

Bipolar Disorder in Youth: An Update on Diagnosis and Treatment - Pediatric Grand Rounds-8-1-2025-Meeting Recording: featuring Melissa P. DelBello, MD, MS

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1h 7m 33s

🕒 **Kamat, Deepak M** started transcription

 **Jane Fried** 0:12
Picture's not gonna be there.

 **Kamat, Deepak M** 0:41
Good morning. It's 7:30 in San Antonio and it's time to start our grand rounds. Welcome. The CME code is in the chat box and we'll keep repeating IT every 1015 minutes. Just A. reminder that please complete the evaluations at the end of the grand rounds.
It's my great privilege and pleasure to introduce this morning's Grand Round speaker, Doctor Melissa Del Bello, who is A. Professor of Psychiatry and Pediatrics and Stanley and Mickey Captain Chair of Psychiatry and Behavioral Neurosciences at the University of Cincinnati College of Medicine.
Doctor Delbello received her Medical degree from the University of Rochester and completed her psychiatry residencies at the University of Cincinnati College of Medicine and Pain Whitney Psychiatric Clinic of New York Hospital Conan Medical Center. Doctor Delbello completed A. fellowship in child and adolescent psychiatry. Cincinnati Children's Hospital Medical Center and obtained A. master's degree in Epidemiology and Biostatistics from University of Cincinnati College of Medicine. Dr. Delbello has co-authored over 400 articles and has served as A. principal or Co investigator.
On several NIH PCORI Foundation and pharmaceutical Research brands, investigating risk and resilience factors associated with onset and course of mood disorders. Dr. Delgola, thank you very much for accepting our invitation and we're looking forward to your presentation. The floor is yours.

 **Delbello, Melissa (delbelmp)** 2:13

Thank you very much and thank you for inviting me to present this morning. We're going to spend the next 45 minutes or so talking about bipolar disorder in kids, talking about diagnosis and then touching on some of the neurobiology and treatment.

Wanted to disclose potential conflicts, mostly in the form of Research Support for A. variety of companies that Support some of the medications that we will be discussing. So first we'll talk A. little bit about the phenomenology and course of illness. We'll talk about.

Treatment of the different phases of bipolar disorder, Treatment of mania, Treatment of depression associated with bipolar disorder, and then A. little bit about maintenance treatment, early intervention, which is kind of A. hot topic. How do you know when to treat for bipolar versus treating for?

other prodromal presentations. And then we'll talk A. little bit about some of the metabolic adverse effects of the medications that are most effective to treat this illness. So just to kind of make sure we're all talking the same language, and this may be A. REVIEW for some people.

Bipolar one disorder is defined by the presence of having at least one full-blown manic episode, and we'll talk about specifically what those criteria are. Bipolar 2 disorder is defined by having hypomanic episodes with depressive episodes. So for. Bipolar one, you never have to have A. depressive episode, although A. majority 80% will have A. depressive episode some time during the course of their illness. For bipolar 2, you must have hypomanic episodes with depressive episodes.

Cyclothymia, which is fairly common in Kids compared to adults and maybe an early presentation, is hypomanic and depressive symptoms that last over the course of A. year for kids. It's two years for adults and then.

HL **Hank Lipsitt** 4:17

Hello.

OK.

DM **Delbello, Melissa (delbelmp)** 4:28

The most common diagnosis was historically bipolar, not otherwise specified. Now we have those divided into two different diagnoses, other specified bipolar and related disorders. That is actually when you want to specifically state why they don't meet.

meet full criteria for A. manic episode and unspecified bipolar disorder. That's when they don't have the duration criteria or the number of criteria, but you don't really specify why they don't meet full criteria.

OK, so A. manic episode. A manic episode is defined by the presence of elated, expansive, or irritable mood. You have to have one of those characteristic moods. And as we'll talk about, the problem is for kids, depression, also irritability is A. criteria. So sometimes when the mood is irritable, as we'll talk about, IT can be very difficult to figure out what the underlying diagnosis is. So elevated, expansive. or irritable mood and an abnormally persistent goal-directed behavior with high energy lasting at least A. week. And that's A. new part of A. criteria for A. manic episode. The goal-directed behavior has to be increased.

energy that lasts at least A. week. It has to be present nearly every day. And then, depending on whether the mood is irritable, elated, or expansive, you have to have three or four of the other criteria. So it's increased grandiosity.

When the Kids think they're better than the adults in their lives, most Kids think that, but they act on it. They will tell their teachers they know how to teach the Class better than themselves, better than the teachers do. They will be very defiant.

But to the point where they really believe that they have the ability to do things that they don't, they have A. lot of grandiose IDEAS about the future, about where they fit into the future.

They have decreased need for sleep, and it's not just poor sleep, it's poor sleep and high energy, increased pressured speech, flight of IDEAS where their thoughts are jumping from idea to idea, distractibility, increased goal directed activity and excessive involvement.

In high risk activities, pleasurable high risk activities, buying sprees, you know, purchasing A. lot of things on the Internet when they don't have the ability to do that financially and then multiple sexual partners during A. brief period.

