adolescent Psychiatry and Allied Professions (IACAPAP) World Congress of

CAP this year in Paris there was a debate: “Paediatric bipolar disorder, severe mood dysregulation or what?” where the widely discrepant international views were again apparent (learn more at <http://bit.ly/TQh5r4>).

So Why the Discrepancy?

From my perspective, PBD in the USA has arisen during a time when the biomedical paradigm has dominated. Quantitative data is valued over qualitative data with diagnoses based on structured interviews rather than multiple, less structured sessions with children and families. The US health system encourages “diagnostic upcoding” based on DSM diagnoses, which since DSM-III, have mostly been decoupled from psychosocial contexts. In addition, the pharmaceutical industry has exerted an unhealthy influence in research, medical education, and consumer awareness; and attachment and trauma factors are often overlooked (Parry P & Levin E, *J Trauma & Dissociation* 2012;13(1)51–68).

“Not Everything that Counts can be Counted and Not Everything that can be Counted, Counts”

This quote of Einstein’s is worth reflecting upon. The use of structured interviews/rating scales for diagnosing PBD has been criticized (Carlson GA, *J Affect Disord* 1998;51(2):177–187). Dr Stuart Kaplan gives a detailed critique in his book *Your Child Does NOT Have Bipolar Disorder* and on his *Psychology Today* blog of the same title (www.psychologytoday.com/blog/your-child-does-not-have-bipolar-disorder). In summary, the reliability and validity of the instruments are less robust than one might realize, with several points of ambiguity and interpretation that may lead to skewed results.

Beyond the USA, the mainstream view is that pre-pubertal mania is extremely rare to non-existent. This view is rooted in traditional phenomenology, attachment theory, psychodynamic theory, developmental psychology, family systems theory, and developmental trauma research. It is borne out in long term family therapy, intensive parenting

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bipolar depression, and the treatment of comorbid anxiety.

Another important topic that has received very little attention is the treatment of bipolar-spectrum conditions including bipolar II disorder, cyclothymia, and bipolar disorder not otherwise specified. There is compelling evidence that the latter progresses to bipolar disorder type I or II in 40% to 60% of cases, depending on the presence of a family history of bipolar disorder. Irrespective of diagnostic conversion, bipolar spectrum conditions are highly impairing and persistent, and these conditions are far more similar to bipolar I disorder than they are different. This invokes unique pharmacologic treatment considerations that have not to date been examined rigorously.

Our field needs some traction in terms of objective markers that can be used in the selection and monitoring

of pharmacologic treatment. Examples include blood tests for serum biomarkers, neurocognitive testing, neuroimaging, and genetic testing. Despite recent gains in these areas, so far the existing science has not translated into clinical decision making. That type of progress is urgently needed, and overlaps substantially with the need for these same technologies to help optimize diagnostic accuracy. Bipolar disorder is a systemic illness associated with inflammation and oxidative stress. Incorporating this evidence in our search for novel treatments may lead us to “out of the box” approaches based on existing treatments from other branches of medicine, including medications with anti-inflammatory properties.

Finally, we cannot ignore the deleterious impact of treatments, particularly SGAs, on the cardiovascular system, and the vastly increased risk for premature cardiovascular disease and

related conditions that is independently associated with bipolar disorder. Future studies should incorporate primary tolerability outcomes as well as primary efficacy outcomes. The potential role of complementary and alternative treatments, such as fish oils and curcumin, warrants further investigation. These agents may present options for bipolar depression, early intervention in milder bipolar spectrum conditions, and adjunctive treatment that improves residual symptoms with attractive risk-benefit balance.

The past decade has seen progress in the pharmacologic treatment of bipolar disorder among youth. With continued research we will hopefully be able to offer more personalized treatment options that better balance efficacy and tolerability for youth with bipolar disorders across all phases and stages of illness.



Pediatric Bipolar Disorder (PBD): A Skeptical, Mainstream, Non-US Perspective

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training, dyadic parent-child post-trauma therapies, and play therapy. This is traditional clinical practice which finds biopsychosocial case formulations to be more informative than most DSM diagnostic labels.

