Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/how-do-you-risk-stratify-bipolar-i-and-ii-depression/15293/

Released: 03/31/2023
Valid until: 03/31/2024
Time needed to complete: 1h 46m

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

How Do You Risk Stratify Bipolar I and II Depression?

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCME curriculum.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Goldberg:
Hello everyone. Welcome to our presentation today, entitled “How Do You Risk-Stratify Bipolar 1 and Bipolar 2 Depression?” I’m Dr. Joseph Goldberg. I’m a Clinical Professor of Psychiatry at the Icahn School of Medicine at Mount Sinai in New York. I’ll be walking you through some information today about phenomenology in bipolar 1 and bipolar 2 disorder, and the depressed phase in particular, and some of its implications, and then some of the treatment consequences, once an accurate diagnosis is made.

So, let’s start with just some clinical comparative points between bipolar 1 and bipolar 2 disorder. Studies have told us a number of characteristics that are useful to clinicians, in thinking about differences among bipolar 2 and bipolar 1 depression. Bipolar 2 disorder patients tend to have a longer duration of untreated illness, from the inception of symptoms. Maybe that’s because in bipolar 2 disorder, your highs may not get noticed as readily as if you have bipolar 1 disorder, where full manias may lead to hospitalization or functional impairment. Bipolar 2, the highs may get mistaken for just euthymic periods. There tend to be more frequent comorbid anxiety disorders or even just symptoms, so anxiety is a common co-occurring phenomenon in people with bipolar disorder, but especially so in bipolar 2. The frequency of depressive episodes and durations of depression tend to be longer in people with bipolar 2 than bipolar 1 disorder. The age at onset of the illness tends to be somewhat later than in bipolar 2 disorder – than in bipolar 1 rather. Fewer lifetime hospitalizations – now this is a little tricky because in – in bipolar 1 disorder, you can certainly get hospitalized for manias or depressions. In bipolar 2 disorder, if hospitalizations occur, they’re by virtue of the depressions not the manias, so it’s something of a misnomer to say oh, that’s just bipolar 2 disorder. The disability comes from the depression side more so than the high side. Antidepressant use tends to be more frequently prescribed in people with bipolar 2 than bipolar 1 disorder. Frequent episodes – that is, rapid cycling – 4 or more episodes per year seems somewhat more prevalent in bipolar 2 than bipolar 1 disorder, and after a depressive episode, residual depressive symptoms seem to be more persistent and more linked with functional impairment in people with bipolar 2 than bipolar 1 disorder.

Now arguably, one of the greatest forms of morbidity and mortality in – in all of psychiatry, really is – is suicide risk, and people with mood disorders are among the highest risk, and people with bipolar disorder are yet further among the highest risk. And in comparisons of bipolar 1 and bipolar 2 disorder, there’s actually a bit of a divided literature as to whether or not suicide attempts or completions are meaningfully different in one versus the other. Studies say about a third of people with bipolar 1 or bipolar 2 disorder will have at least 1 lifetime suicide attempt. Whether bipolar 1 or bipolar 2 is higher can vary on the study, but by and large, they – they’re both fairly substantial. It has been shown in some studies that bipolar 2 disorder patients tend to use more violent methods of suicide attempts compared to bipolar 1 patients. More violent methods may implicate greater lethality as a consequence. Cognitively – this is a sort of interesting area – people with bipolar 2 disorder, who attempt suicide, may show greater deficits in executive functioning compared to bipolar 1 suicide attempters. What – what’s the relevance of that? Well, executive functioning is planning and organizing and reasoning through, and while it is true in many instances suicide attempts are driven more by impulsivity than planning, as a general rule, when

one is sort of thinking through consequences, or – or issues around feeling hopeless, or – or the ability to problem-solve, the – th – that relies very heavily on executive functioning and if that is compromised more so in bipolar 2 patients, th – that may be an implication for suicide risk. Similar risk factors for suicide attempts in bipolar 1 and 2 patients include sex, presence or absence of rapid cycling, substance use, comorbidity, other psychiatric comorbidities, and an early age in onset. So in many ways, BP-1 and BP-2 are more similar than different, vis a vis suicide risk.

Alright, so where are bipolar 1 and bipolar 2 depression more different than similar? One realm here is the use of antidepressants. So while people with bipolar disorder in general have not been demonstrated to have an excellent response to antidepressants, say compared to unipolar depressed patients, and may have a higher risk for induction of mania or activation symptoms of antidepressants, that risk may stratify. Bipolar 1 disorder patients seem to be about 1.8 times more likely to have a destabilization of mood during antidepressant use, as compared to patients with bipolar 2 disorder, which is to say that there may be a somewhat greater margin of safety, if not efficacy, in the use of antidepressants in bipolar 2 depression.