Period or running away from home. These are all the kind of classic symptoms for A. manic episode, hypomanic episode. Really, the only difference between A. manic episode and A. hypomanic episode is that for A. hypomanic episode, it's four days. And IT does not have as severe impairment. So the impairment for A. manic episode is pretty severe. For A. manic episode, IT needs to last seven days or you have to be hospitalized in the course of that manic episode. So IT has to be pretty severe and. Functionally impairing A hypomanic episode. It's not fewer criteria. It's all the same criteria, but it's not as much impairment. Major depressive episode. Just everyone

knows ciggy caps, but it's more than or equal to 5 symptoms and depressed.

Anhedonia, failure to gain the weight they're supposed to, or weight loss, decreased appetite, insomnia, psychomotor agitation or retardation, fatigue, loss of energy, worthlessness, suicidal ideation and poor concentration.

So any constellation of those symptoms 5 or more, but you have to have the depressed or irritable mood or anhedonia. OK, so the problem with DSM-5 was that for Kids with bipolar disorder, we used to diagnose in the majority of.

Kids A. mixed episode which is Co occurring mania and depression. In DSM 5 there is no such thing as A. manic or A. mixed episode. What IT typically ends up being is mania with mixed features.

And you could have A. depressed episode with mixed features as well, but there's no episode that is defined as A. mixed episode any longer. Also, the change in energy level is emphasized, as we discussed in the manic episode definition.

And because of that, it's very hard sometimes with the differential and the comorbidity of ADHD that we'll talk about because that makes IT even more difficult because you have to have the increased energy or goal directed activity.

And then as we mentioned, there's no longer the BPNOS, which a majority of kids were getting that diagnosis. Now it's other specified bipolar and related disorders as we talked about. So those are some of the drawbacks of DSM 5 for kids, the criteria for a manic episode.

Is no different between adults and kids at this point. So what is the epidemiology of bipolar disorder in kids? About 2% of kids will meet criteria for bipolar spectrum.

That's bipolar one, bipolar 2 or bipolar.

bipolar, other specified. And so it's about 2%. 50 to 60% of adults, when you ask them when their onset of bipolar or manic episodes or hypomanic symptoms were, most of them, 2/3, up to 2/3 will say that they had it as early as during childhood. Irritability is one of the earliest symptoms of bipolar disorder when you do retrospective studies, but but it's also very nonspecific. But most people who grow up to have a bipolar diagnosis will

We'll tell you retrospectively that irritability was one of the earliest manifestations, and overall we know that early onset bipolar disorder is associated with poor outcome, increased risk for lifetime suicide compared with adult onset bipolar disorder.

And bipolar depression is more common than manic episodes. They spend more time in the depressed phase of bipolar after the onset of their manic episode when

their onset is younger.

So those are more of the kind of characteristics or epidemiology of early onset bipolar disorder looks like. We also know that there are very high rates of comorbidity. ADHD is almost ubiquitous when your onset of bipolar disorder is prepubescent. It's about.

85% will have comorbid ADHD. That has been an area of our research interest. Is this real ADHD? That's like a whole other topic of a presentation, but regardless, they do meet criteria for ADHD.

ADHD about 50% when the onset is during adolescence and other common comorbidities, conduct disorder, anxiety is high rate of anxiety, substance use disorders, about 40% who have their onset during.

adolescence will have co-occurring lifetime substance use disorders. But generally speaking, comorbidity is the rule rather than the exception. Irritability, as I mentioned, is nonspecific. It could be part of normal development, it can be part of A cadre of diagnosis and we consider it like a fever. It just tells you something is wrong, especially when they're getting to see as their chief complaint, whether it's us or pediatricians, when the chief complaint is irritability, it really is just a symptom and it's hard.

Job.

Figure out what the underlying diagnosis is. Sometimes it's because they're being bullied at school, and we kind of diagnose that, generally speaking, as an adjustment disorder. Sometimes it's depressed depression. Sometimes it's ADHD, about 3/4 of kids with ADHD.

Present with irritability at different times. Anxiety disorders. Irritability is very common. We'll talk in a minute about disruptive mood dysregulation disorder. That's a newer diagnosis that you may or may not have heard of.

And oppositional defiant disorder, which I am a big advocate of never giving somebody oppositional defiant disorder as a diagnosis. It does not exist. It is irritability and defiance.

It is a symptom. When you do epidemiologic studies, only a small, small number of kids will have just an ODD diagnosis. They always have it in conjunction with another diagnosis, ADHD, mood disorders. And so it is.

It's very rare that a child will have ODD. We never give that diagnosis in isolation.

There's always some reason they're irritable or defiant. Kids are not by nature irritable or defiant for the most part.

OK, so DMDD, you may have heard of this diagnosis. We typically do not give it at a reliable rate because the criteria are.

Very complicated, but in most of the research studies that have examined DMDD, there is you can't have a manic episode and be diagnosed with DMDD. So it's kind of a diagnosis of exclusion. Some people will call it like having.

