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

Thinking Out of the Box: Monotherapies versus Adjunctive Therapies in Bipolar I and II Depression

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Dr. Goldberg:
Hello everyone. Welcome to our presentation today, entitled “Thinking Out of the Box: Monotherapies versus Adjunctive Therapies in 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’m going to be walking us through some information today about issues in combination therapies in bipolar depression, as well as evidence-based monotherapy approaches.

A lot of things have been tried in the treatment of bipolar disorder, and particularly depressed phase. Many have been shown not to work. Today we’re going to talk about what has been shown to work. Starting with polypharmacy or complex combination therapy, this is a – a sort of a double edged sword. On the one hand, we can often think of the notion of putting together medications that have complementary receptors, or mechanisms of action, or pharmacodynamic synergies, where we can actually get potentially greater effects from adding more things on. We do this in infectious disease. We do it in oncology. We do it in cardiovascular medicine. It ought to be no different in psychiatry, a – although sometimes we hit upon combinations that meet this description I just gave us, of – of synergy and capitalizing on complementarity. Other times, combination therapies are not always as – well, scientifically informed or evidence based. So, this is a study that one of our trainees had done just a couple of years ago, looking at prevalence rates of extensive polypharmacy in the literature, in bipolar disorder. Dr. Kim and colleagues found about a third of people with bipolar disorder end up receiving 3 or more psychotropic medicines, and some proportion take even – even more than that. In one of the earlier studies that went into this one, the NIMH STEP-BD program, we actually found as many as – I think the – the high mark was 26 medicines – psychotropic medicines. And what was really interesting with extensive polypharmacy is what drives it. So you might just assume, well complexity probably drives it. As shown on – on this slide, indeed, history of psychosis, more extensive comorbidities, lower treatment adherence – but 1 thing that really stood out was greater burden of depressive illness. That was a finding we had in STEP-BD, and it emerged in some of these other studies that our group reviewed as well. So if depression, which is the most common mood state we see in bipolar disorder, was a piece of cake to treat, you might not need 17 medicines to try to treat it. Or – or rather, depression might not necessarily evoke such a desperate response among prescribers who will throw anything and everything toward a depression, sometimes using medicines that have been efficacious and shown to work, but other times, not – not as much.

So the most common class of medicines that are still used today in bipolar disorder are antidepressants. The name does imply they should treat depression, an – and the biggest risk or concern with antidepressants is, not one has yet been shown to work better than a mood-stabilizing agent alone. This is arguably the biggest study in that realm – the NIMH STEP-BD study, where we rounded up about 170-some-odd bipolar 1 and 2 depressed phase patients. Everyone got an antimanic mood stabilizer, such as lithium or valproate or an atypical antipsychotic, either alone or with a monoaminergic antidepressant. We studied paroxetine or bupropion. And to our surprise,

there were really no differences in the ones for whom an antidepressant was added to a mood stabilizer versus a mood stabilizer alone. In various measures of remission, recovery, durable recovery, transient recovery, or even affective switch that is going from a depression into a high, was about 10% with or without an antidepressant. So the main finding from STEP-BD, somewhat surprisingly, was that for most – not all – but for most depressed-phase bipolar patients, adding on an antidepressant to a mood stabilizer was a waste of time. It neither helped nor hurt.

Here's another more recent study, with a similar kind of design, adding an SSRI – here, citalopram – onto treatment as usual plus placebo. So that treatment as usual here was usually lithium or a similar agent. And, similar to the STEP-BD study, what was found was the augmentation of usual care – a mood stabilizer, with citalopram – brought you no greater advantage. In the beginning phases, there was some numerical advantage over the first few months with citalopram, which then by the end of the study sort of lost its significance. So – so a finding here – a challenge for us as clinicians, is if you – if you are enamored of the notion of combination therapy, what should you add to a mood stabilizer that will enhance efficacy, because and SSRI hasn't been shown to do that.

Lurasidone has been shown to do that. Here's one of the very few combination therapy studies in bipolar depression where there is greater oomph with a combination, so patients who are given lithium or valproate as adjunctive therapy, that is combina – combined with lurasidone or placebo, we actually see a greater degree of depression improvement with adjunctive lurasidone than with lithium or valproate alone. Very similar to what was seen as monotherapy with lithium or valproate, and the number needed to treat – that is, how many people do you have to expose to the treatment before you'll see an additional beneficial case – was nicely low, 7 in the case of augmentation therapy, 5 in the case of monotherapy. So this would count as an augmentation strategy that's evidence-based in acute bipolar depression.