Of course, many US clinicians still practice in the traditional way (for example Williams, Laurel L. Mental health and children. *Los Angeles Times*; December 14, 2008). There is mounting disquiet with the current DSM paradigm that has “atheoretical” diagnoses made with minimal regard to psychosocial context, as evidenced by an online petition (see <http://bit.ly/UPPSrx>).

PBD (and DMDD) Literature Overlooks Attachment and Trauma

I conducted a systematic literature review for concepts such as attachment theory, post-traumatic stress, child abuse, maltreatment, and neglect in the PBD literature and found virtually nothing (see Parry PI. Paediatric Bipolar Disorder—Are Attachment and Trauma Factors Considered? In: Barnhill J, ed. *Bipolar Disorder—A Portrait of a Complex Mood Disorder*. InTech; 2012:165–190). The

PBD literature focused on symptom clusters, rating scales, pharmacotherapy, genetics (though no clear answers), and neuroimaging (though no discernible reference to identical neuroimaging findings from the attachment-trauma literature). There was minimal mention of psychodynamic or family dynamic factors. A similar picture was evident in a brief review of the severe mood dysregulation/disruptive mood dysregulation disorder literature (Parry PI. Diagnostic Labels and Kids: A Call for Context. *Clinical Psychiatry News*; February 22, 2012).

Dr. Jennifer Harris has noted that developmental trauma/maltreatment was a factor for children erroneously diagnosed with PBD in a Boston inpatient unit (Harris J, *Psychiatric Serv* 2005;56(5):529–531). During my five years on an inpatient unit that serviced a whole Australian state, the youngest case of mania was aged 14. Colleagues since informed me of a 12-year-old pubertal boy with definite mania and a five-year-old girl who presented as quite manic and this aroused interest as a possible true pre-pubertal case—until it was noticed her manic symptoms appeared

only when her mother was present. I saw one possibly manic seven-year-old boy, but his manic-defense coping mechanisms completely resolved after disclosure of sexual abuse and jailing of the perpetrator.

Trauma denial has a long history. Freud theorized about infantile libido on the basis of incredulity of child sexual abuse disclosures by his Viennese female patients. Abuse, pathogenic family dynamics and attachment insecurity are frequent amongst stressed families. The desire for a shame-free biological explanation and medication fix can be high.

Dr Edmund Levin describes how addressing underlying trauma, using developmental trauma disorder rather than PBD as a diagnosis, and appropriate staff training in two therapeutic residential units was useful in reducing medication prescriptions by 80% and violent incidents by 100% over a two-year period (Levin EC, *J Am Acad Psychoanal Dyn Psychiatry* 2009;37(3):519–538).

Additional Drivers of Diagnosis

Blader and Carlson argued that

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Q & A
With
the Expert

Expert Interview

**Severe Mood Dysregulation (SMD) and
Pediatric Bipolar Disorder
Ellen Leibenluft, MD**



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Dr. Leibenluft has disclosed that she has no relevant relationships or financial interests in any commercial company pertaining to this educational activity.

CCPR: Dr Leibenluft, you are a well-known researcher on pediatric bipolar disorder. How did you come to be in the middle of the pediatric bipolar controversy?

Dr. Leibenluft: Back around 2000, there was argument in the literature about the boundaries of bipolar disorder in children. People were claiming that bipolar disorder in children presents differently than it does in adults—they were saying that instead of episodes of mania like in adults, pediatric bipolar disorder presents as very severe, chronic irritability. But these very severely, chronically irritable children that people were arguing about were not really being studied. So I got involved in doing just that.

CCPR: And how did you design your research to include these kids?

Dr. Leibenluft: In order to study these children, we had to first define criteria that would capture them, then recruit a bunch of them, study them, and compare them to children that everyone would agree have bipolar disorder—those with true episodes of mania.

CCPR: How did you develop criteria to define these chronically irritable children?