Extreme temper tantrums, but it is basically a lot of the criteria for persistent depressive disorder. So generally the mood and and that's where it's listed in DSM is under a mood disorder, but more under the depressive spectrum of.

disorders. So it's people who are very depressed and irritable as their predominant mood. But these are the specific criteria. Most of the people who give this diagnosis, the kids don't necessarily meet all these criteria.

A lot of times they will have depression when you do studies comparing what used to be severe mood dysregulation, now called DMDD. And basically the family history of bipolar is extremely unlikely. And so that is one of the criteria.

Criteria that we will use to differentiate. If somebody comes in and there is a family history of bipolar disorder, those kids do not have DMDD. It is like less than 5% and so that is really one of the.

Biggest questions to ask about a family history of bipolar or manic like behaviors. So again, if you have a diagnosis of bipolar one or two in your family, you're not gonna give them a.

Diagnosis of DMDD and if you have criteria for ever having a hypomanic or manic episode, again, typically they will not have DMDD, they will have bipolar disorder.

This is an interesting study that was done or analysis that was done looking at all the different studies of DMDD and in one study in particular when you looked at who has just a diagnosis of DMDD without ADHD.

Do you?

ODD or conduct disorder. Out of almost 500 kids, only four did not have another diagnosis. And so we again, like ODD, think of DMDD as it's a symptom of extreme irritability, temper tantrums, but we need to figure out what the.

Underlying diagnosis is a lot of times it's ADHD in a majority of cases with extreme irritability, but again, using the criteria for a manic or hypomanic episode, you cannot have this diagnosis.

And interestingly, when you look at the treatment studies of DMDD, they're kind of all over the place in terms of sometimes stimulants work, sometimes antidepressants work, sometimes second generation antipsychotics work. So it kind of really is not.

Very homogeneous diagnosis. It's a lot of different diagnosis with extreme irritability and temper tantrums. So what are outcome predictors of kids with bipolar disorder? Well, non-adherence is very common, especially in adolescents. Most of the.

Kids will not be fully adherent with their medications during the course of their initial diagnosis, but so non adherence is obviously a predictor of poor outcome.

Comorbidity makes the diagnosis more difficult to treat.

Girls have a worse outcome. They remain more symptomatic. Being prescribed stimulants and antidepressants in conjunction is often associated with poor outcome and we'll talk a little bit more about that later. Having Co occurring substance.

Use independent of non adherence, although substance use comorbidity is more prevalent in those who have poor adherence. Substance use by itself is a predictor of poor outcome having no psychotherapy. And this has been in a variety of studies, interestingly, and it doesn't matter.

Matter what type of psychotherapy, but having any type of psychotherapy is predictive of having a good outcome. Socioeconomic status is lower, socioeconomic status is predictive of poor outcome and having a lack of maternal warmth.

and maternal warmth could be paternal warmth. It's just having a caregiver that is participating in the child's care on a day-to-day basis. So basically, a lack of maternal warmth is associated with poor outcome. It doesn't mean it causes

of the illness, but it is associated with poor outcome. And then in some of the largest studies, we know that kids who have a diagnosis of bipolar II disorder or bipolar NOS in prior studies, most of them will go on to have bipolar

One or bipolar 2 if they have NOS and if they have bipolar 2, about 1/4 will go on to have bipolar one during. This is during about five years of on average follow up. So bipolar NOS and bipolar 2 will often progress.

Now what about kids who have family histories of bipolar disorder? The BIOS study is a multi-site study that was done predominantly in Pittsburgh, but it is a study and the only study we have that compares kids who have parents with.

Bipolar disorder and bipolar disorder is one of the most familial illnesses we have in psychiatry. If you have a parent with bipolar disorder, the child has a 30% chance of having bipolar disorder. One parent with bipolar, the other with a mood disorder.

If it's depression or bipolar disorder, it has ranged from 70 to 85% of those kids will have a bipolar diagnosis, so it's very familial diagnosis. But this study looked at offspring of parents with bipolar disorder and compared them to.

Control offspring who had parents without any psychopathology, but then uniquely

compared them to also kids who had parents with other psychopathology other than bipolar disorder. So we have three groups. So it's one of the only studies that has. Looked at it that way, and what this study found is that across the board, kids who have parents with bipolar disorder are at higher risk for, of course, having a bipolar spectrum illness, and the middle column is compared to those.

Who have a non bipolar diagnosis in the parents. So another you know population or sample that has psychopathology in the parents and there's nine times the risk of having a bipolar spectrum diagnosis but also.

Four times the risk of having any mood disorder in the kids. And across the board, most diagnoses are higher in the kids compared to the kids of parents who have other psychopathology compared to kids who have control parents who don't have psychopathology.

Pathology, the risk is even higher of any mood disorder. It's about about 20 times the risk. So again, it's a familial illness. Other risk factors that are associated with having a.

A parent with bipolar disorder and the kid themselves having a diagnosis of bipolar is having a younger parental age at the child's birth. Of course, we mentioned having both parents have bipolar disorder and if you have a.

Parent who had early onset bipolar disorder during childhood or adolescence. The child themselves is at more risk for having early onset bipolar disorder. And then in the child themselves, if you have parent a parent with bipolar disorder, if the child. child has depression or anxiety, mood liability, if they have exposure to antidepressants or stimulants, if they have anxiety or disruptive behavior disorders in themselves, they are longitudinally more at risk for developing bipolar disorders.