But, well, what about efficacy? So, interestingly enough, there have been a handful of small, preliminary, randomized controlled trials looking at antidepressant response rates, and switch rates, with the use of an SSRI such as sertraline, or lithium, or the combination of two. And this is some interesting data from the Stanley Foundation Bipolar Network, which i – identified really no difference in the risk of switching from depression to hypomania – these are bipolar 2 patients, so by definition nobody gets manic, they can get hypomanic – if patients receive lithium, or sertraline, or the combination. And even more interestingly, in terms of treatment response rate over time, here again there was no clear difference in this particular bipolar 2 sample in time-to-response, in bipolar 2 patients receiving lithium, sertraline, or the combination. There was more dropout with the combination, but somewhat contrary to what one might expect, sertraline and lithium had a very similar pattern of efficacy. That's monotherapy in bipolar 2, not bipolar 1 patients.

Here's another piece of evidence looking at bipolar 2 depression and its unique response rates that we see with antidepressants. So, about 12-13 years ago, this was a randomized comparison of lithium alone or fluoxetine alone or placebo, in relapse rates for bipolar 2 depression. Interestingly, this study found that fluoxetine was superior to placebo, but it was also superior to lithium. Lithium was actually not an efficacious preventative strategy for recurrences in bipolar 2 depression. Now, there's a catch to this study. This study was predicated on the initial response in bipolar 2 depressed patients to fluoxetine alone. A little less than half of patients had a robust initial response, and of those enriched patients si – continuing, remaining on fluoxetine monotherapy, had a lower risk for relapses compared to patients who were randomized to take lithium or placebo. So, this study says that a lot depends on initial responsivity, that bipolar 2 depression may be different than bipolar 1 depression in terms of antidepressant potential efficacy, that even monotherapy – which is frowned upon in bipolar 1 depression – may not be as much of a risk for mood destabilization in bipolar 2, and lastly this study does not replication. It's just one trial.

So if we move on to some of the FDA-approved treatment options for bipolar 1 and bipolar 2 depression, this is a recent study looking at the drug lumateperone, here as monotherapy. It's also been studied as augmentation of lithium or valproate. And a reduction of depression symptoms was statistically significantly greater with lumateperone 42 mg a day, as compared to placebo, both in bipolar 1 and bipolar 2 depression, but what's really interesting here is the magnitude of difference – the clinical meaningfulness of the effect – was about twice as great in bipolar 2 than in bipolar 1 disorder. The drug was efficacious in either subtype, but had an even bigger effect in bipolar 2 than bipolar 1 patients. This effect size is a – a decimal effect size. About 0.5 would be considered a medium effect size. An effect size of 0.8 is a large effect size. So, both meaningful, but an even bigger effect in bipolar 2.

By contrast, the only other FDA-approved treatment for bipolar 2 depression is quetiapine, where both bipolar 1 and bipolar 2 depression was studied, and interestingly enough, here we – we saw the opposite. The magnitude of efficacy – the degree of improvement compared to placebo was more robust in bipolar 1 than bipolar 2 depression. And in fact, that difference - bipolar 1 and bipolar 2 subtypes wa – was one of the biggest predictors of differentiation in outcome between quetiapine and placebo. So, dose not so much of a difference, duration of treatment not so much a difference, sample size not so much of a difference. Re – really, the – the biggest effect that was seen was bipolar 1 depressed patients – robust effect in bipolar 1 disorder.

So what can we conclude from these data? Well, morbidity, suicide risk and functional impairment in bipolar 2 disorder seems largely comparable to bipolar 1 disorder, largely based on residual depressive symptoms. There are few randomized pharmacology trials in bipolar 2 disorder. We've described the two FDA-approved treatments for bipolar 2 depression – lumateperone and quetiapine – and then a smattering of some smaller proof of concept studies, such as the data we looked with lithium and fluoxetine, or lithium with sertraline as monotherapies or as combinations. So, there may be a – a somewhat lesser risk for antidepressant-associated polarity switch in bipolar 2 than bipolar 1 disorder, and that may imply some greater measure of safety, and perhaps efficacy, based on these small proof of concept studies that we've talked about – preliminary data. More robust placebo-controlled findings, with lumateperone and with quetiapine are seen in bipolar 2 depression, and – and both of these agents would, at the moment, represent state-of-the-art, evidence-based treatments for bipolar 2 depression. So thank you for joining us today.

Announcer:
You have been listening to CME on ReachMD. This activity is jointly provided by Global Learning Collaborative (GLC) and TotalCME, Inc. and is part of our MinuteCME curriculum.

To receive your free CME credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.