Dr. Leibenluft: In 2003, my research team and I published a paper in the *American Journal of Psychiatry* on the criteria for severe mood dysregulation (SMD), which described these controversial children. We wanted to capture children with very severe, chronic irritability—no manic episodes, just irritability day in and day out. And we defined irritability very specifically because we wanted trained clinicians to be able to agree on it reliably. We defined two core features of irritability. First were developmentally inappropriate outbursts—or in other words, terrible temper tantrums—at least three times a week, for at least a year, without two months asymptomatic. Second, in between the outbursts, they had to have negative mood. You can have kids who have outbursts and then in between they are very happy—that wasn't who we wanted. We wanted the children who were always grumpy. We also wanted these children to be very impaired, since children with pediatric bipolar disorder are very sick and we wanted to compare the two groups directly. We said that the irritability has to be impairing in at least two out of three settings; school, home, or in interaction with peers. It has to be severely impairing in one and at least mildly impairing in the other. Finally, we said that it has to start before age 12.

CCPR: How was this different than disruptive mood dysregulation disorder (DMDD)?

Dr. Leibenluft: The biggest difference between DMDD and SMD centers around so-called hyperarousal symptoms. In the criteria that we created for severe mood dysregulation, we required that the child have three of seven hyperarousal symptoms. These are symptoms that overlap between the so-called “B” criteria of mania and ADHD. The “B” criteria include agitation, racing thoughts, and pressured speech. A lot of those features overlap with ADHD, as well. It was this combination of irritability and hyperarousal that caused people to argue that these children had bipolar disorder—so that's why we required hyperarousal as well as irritability for SMD. The DMDD criteria don't require hyperarousal symptoms. The DSM 5 work group's thinking was that children with DMDD who also have the hyperarousal symptoms would just get the diagnoses of both DMDD and ADHD. Finally, SMD requires onset before the age of 12, whereas DMDD requires onset before the age of 10.

CCPR: What were your exclusion criteria?

Dr. Leibenluft: Any manic episodes—even if only a day long—excluded a child from our SMD group. We also excluded children with PTSD because of the hyperarousal and irritability you can see with that; and children with irritability in the context of separation anxiety, depression, or PDD.

CCPR: So once you defined these children, you then asked: “Do children with severe chronic irritability have a form of bipolar disorder?”

Dr. Leibenluft: Yes. To answer that, we compared two groups, the SMD kids and the bipolar kids, on what are called “psychiatric validators.” One of the most important psychiatric validators is longitudinal course. What happens to these children as they grow up? If severe, chronic irritability in children is a form of bipolar disorder, you would expect that these chronically irritable children would develop manic episodes as they grow up.

CCPR: And did they?

Dr. Leibenluft: We found that only one child out of 84 developed any type of manic episode. So these very sick children are not in any large number developing bipolar disorder. And of course, our bipolar sample continued to have manic episodes. Then, because we really want to follow many children for a long time and our study did not do that, we also worked with community-based longitudinal datasets that have followed children for a number of years.

CCPR: And what did you learn from those datasets?

Dr. Leibenluft: The first one that we published was from the Great Smoky Mountain Study. In this sample about 1,400 kids were followed from a mean age of around 10 to around 18. We did a *post hoc* analysis of the data. *Post hoc* analyses have their problems because you are looking at data that wasn't specifically designed to answer the question that you are asking. For example, the interview in this study was not designed to ascertain SMD, but it did include detailed questions about irritability. So we made a proxy for SMD from the questions in their interview. We identified the children at age 10 who had SMD, and we asked the question, "What are they at increased risk for when they are 18, relative to the kids who didn't have SMD at age 10?"

CCPR: And what was that?

Dr. Leibenluft: Unipolar depressive disorders. It actually turns out that SMD at age 10 is a better predictor of depression at age 18 than is depression at age 10. The limitations here are: 1) the dataset had very few bipolar children in it, so you really don't have the statistical power to say much about bipolar disorder *per se*, and 2) at the end of the study the children were 18 and they still could have gone on to develop bipolar disorder.

CCPR: Interesting. Did you look at any other datasets to help overcome the limitations of that one?

Dr. Leibenluft: Yes, the Children in the Community dataset gathered by Pat Cohen at Columbia. In this dataset we asked the question, "What does chronic irritability at age 13 (which is when the study began) predict at age 33?" This data set included 20 years of follow-up, until the subjects were age 33, and most people who will develop bipolar disorder have already developed it by that age. Also, there were enough people who met criteria for bipolar disorder in the sample for us to really look at predictors of bipolar disorder.

CCPR: So does chronic irritability at 13 predict bipolar disorder at 33?