So those are kind of what we consider maybe prodromal presentations of bipolar disorder in offspring of parents with bipolar disorder. So we kind of characterize the development of bipolar disorder into different stages.

And depending on the stages and we'll talk a little bit about how treatment plays a role here, but there's stage 1, which is having risk factors. So as we mentioned having a first degree relative number one risk factor, but these are other well established risk factors.

For having a bipolar diagnosis in the more risk factors you have, the more likely you are to go on to have a bipolar diagnosis. For those of you who are interested, Pittsburgh has developed A.

A predictive scale that looks at what it takes a child and it's not been validated in a

lot of different samples, but it has been validated in more than one sample and it looks at the risk factors that a child has and.

the potential for them to go on to develop bipolar disorder. So if you're interested, it's it's worth at least looking at and knowing that it exists. And then there's the prodromal clinical features. All of these diagnoses have been

Establish to be risk factors for going on to have bipolar one disorder. So that's kind of how we think about it in terms of staging. We also think about the more.

The the increased stage that you're at, the more likely you are to go on to have a more significant intervention or need a more significant intervention. So earlier on you might be treated with.

You know, a omega-3 fatty acid for example, or some type of therapy where as you progress on to stage two and stage 3, particularly stage 3, you that's where you would need a mood stabilizer or antipsychotic.

What about neuroimaging and what do we know about brain development in these kids? So I'm only going to briefly touch on this. This is also an area that we do a lot of research in, but there have been pretty consistent findings in terms of.

Of prefrontal connectivity with subcortical and amygdala regions, the uncinate fasciculus has been pretty well established and consistent finding and imaging studies.

That there are alterations, and if you think about adolescence as a time where prefrontal amygdala connectivity is very much being established, there's a lot of. Pruning going on and you know there there's a lot of these pathways that are being developed, but they don't seem to develop normally in kids who have bipolar disorder and particularly ventral prefrontal interesting.

insula, and amygdala. Those connectivity, those regions are have been consistently shown to not develop normally in these kids. This is just an example of one study that looked at the amygdala and structural findings.

things that showed that at baseline, kids with bipolar disorder, ADHD, and control kids all kind of look the same. But so so it's not like amygdala structural abnormalities are present prior to the onset, but during the

First year of illness, you can see that there's normally during adolescence an increase in amygdala volume. That's been consistently shown in a lot of studies, but in the bipolar kids, both the left and right amygdala seems to.

Not increase in size and in some cases decreases in size or stays the same. And so the development of amygdala volume, probably as a result of connectivity with

prefrontal regions, does not seem to develop normally.

Yeah.

And again, just to highlight the regions that have been studied most have also shown the most effect of pharmacologic intervention and we'll talk a little bit more about that, but.

Some of the studies have shown that there is changes as a result of intervention with specific medications that normalizes development. So we'll talk a little bit more about that.

about that. So we're going to switch gears now and talk about treatment. And these are the FDA approved medications for the different phases of illness. So during acute mania for kids, the medications listed are the ones that are evidence-based that there have been

Placebo control studies. Historically, lithium was grandfathered in by the FDA, but more recently we do have data to support its efficacy for mania for acute bipolar depression, which is probably, in my opinion, the more severe phase of.

Illness, because that's when kids are most at risk for attempting suicide. We only have two options, olanzapine fluoxetine combination, otherwise known as Symbiox, which is very rarely used. We'll talk about because of the side effects and loral.

Plazodone, which is the first and only monotherapy we have for bipolar depression and then for long term treatment we only have lithium and aripiprazole that are FDA approved for use.

And we'll talk about the evidence for that. So we really have an unmet need in terms of acute bipolar depression and maintenance or long-term use. This just looks at some of the effect sizes and the scale that we.

Use for for rating manic symptoms is a clinician administered scale called the Young Mania Rating Scale and it's an instrument that basically clinicians will interview the parent, the kid and.

Observe behavior and rate this instrument, and that is the main outcome measure for manic episodes in kids. What we see here is the effect size of these different medications. These are mood stabilizer medications like Divalproex lithium.

Oxcarbazepine and topiramate and you can see here that unlike adults with bipolar disorder or manic episode, Divalproex is not been very effective. The effect size is .28 compared to.

Other effect sizes. Lithium is .37. Generally speaking, for efficacy, you want it to be about .4 to .5 for mania. That's what the FDA is in general, you know, required for

approval to pyramid is kind of an interesting.

Story because it was studied in adults with bipolar disorder for mania, but it was found in multiple studies to be ineffective for adult mania. And then the one study that was done in kids was stopped with only 1/4 of the.

Projects that were to be enrolled, who were enrolled. And then when when it was looked at, the effect size was .5, but no other study has been done really looking at efficacy. So we're kind of left with an open question about topiramate.

When you look at second generation antipsychotics across the board, these medications have been shown to be effective for manic symptoms and really the effect sizes are fairly similar across the different antipsychotics.

But when you directly, there's only a handful of studies directly comparing a second generation antipsychotic to a mood stabilizer. This is the team study Treatment of Early Age Mania that was done that was ranged in age from.

To 15 year olds and risperidone was compared to lithium and Divalproex and you can see here that only 1/4 of the patients on Divalproex responded. In general, the studies that have looked at Divalproex compared to placebo have found.

That placebo responses are generally higher than Dival Pro X and this study again is fairly consistent. Lithium has a response rate of about 35% and risperidone very consistent with the other SGA's is about 70%.

Response rate and looking at side effects though, as we'll talk about, weight gain was the most significant with risperidone. Prolactin elevation was more significant than with lithium or Divalproex as expected, and so the side effects are greater.

However, the discontinuation rate was greatest for lithium in this study. So that is one of the only studies we have comparing the two. We've done a study actually comparing quetiapines to lithium.

And this was a double-blinded, double dummied study where patients were taking pills for both the lithium and the quetiapine. And we were yoking it in terms of increases, decreases because we wanted to lithium has to be titrated to a.

therapeutic level. And here in this study was a six-week study of acutely manic early course um adolescents with bipolar disorder. And you can see that lithium and quetiapine at the end of six weeks were similar in efficacy, although quetiapine did of the slight edge. Quetiapine resulted in greater weight gain than lithium, although lithium was not weight neutral. And those with a family history of bipolar were in general in the lithium group more likely to respond than those

Without a family history of bipolar. So family history was predictive of lithium

response. And in the lithium group, those without prior stimulant treatment were five times more likely to respond and that was.

Only predictive of lithium response. The response was quicker in the quetiapine group.

So there have been a couple of systematic reviews and network meta-analyses. We won't go into detail on either of these, but they've been published in the past couple of years and they're worth at least knowing about and looking at. If you're interested, they both.

Summarize a little bit differently the literature. This is a systematic meta-analysis that looked at 18 studies of acute manic adolescents and basically performed a network meta-analysis, did not look at dosing within the.

Studies combined, if a study had two different dosings of the medication versus placebo, it only looked at the two different doses as one dose and what you can see here in terms of efficacy and this is just the top and the bottom are just.

Different definitions of response. The top is change in or continuous change in improvement in manic symptoms as measured by the Young Mania Rating Scale. The other was a dichotomous.

50% or greater response or improvement in the Young-mania rating scale.

Regardless, risperidone, aripiprazole or ziprasidone were generally the most effective.

And then valproic acid, as you can see here, either definition was no more effective than placebo.

So it's a way of combining the different studies to kind of rank which is most effective. And in general, when they looked at mood stabilizers versus second-generation antipsychotics, you can see here that again, second-generation antipsychotics as a group.

Are more effective than mood stabilizers. In general, mood stabilizers don't seem to be very effective, and that is in contrast to adults with bipolar disorder, where SGAs and mood stabilizers have very similar efficacy.

This is a second meta analysis which looks at dosing specific. So a lot of the second generation antipsychotic studies had two different dosing of the treatment versus placebo and it actually just.

Kind of gives you a better sense of what dosing is most effective. I think it's most helpful actually for risperidone and aripiprazole. For risperidone, the lower dose is more effective and the higher dose just gives you more side effects. So for risperidone we will rarely go above.

Of 2.5 milligrams because we don't get in general better efficacy, we get more side effects and our piperazine, we do tend to need to push the dose to get better efficacy. So this just breaks it down by dose, but it's similar findings to the other meta-analysis.

We did a meta-analysis for bipolar depression, and in bipolar depression there have been four studies, two with quetiapine, which you may or may not know is approved for bipolar depression in adults, and then the olanzapine fluoxetine combo Med and lorazodone and you can.

You can see here that ranking of a lower ranking is better and so lorazodone in terms of efficacy outcomes is the most effective in terms of side effects. Olanzapine fluoxetine combination has the worst profile.

And quetiapine was found to be ineffective in both of those studies and so both of the studies of quetiapine, so lorazidone really in terms of efficacy and outcome.

Safety seems to be the best in terms of for bipolar depression. OK, so talking for a couple of minutes, there aren't very many maintenance studies or long-term studies.

We have one with Lamotrigine and these studies are very hard.

Do this was a randomized withdrawal study, so patients were stabilized if they could be stabilized on a junctive Lamotrigine. So Lamotrigine was added on to whatever they were on. They could have been on up to two conventional mood stabilizers.

And they had up to 18 weeks to stabilize. And there were specific definitions of stabilization. And then they were randomized to placebo or Lamotrigine. They were allowed to again continue on whatever medication. These studies you would imagine once the patient stabilized, it's very hard.

To to justify and continue these patients and risk the randomization to placebos. So there is a large dropout even of patients who stabilize for people who don't want to take the risk of.

Randomizing. So they're very difficult and this was an adjunctive study. So what this study found was that in the older age, 13 to 17, there was an advantage. These are survival curves of being treated with Lamotrigine, whereas in the younger age, the 10 to 12 year olds.

There was no difference between staying on Lamotrigine or placebo. So again, for the older age, they were less likely to need any other intervention if they were on Lamotrigine versus placebo.