Dr. Leibenluft: No. Instead, it predicts increased risk for unipolar depressive disorders just like we saw in Great Smoky Mountain, and it also predicts increased risk for anxiety disorders.

CCPR: What other data did you look at in regard to chronic irritability and bipolar disorder?

Dr. Leibenluft: We looked at family history. Bipolar disorder is very heritable, and so you would expect that, if chronic irritability in children is a form of bipolar disorder, then children with chronic irritability would have strong family histories of bipolar disorder. So we interviewed parents of our SMD and our bipolar children, and we found that the parents of the children with bipolar disorder themselves had very high rates of bipolar disorder, whereas the parents of the SMD children did not. The two parent groups had similarly high rates of major depression, anxiety disorders, and substance abuse. Now there are a couple of caveats to that study. It is relatively small and there is what is called "ascertainment bias" because it is from a sample that specifically came to the NIH to participate in studies, not a random sample. However, other people have looked at the question in other datasets and found similarly.

CCPR: So at this point you're quite certain SMD does not lead to bipolar disorder.

Dr. Leibenluft: Yes, in the sense that the evidence indicates that the vast majority of children with severe irritability will not grow up to have manic episodes.

CCPR: Did you look at any other validators?

Dr. Leibenluft: Another thing that we have looked at is brain function, using brain imaging techniques. Brain function is not yet a psychiatric validator. That is, you can't make psychiatric diagnosis based on brain imaging yet; it is still just a research tool. But we wanted to see what is going on in the brains of children with bipolar disorder and in the brains of children with severe chronic irritability, particularly when they process emotional stimuli. While we don't have clear answers yet, the hints lead us to believe that the children with bipolar disorder and the children with SMD have some similar deficits in brain function when compared to "normal" children, but there are also differences.

CCPR: So how do you suggest a practicing clinician make the distinction between what may be SMD and what may be bipolar?

Dr. Leibenluft: By clinical interview, and, in particular, looking for clear episodes that represent a distinct change in mood from the child's baseline. You need that to diagnose a child as having a manic episode, and hence bipolar disorder. I will give you an example: You have a child who gets up in front of the class and says "I am smarter than the teacher." The questions that a clinician might struggle with are: Is this manic grandiosity? Or is this oppositionality? To answer that, it's very important to determine if this behavior is different from the child's usual behavior. If this is totally unusual behavior for this child—and if this unusual behavior started at around the same time that the child started to exhibit other unusual behaviors, such as difficulty sleeping, increased activity, etc—it's more likely bipolar disorder. On the other hand, if this is typical behavior for this child, and if this child is very irritable a lot of the time, then it may be SMD.

CCPR: Thank you, Dr. Leibenluft.

The evidence indicates that the vast majority of children with severe irritability will not grow up to have manic episodes.

Ellen Leibenluft, MD

Parents who might be interested in having their children participate in Dr. Leibenluft's research program can call 301-496-8381 or email irritablekids@mail.nih.gov. The group is currently conducting studies with children with SMD, children with bipolar disorder, and children who have a parent or sibling with bipolar disorder.



Q & A
With
the Expert

Expert Interview

Brain Function and Bipolar Disorder
Mani Pavuluri, MD, PhD

*Professor of child psychiatry
Berger Colbeth Chair in Child Psychiatry
University of Illinois at Chicago College of Medicine*



Dr. Pavuluri has disclosed that she has no relevant relationships or financial interests in any commercial company pertaining to this educational activity.

CCPR: Dr. Pavuluri, please share with us your interest in pediatric bipolar disorder.

Dr. Pavuluri: I am the director of The Pediatric Brain Research And Intervention (BRAIN) Center at the University of Illinois at Chicago. I study the brains of children with bipolar disorder. I am interested in the brain's plasticity in these patients and learning how to develop interventions capitalizing on the plasticity.

CCPR: What is so interesting about the brains of children with bipolar disorder?

Dr. Pavuluri: Children with bipolar disorder give you a wonderful example of a brain that is impacted by cognitive and emotional problems, with impairment in many domains that are interrelated.

CCPR: In your research, you have found that kids with bipolar disorder understand things differently than kids without. What are some of these brain differences?