There has been another study with aripiprazole that is aripiprazole versus placebo monotherapy after stabilizing on monotherapy of aripiprazole. And this was a smaller

study where 96 people were allowed to given the opportunity. to stabilize, 60 did, and they were randomized to ipiprazole or placebo for up to 72 weeks. And reason for discontinuation, any reason was considered not surviving in this study. And again, as you can

See here a lot of people rapidly discontinue because they are worried and in this study even more so that they were only on placebo after stabilizing on aripiprazole. And despite that, aripiprazole was more effective than placebo long term if you stayed on aripiprazole.

you did stabilize and maintain stabilization after the initial, what we call a nocebo effect, where they drop out because they could be on placebo. There has been one small study with, called the COLT study,

This were people who responded to lithium and then randomized to lithium or placebo for up to 28 weeks. And you can see here that for maintenance purposes, lithium was highly more effective than placebo.

Dropout in placebo was fairly high.

OK, long term lorazidone. Just to briefly mention, this is a study that was open label lorazidone after stabilizing. This was either they were they were depressed coming into the study, but they could have been in the open label part.

Coming in with any phase and because we don't have a placebo, we don't really know. But looking at trajectories for kids who you know over the course of two years are going to gain weight, you see here that on lorazodone during the course of two years.

The weight gain was exactly what was predicted for over the course of two years. So lorazidone is probably the only second generation antipsychotic that is generally weight neutral. Not always, but generally.

Just want to briefly mention a couple of other medications that are being studied for bipolar depression. At this point, Cariprazine is a medication. The advantage of Cariprazine is that it has a very long half-life.

And it is being studied for bipolar depression in kids. At this point, it's approved in adults for depression, mania and schizophrenia.

Lumeteparon is another medication that works a little bit differently. It's a 5HT2A antagonist and we know that historically some of the best antidepressants have been 5HT2A antagonists.

And this medication is approved in adults for bipolar depression and schizophrenia. It's approved for bipolar one and bipolar 2, and it is now being studied in kids. So I

just wanted to mention these are other potential treatments in the future for kids. Kids with bipolar depression. Just to touch on kids who have a family history of bipolar disorder, they present with ADHD, with anxiety, with mood symptoms. And one of the biggest dilemmas in child psychiatry is how do we treat these kids without?

Making them accelerate their progression to bipolar disorder. We do know that a lot of these kids, when they are treated with antidepressants, will have significant adverse effects. So having a bipolar family history and.

Being treated with an antidepressant is one of the strongest predictors. So if you're age and you have a parent with bipolar disorder and you're treated with an antidepressant, almost all of those kids will have a severe adverse reaction. So suicidality, psychosis.

Ending up in the emergency room in this study, on average, if you're about 14, that's the average age. About 50% will go on to have a bad side effect. The older you are, the more likely you are to tolerate an antidepressant, probably because you pass through some of the risk of accelerating the onset of bipolar disorder. Again, other studies have shown this, that if you're treated with an antidepressant and you in general are treated with an antidepressant and you have a bipolar spectrum illness, so you're at risk, about a third of those kids will have new onset suicidality.

OK, so there have been a whole bunch of studies looking at kids who have parents with bipolar, but they themselves don't have bipolar and they they have been open label studies that have shown some effectiveness double-blind studies.

Studies of Divalproex show that only if you have a multi-generational family history of bipolar will it be effective. Iripiprazole is a study that there have been. There has been a study that has shown it's effective for high risk kids, but at this.

Point really trying to avoid an antidepressant is probably or getting away with the lowest dose possible is probably the best strategy if they're presenting with depression, but monitoring them very carefully, particularly in the very young kids and of course screening very.

Carefully for manic symptoms. I also just want to mention nonpharmacologic evidence based interventions, family focused therapy, which is David Miklowitz's therapy, which is to reduce stress conflict in the family.

Affective arousal and it involves the family or a caregiver and the patient. And that's been shown to be very effective compared to an enhanced care treatment and

mindfulness based cognitive therapy, particularly for anxiety in high risk kids. So kids who.

have parents with bipolar has been shown to be effective. Just want to end with mentioning the adverse effects of antipsychotics. Of course, we have weight gain as the primary adverse effect that most people are familiar with.

Up to 70% of kids will gain weight with antipsychotics with second generation antipsychotics. Unfortunately, those are the medications that are most effective for acute mania at least.

And there are some side effects that kids are at lower risk for. So it's tardive dyskinesia, developing full-blown diabetes that tends to occur more in adults who are on antipsychotics.

But in kids, they're more at risk for prolactin elevation and for the dyslipidemia and the weight gain. So again, this is part of that meta-analysis that looked at olanzapine is probably the worst, aripiprazole, quetiapine and it's just kind of.

Gives you aripiprazole, probably one of the better second-generation antipsychotics.

Umm And this is from the other study. As you may or may not know, topiramate is used adjunctively for the weight gain oftentimes, and you can see here.

Again, olanzapine is the highest risk for weight gain and quetiapine, aripiprazole. And we talked about how olanzapine, fluoxetine combination is particularly, particularly problematic for the metabolic side effects and for weight gain.

And just looking at some of the other metabolic parameters, Risperidone is high risk for increasing glucose as well as triglycerides as well as quetiapine and the other SGAs.

We have done a study with topiramate adjunctive to olanzapine and it doesn't completely neutralize it, but it halves the weight gain and looking at it, whether you define it with change in BMI or a change in weight, it halves the weight gain when used adjunctively compared to.

CBO.

I want to spend the last couple of minutes talking about metformin. There are now pretty strong recommendations. If you are treating kids with a second-generation antipsychotic that has a moderate or greater potential for weight gain, then you should always.

Is true.

them with metformin. And this is based on several studies. Dr. Klein, who was an endocrinologist in Cincinnati, did one of the first studies that shown metformin can

plateau the weight gain versus placebo that is associated with second generation. And antipsychotics. So some kids lose weight, but most of them don't continue to gain weight. There has been the IMPACT study, which is more of a controlled study that looked at three groups.

It compared three groups with who were treated with second-generation antipsychotics and had significant weight gain from them over the past three years, and they were ages 8 to 19. There were three randomized arms of the study.

Obviously.

were not blinded, but continuation with the SGA they were on, plus a healthy lifestyle intervention, continuation with the SGA plus addition of metformin and a healthy lifestyle intervention, or switching to aripiprazole, or if they were on aripiprazole, switching to Provenesin.

seen plus a healthy lifestyle intervention. So three treatment arms. And what was found was that switching to a lower propensity antipsychotic for weight gain and switch adding metformin were both effective compared to just a healthy lifestyle. Intervention at decreasing BMI Z score and then unfortunately switching to a different antipsychotic was associated with increased risk for mood instability. So aggression, impulsivity, anger, irritability was.

Very high in the switch group compared to the metformin and the control group was similar to the switch group. So it's not to say metformin helps with that, but it actually doesn't destabilize these kids.

And so we did a study that was a pragmatic trial that involves sites from all over the country, including Texas. And this was a study that patients in clinic settings were who were overweight or obese were.

randomized to a lifestyle intervention or a lifestyle intervention plus metformin, and they had to have a bipolar spectrum diagnosis. If you're interested, you can visit our website. There is a healthy lifestyle video on there.

It's a 7 minute video that was done by Health Works, which is our weight loss intervention program by our Pediatrics department and it's based on the traffic light, low glycemic, high glycemic, moderate glycemic diet and.

And that is the intervention that was done in mobility, this study, and this was the recommended titration by our pediatric endocrinologists. And again, kids were eight to.

18 In the study, 1500 kids were randomized, average age of about 14. Most had been on an SGA for at least a year, so about 50%. We did have some SGA naive kids.

And I'll skip to the main findings in the interest of time, but metformin plus a lifestyle intervention resulted in a decrease in BMI Z score for up to 24 months.

And then compared to a healthy lifestyle intervention, which at month 6, which was one of our primary outcome, they were weight neutral, little bit increase in weight and then at month 24 had some weight decrease but less than.

than metformin. And so um people who reached 1500 with metformin had more weight loss or BMI Z score loss than those who didn't get to 1500. So based on this study, we recommend

1500 milligrams per day. Rates of suicidality were half as much in the group that got metformin. Again, I'm not saying metformin's effective for the mental health part, but because of the weight loss, these kids generally did.

better in terms of peer relationships, in terms of self-esteem. GI side effects were the primary side effects that we saw. We advised people to switch to the extended release and again with the titration

We told people to go decrease the dose and go in the lower dose for a longer period of time. It was a pragmatic study, but again, based on this and based on the guidelines that have recently been released, kids who are.

Prescribed SGA that has that has moderate or more potential for weight gain and the guidelines actually suggest they don't have to be overweight or obese, but the studies we've done have been overweight or obese, but they suggest if you're going to prescribe.

And SGA, they should be on metformin as well. So with that, I know we're kind of out of time. I will stop and maybe we have a couple of minutes for questions.



Kamat, Deepak M 59:02

Thank you Doctor Debra, for that wonderful presentation on bipolar disorder. In you there are two questions already on in the chat box. Should all children with ADHD symptoms and family history of bipolar be referred to child psychiatry?



Delbello, Melissa (delbelmp) 59:16

I think, you know, there's the reality of how hard it is to get people, at least here, into child psychiatry. But I think probably I think they should be monitored very closely for symptoms of.

mood disorder. If you, they they tend to, these kids tend to have really bad rebound on if they're using short acting or if you're using long acting in the evening, it tends

to be very difficult.

For these kids. And so I do think if you're going to try a stimulant, use the lowest dose possible and instead of titrating quickly by weight as we would do for a kid who does not have a family history.

You know you can try them and start them on one while you're waiting for them to get in to see a child psychiatrist.



Kamat, Deepak M 1:00:19

Thank you, Doctor. Another question by Doctor Lopez. Who should prescribe metformin? Are they referred to endocrinologist?



Delbello, Melissa (delbelmp) 1:00:27

Yeah, that's that's a great question. We've had a lot of debate about this. And you know, I advocate that, and this is what we've done in Cincinnati for years, is, you know, talk with the pediatrician as a child psychiatrist.