Dr. Pavuluri: We have mapped five main circuits in the brain so far. There is one circuit that modulates emotions, another that helps recognize facial emotions, another that shows immediate reaction to emotionally negative stimuli, another one that underlies impulse control, plus a circuit that connects the emotional/feeling and thinking regions. A quintessential clinical problem with bipolar disorder is that patients are excitable, irritable, and overly reactive, and these become problematic more so in the context of reactivity to perceived negativity. All of the five circuits are impaired and there is a complex problem with the wiring.

CCPR: How do you differentiate then between bipolar disorder and ADHD, since ADHD presents with impulsivity, emotional reactivity, and irritability, too?

Dr. Pavuluri: ADHD, by diagnosis, is a disorder with attention problems and response inhibition. These kids are also emotional, though the emotionality arises from being frustrated. ADHD presents predominantly with inattention, poor executive function, and poor impulse control. Bipolar disorder is predominantly an emotional wiring problem.

CCPR: Do all of these problems originate in the same part of the brain?

Dr. Pavuluri: Impulse control and emotional control problems share the same hierarchical prefrontal cortex area of the brain called ventrolateral prefrontal cortex. It is the CEO that controls impulse control—with wiring shooting towards the caudate; and emotional control—with wiring shooting toward the amygdala. These two sets of wires are connected again at the subcortical level (in other words, caudate and amygdala). In some ways, if you pull one wire, it affects the other.

CCPR: Do you think this connection is why kids often are first diagnosed with ADHD when later it becomes clear that they have bipolar disorder?

Dr. Pavuluri: I think there are three reasons for that. The first reason is sometimes kids actually present with ADHD first. In a young formative brain, there might be problems with ADHD that spill into the bipolar spectrum over time. The second scenario is that people get it wrong because they may not recognize the emotional problems that indicate bipolar disorder. And the third reason is that one disorder may be present in full and the other disorder may be present in part, as I described earlier, due to entangled wiring problems across the brain. I want to point out that these are man-made labels. I believe that no matter what the disorder is, the labels are important only insofar as they help us communicate the larger picture.

CCPR: Knowing what you do about the brains of kids with bipolar disorder, how can we better treat them?

Dr. Pavuluri: We should take a “double-pronged approach,” as I call it. In addition to treating the disorder, we need to focus on treating the domain dysfunction in the brain. Executive function, impulse control, emotional control, emotional response, emotion processing, emotion recognition, perspective taking, concentration, attention, and memory are some of them. So we try to address any number of these difficulties that each child may be facing. It is the predominant symptom structure that dictates the treatment plan.

CCPR: You did a really interesting study looking at two different medications and what they do functionally in the brain. Can you tell us about that?

Dr. Pavuluri: We have done a number of studies comparing risperidone (Risperdal) and divalproex (Depakote) (Pavuluri M et al, *J Am Acad Child Adolesc Psychiatry* 2012;51(2):157-170). Risperdal is a serotonin dopamine antagonist—an atypical antipsychotic—that works in the subgenual cortex. And divalproex (Depakote) is an anticonvulsant that works in the frontal and temporal regions of the brain to stabilize mood at the cellular level through calcium channels. Risperdal moderates emotional regions such as the insula, amygdala, subgenual cortex, and the prefrontal cortex. Depakote does similar things, but it works in regions that are slightly different, and works especially in the medial prefrontal cortex, which is the emotional evaluative area. Sometimes these drugs don't

Bipolar disorder is predominantly an emotional wiring problem.

Mani Pavuluri, MD, PhD

work well at regulating emotions on their own as a single drug, but when they are given together to treat mood, they complement each other as they work on different regions of the brain.

CCPR: So a lot of us know combinations can work better than some drugs alone, but this explains why that is.

Dr. Pavuluri: Yes, and this means that in the future we can develop new drugs, new treatments, and new techniques and tools using this knowledge and foster the brain's ability to repair the dysfunctional circuits back to health.

CCPR: Do you think that there is a way to tell which kind of medication would be better based on the presentation of a child?

Dr. Pavuluri: I would say: "sometimes." If there is somebody who is very smart, and you really want to preserve cognition, lamotrigine (Lamictal) is one mood stabilizer that I often prescribe along with, say, Risperdal, because of the cognitive preservation that lamotrigine offers. Risperdal is a drug that offers response really quickly. So if someone is very sick it's a good choice to get them feeling better fast. If someone has more depressive symptoms, then you might want to think about lithium, which is known to reduce suicidal symptoms a bit better (Baldessarini RJ et al, *Pharmacological treatment of bipolar disorder throughout the life-cycle*. In Shulman KI et al (eds): *Bipolar Disorder Through the Life-Cycle*. Wiley & Sons, New York, NY, 1996, pp 299–338). We just discovered that lithium changes genetic makeup that fosters nerve growth, which is why it may take longer for it to show its full effect! There are more drug studies done through clinical practice than through brain, so we are still trying to use brain studies to decode the drugs one by one.

CCPR: You mention cognitive preservation with lamotrigine. Do you find that kids with bipolar disorder have cognitive problems in addition to their issues interpreting emotional stimuli?

Dr. Pavuluri: Emotional dysregulation is critical: even though these children are very smart, emotional dysregulation sometimes trumps their obvious intelligence. The brain shows complex impairment in bipolar disorder. To repeat, there are problems with executive function, attention, working memory, verbal memory, and impulse control.

CCPR: Do these problems improve with treatment?

Dr. Pavuluri: We have shown in bipolar disorder that over three years of follow-up, some get a little better, some get worse, and some stay the same over time, compared to their healthy peers (Pavuluri et al, *J Am Acad Child Adolesc Psychiatry* 2009;48(3):299–307). Executive function and verbal memory either stay the same or get worse sometimes. Attention problems, because we can treat them with stimulants, seem to respond a little better and quicker over time. Working memory also has been shown to improve with drugs that enhance the working memory and attention, such as lamotrigine and Focalin. Lithium has a reputation for impairing cognition, but in our study lithium did not worsen it, but it did not fix the cognition, either (Stevenson JM et al, *J Pharm Prac* 2012;25(2):274). Sometimes, lithium helps cognition in part, via stabilizing emotional control.

CCPR: Sometimes people come into the office and say, "I want my kid tested for bipolar disorder!" How close do you think we actually are to being able to do that?

Dr. Pavuluri: I still think that clinical diagnostic assessment is the best option. We are developing more measures and more techniques to show exactly where "the (brain) engine" is not working. We have a long way to go to rely on these tools.

CCPR: Thank you, Dr. Pavuluri.

How We Got Here: The Psychodynamics of Juvenile Bipolar Disorder and the Clinician

Continued from page 3

Our narcissist defenses move us towards accepting ideas that make us feel useful and powerful, sometimes without appropriate credulity.

Often the families of the children who might be diagnosed with JBD are also quite impaired. Whether they are struggling with a purely difficult child, or whether some of the child's problems may have stemmed from the family milieu, these families present challenging dynamics to the child psychiatrist. There may be a strong push to label the child because it will alleviate parental guilt by seemingly confirming that there is "something wrong" medically with the child and therefore not the parents' fault. Alternatively, it could mean that the parents do not need to look too closely into their child's suffering because the answer is a medication adjustment, not

a deeper emotional one. Sometimes as providers we are pulled into these dynamics unawares.

Sometimes we consciously react against family dynamics hoping to intervene positively. Parents who see their out-of-control children as all bad, hostile, or manipulative may move us as providers to give an alternative narrative that is less pejorative to the child. In an effort to protect the child, we may feel drawn to giving a label that implies that the child's behavior is not the child's fault, and makes the parent more empathic. Parents more easily understand something that has a clear label and a history behind it, than a discussion of why it's important to be understanding.

Finally, it is worth admitting that as clinicians we are also susceptible to the stigma and uncertainty surrounding

mental health care. In the face of societal skepticism and sometimes hostility to mental illness, it is tempting to flee to certainty. It is uncomfortable to say, "I don't know, and I'm not sure how to help." The reality in child psychiatry, however, is often that we don't know. It takes time for illnesses to reveal themselves, and even when they do they often don't fit clear diagnostic boxes. It takes a tremendous amount of resilience and ego to be able to feel comfortable with that, and meet families where they are (which is often confused, upset, guilt-ridden, scared, and sometimes angry). The temptation to offer a diagnosis, and make ourselves feel smart and useful, is very strong and shouldn't be ignored.