Talk with the pediatrician. If you are A. pediatrician, then you should be prescribing IT if you're prescribing the SGA. But if we're as psychiatrists or as nurse practitioners in mental health.

If we were to prescribe an SGA and somebody were to have A. dystonic reaction, IT would be standard of Care for /US to give them Cogentin or Benadryl. Like we would not withhold that. So if we're prescribing an SGA and they are gaining weight from the SGA as a.

side effect, or they are overweight or obese to begin with, and we're prescribing A. medication that has the potential to make IT worse, I think IT is our obligation to, after at least talking with the pediatrician, to prescribe it. But we really

really can't get caught in isn't the endocrinologist. There aren't enough

endocrinologists to go around, and I can tell you our endocrinologist here in

Cincinnati does not want to see every child who has gained weight on an SGA.

But I think pediatricians and family docs should absolutely be prescribing

metformin. And you know, the American Academy of Pediatric Guidelines, the new guidelines that came out are fairly aggressive about pharmacologic intervention.

For weight gain in obese and overweight kids, and it's just worse in Kids who have bipolar disorder. The comorbidity is because of lots of different reasons and we're just making IT worse. And so I do think.

It is 100% pediatricians and family docs that should be prescribing it.



Kamat, Deepak M 1:02:43

It is, I think, continuation of what about training more pediatrician or family docs to diagnose and manage bipolar disorder? Would this increase medication evidence and treatment?



DM Delbello, Melissa (delbelmp) 1:02:55

Sure, I think so. I think that would be great. It's it's hard because I know, you know, most pediatricians have to, you know, see A. lot of patients in A. in A. quick amount of time and so.

I think if you have the time, absolutely now.



Kamat, Deepak M 1:03:18

Doctor Hunran, you have raised your hand. Can you ask your question please?

You're you have to unmute.

We cannot hear you, Doctor Handan.



PH pat herndon 1:03:35

Thank you.



Kamat, Deepak M 1:03:37

OK.



PH pat herndon 1:03:38

OK, I've noticed that some of these kids get diagnosed as borderline personality disorder. They have, you know, explosive episodes. But if you look at it, the episode will occur over 5, maybe seven days.

These things will last and they've been treated with all kinds of things. And I was just wondering, if you look at the family situations, a lot of those kids have been prenatally exposed to alcohol.

And I mean, you know, you look at the South African studies, I mean, you just see hundreds of thousands of people who've been prenatally exposed to alcohol and have inhibitory behavior problems.



DM Delbello, Melissa (delbelmp) 1:04:24

Mhm.

Yeah, I I, yeah, there are A. lot of Kids and I kind of call them A. phenocopy of ADHD. They more the Kids who have been exposed to alcohol and other substances in utero.

They look more like ADHD Kids that don't respond to regular doses of medications. They oftentimes need higher doses of stimulants, whereas the Kids with bipolar don't don't do well with higher doses of stimulants. Generally, that kind of.

 **pat herndon** 1:04:57
I see.

 **Delbello, Melissa (delbelmp)** 1:05:01
destabilizes them and there's usually more developmental issues. Most of the time there's some developmental issues and those Kids tend to like need A. lot of OTPT speech intervention. And so they kind of seem more like A. phenocopy of severe ADHD.

 **pat herndon** 1:05:15
Mhm.

 **Delbello, Melissa (delbelmp)** 1:05:21
Rather than bipolar disorder, going back to your borderline disorder, we tend to not give Kids the diagnosis of borderline and try and stabilize their mood with as much structure and caregiving as we possibly can and.
Hope that they won't have A. long term personality disorder.

 **Kamat, Deepak M** 1:05:46
Thank you, Doctor. There's one question by Doctor Williams. When a strong family history, there is a nature or genetic component, but there is also nurture component which is role modelling of behaviour that is normalised in that family, but behaviourally are poor interpersonal behaviours.

 **pat herndon** 1:05:47
Like.



Kamat, Deepak M 1:06:04

What is done in therapy and family therapy to address this aspect?



Delbello, Melissa (delbelmp) 1:06:08

Yeah, I think that's why family focused therapy is highly effective. And again, IT reduces the conflict in family, IT increases the structure and IT kind of.

Kind of gets into not giving in to the Kids and to like set limits and it's OK and how the Kids deal with those emotions. So family focused therapy that that's why I think it's the most effective. I encourage you if you're interested.

Dr. Miklowitz has written several books on family focused intervention, and Mary Freistad is the other psychologist whose books I would recommend. She's done more Group therapy, psychoeducation.

With kids.



Kamat, Deepak M 1:07:06

Debra, thank you very much for presenting this morning's Randran. Truly appreciate it. We really enjoyed your presentation. I'm going to conclude this morning's presentation. Thank you all for attending this morning. Have a wonderful Friday. I will see you next Friday.



Delbello, Melissa (delbelmp) 1:07:14

Yeah.



Kamat, Deepak M 1:07:23

And thank you all.

● **Kamat, Deepak M** stopped transcription