Amber Light Therapy for Bipolar Disorder

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Dr. Kurtz has disclosed that he has no relevant relationships or financial interests in any commercial company pertaining to this educational activity.

When you suffer from bipolar disorder, life may seem like it's all about sleep. It's no longer an apple a day, but rather a full night's rest that keeps the doctor away. Sure, a single night of poor sleep may just leave you feeling lousy, but when one bad night succeeds another, anxiety starts to build as you wonder if this is the start of another attack. Bipolar patients understand better than any that sleep disturbances can not only predict but also provoke manic episodes (Plante DT & Winkelman JW, *Am J Psychiatry* 2008;165(7):830–843; Bauer M et al, *Psycho Med* 2008;38:1069–1071). They recognize that good sleep hygiene and daily routines are essential components of their overall treatment (St-Amand J et al, *J Affect Disord* 2012; online ahead of print). Good sleep hygiene is especially important for adolescent patients, as this age group is well known for having erratic sleep schedules.

What bipolar patients, as well as their doctors, may not know is the amount of current research centered on light-dark therapy and the potential implications of this research on treating bipolar. The past decade has been filled with studies describing retinal ganglion cells and their role in regulating circadian rhythm (Brainard GC et al, *J Neurosci* 2001;21:6405–6412; Thapan K et al, *J Physiol* 2001;535:261–267). These newly discovered receptors in the eye are part of a complex system that senses light and transmits signals to the suprachiasmatic nucleus in the hypothalamus (Gooley JJ et al, *Neurosci* 2003;23:7093–7106). When functioning properly, the end result is a sleep/wake cycle that works in harmony with the solar cycle of the earth. When stimulated inappropriately (like at night), this system suppresses our pineal gland from releasing melatonin,

ultimately resulting in poorer sleep habits (Brainard op.cit).

Additional studies have shown preferential stimulation of these receptors by blue light (Vandewalle et al, *PLoS One* 2007;2(11):e1247; Wright HR & Lack LC, *Chronobiol Int* 2001;18(5):801–808), which is emitted from our televisions and artificial light sources. The culmination of the research seems to suggest two methods for stimulating sleep: either enforce complete darkness in the hours prior to bed, or create a “physiologic darkness” by somehow blocking out blue light waves.

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For most people, the idea of enforcing complete darkness two to three hours before bed seems impractical. Fortunately, it's been suggested that amber lenses can be worn to block blue light from activating the retinal ganglion cells in our eyes (Phelps J, *Med Hypotheses* 2008;70:224–229). Theoretically, glasses are worn for a couple hours before bedtime, blocking out all blue light emissions from the TV, lamps, etc, allowing the brain's production of melatonin to continue uninhibited. Even better, a pair of amber lenses can be picked up for as little as \$7 and have a significantly better side effect profile than pharmaceuticals (see <http://bit.ly/VzNxxp>). Early studies were promising, showing melatonin levels actually increase with amber lenses compared to control (Sasseville A et al, *J Pineal Res* 2006;41(1):73–78).

More recently, Burkhart and Phelps conducted a small randomized study to assess whether blocking blue light actually leads to a clinical improvement

in sleep. The study started with 20 participants who had symptoms of insomnia defined as difficulty falling asleep or staying asleep, or waking earlier than desired. Exclusion criteria included prescription medication use, nicotine, excessive alcohol or caffeine use, and prior knowledge of amber lenses. Ten subjects were assigned to the amber lens group and another 10 to a control group using yellow lenses (which do not effectively block blue wavelengths). The study lasted three weeks; one to establish baseline sleep and mood followed by two weeks of using lenses three hours prior to bedtime. All participants kept sleep diaries and performed daily PANAS mood scales. Although results were subjective and lacked compliance checks, their study showed significant improvement in both sleep and mood for patients wearing amber lenses (Burkhart K & Phelps J, *Chronobiol Int* 2009;26(8):1602–1612).

Another interesting branch of therapy involves the use of darkness. Research on patients with bipolar disorder who were treated with darkness therapy is limited, but in two case reports of bipolar patients and one of a schizoaffective patient, short-term darkness therapy helped stabilize mood. In a small study of 32 patients with bipolar disorder who were treated on an inpatient unit, half received darkness therapy in the form of 14 hours of enforced darkness per day for three days. The other half received treatment as usual. The study found that scores of the Young Mania Rating Scale decreased more quickly in patients who received the darkness therapy, provided the onset of mania was within two weeks of treatment. Further, in a study of patients with bipolar disorder who were stable on lithium, it was concluded that lithium actually decreases sensitivity to light.

CCPR'S VERDICT: Although more research needs to be done, amber lenses may provide a low cost, low risk intervention for patients with bipolar disorder and is certainly a promising option.

CME Post-Test

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Below are the questions for this month's CME post test. This page is intended as a study guide. Please complete the test online at www.TheCarlatChildReport.com. Note: Learning objectives are listed on page 1.

1. The large, multi-site Treatment of Early Age Mania (TEAM) study found the greatest response rate with which of the following medications (Learning Objective #1)?
 a) Risperidone b) Divalproex c) Lithium d) Lamotrigine
2. The only placebo-controlled study of mood stabilizers during the depressed phase of bipolar disorder in youths found what response rate in the placebo group (LO #1)?
 a) 14% b) 25% c) 67% d) 71%
3. According to Dr. Peter Parry, what percentage of Australian/New Zealand child psychiatrists that he surveyed thought American psychiatrists "over diagnose" bipolar disorder (LO #2)?
 a) 3.5% b) 6% c) 60% d) 90%
4. Research has found that those psychiatrists who provide psychotherapy to all their patients prescribe medications less frequently than those who provide psychotherapy less often (LO #2).
 a) True b) False
5. Early studies of the use of amber lenses showed what result on melatonin levels when compared to the control (LO #3)?
 a) Melatonin levels increased b) Melatonin levels decreased c) Melatonin levels stayed the same
6. In a post hoc analysis of the Great Smoky Mountain study, what did Ellen Leibenluft and her team learn that severe mood dysregulation at age 10 predicted at age 18 (LO #4)?
 a) Bipolar disorder b) Anxiety disorders
 c) Unipolar depressive disorders d) Personality disorders
7. Impulse control and emotional control problems share the same hierarchical prefrontal cortex area of the brain called what (LO #5)?
 a) The caudate b) The ventrolateral prefrontal cortex c) The amygdala d) The subgenual cortex
8. According to Dr. Mani Pavuluri, working memory in patients with bipolar disorder has not been shown to improve with drugs that enhance the working memory and attention, such as lamotrigine and Focalin (LO #5).
 a) True b) False

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Pediatric Bipolar Disorder (PBD): A Skeptical, Mainstream, Non-US Perspective

Continued from page 5

“diagnostic upcoding” had driven the rise in PBD because the US health system demands more serious diagnoses in order to get treated. No other developed nation has this health system driver for bipolar disorder. However, both Australia and Canada have similar drivers for autistic spectrum disorder and both have seen a clear uptick in diagnosis of ASD. (Skellern C et al, *J Paediatr Child Health* 2005;41(8):407-412; Thivierge J, *NADD Bulletin* 2008;XI(1):Article 2).

Much has been written elsewhere on the topic of pharmaceutical company influence. I’d like to note just one personal experience: A PBD researcher at AACAP 2009 was asked in the session why not call the children “affect dysregulated” rather than “bipolar.” The reply was frank: “If we don’t call them ‘bipolar,’ we won’t get funding.”

Final Comment

Practicing in Australia, I’ve yet to see any pre-teen cases of mania, and neither have most of my CAP colleagues. However I accept that rare true bipolar cases can occur in pre-pubertal children. For example, Carlson described a convincing case of a 10-year-old boy (Carlson GA, *Am J Psychiatry* 2009;166(1):18-24). That said, I invite my US colleagues to at least consider the diagnostic alternatives and cultural pressures before coming to the bipolar conclusion.



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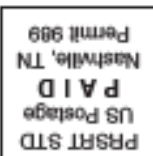
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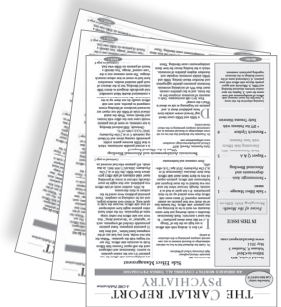
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