How about long-term maintenance? There is 1 randomized published trial of lurasidone for relapse prevention in bipolar 1 disorder, which actually did not show an overall benefit in preventing a future mood episode, with a slight twist or caveat. If patients entered the study initially in the depressed phase of illness, and responded acutely to lurasidone – as one might hypothesize based on its indication – then, there was a greater degree of reduction of risk for a new episode over the course of – of about up to 2 years. So this is an important finding, because it implies that what gets you ill may keep you ill, and we're always asking, well what should I use for maintenance treatment. The axiom "what gets you ill keeps you ill," is – is often something clinicians hold in mind, but here we have some post hoc data saying, well, if there's initial acute response for depression, then there may be value in continuation therapy with lurasidone at a mean dose of about 50 milligrams a day.

Lumateperone – one of the newer atypical antipsychotics that's gotten its indication for acute bipolar depression – also has been studied as monotherapy, or adjunctive therapy, and here we see the magnet of improvement with adjunctive lumateperone is statistically significantly greater – seen on the left – as compared to just a mood stabilizer alone. So, we don't have placebo plus placebo. We don't know what no treatment would look like. We can say that mood stabilizer alone – lithium or valproate – does have some antidepressant properties, but augmentation with lumateperone here, and with lurasidone in the prior study, has an even greater effect.

Here's another example of augmentation therapy in bipolar depression that's evidence based. The combination of quetiapine plus lamotrigine seems superior to the combination of quetiapine plus placebo, so adjunctive lamotrigine seemed to give a greater, more robust antidepressant effect, both in bipolar 1 and bipolar 2 depressed patients, over the course of about a 1-year study.

Second study of lamotrigine as an augmentation is this study that's been colloquially called the LAM-LIT study. This is adding lamotrigine to lithium or adding placebo to lithium, for acute bipolar 1 or bipolar 2 depression. And so again, lithium has some effect. Not a dramatic effect, but it does beat a placebo, and here we see adjunctive lamotrigine has a greater magnet of improvement of depression symptoms over the course of 8 weeks, as compared to lithium alone. Sort of suggests that lamotrigine may – while it is an off-label use for acute bipolar depression as monotherapy or adjunctive therapy – does have this evidence base of augmentation, with quetiapine or with lithium to amplify the effect for depression.

Quetiapine, as you are likely aware, has its FDA indication for maintenance treatment in bipolar disorder – one of the few drugs that has both acute and maintenance therapy indications. The indication for quetiapine as maintenance is as an adjunct, to a mood stabilizer – lithium in particular, and so what we see here is, interestingly, what is quetiapine preventing? So we have this table broken down into any mood episode, or a manic episode, or a depressive episode, and we see quetiapine has a robust effect as compared to placebo in all of these domains. In fact quetiapine is even more efficacious than lithium, as an augmentation, in preventing any mood episode, and in particular, the depressed phase of illness. So look at the right-hand column. Quetiapine is better than placebo. Lithium's also better than placebo, but quetiapine was even more robust than lithium. If one is interested in preventing a depressive episode, this is an evidence-based option.
We've talked about many options that are not so evidence-based.

Now let's look at another study in maintenance treatment, called the BALANCE trial. This is a study of bipolar patients who were given

either lithium or divalproex, or the combination, for maintenance treatment in bipolar disorder. The main finding of the study was that the time until the emergence of any new mood episode was significantly longer with the combination of lithium plus divalproex, than with divalproex alone. The combination was not better than lithium alone, so lithium either as part of the mix or even by itself, may have particular value that divalproex monotherapy does not. If you look toward the bottom, lithium alone, divalproex alone, or the combination and the likelihood of seeing a new mood episode of the depressed phase, is actually highest with divalproex monotherapy and lower with lithium or with the combination. So once again, lithium may have some edge over divalproex, at least as monotherapy and the combination may be a particular more robust strategy to prevent depressed phases, as well as overall episodes in bipolar disorder.

So, what can we take away from these data? To summarize, adjunctive antidepressants have not shown greater efficacy than mood stabilizers alone, in acute bipolar depression, particularly bipolar 1 depression. In bipolar depression, lurasidone or lumateperone plus lithium or divalproex shows an advantage over the mood stabilizer alone – lithium or valproate. And in the case of lamotrigine, augmentation to quetiapine or augmentation to lithium outperforms monotherapies of quetiapine or of lithium. That is the evidence base for augmentation treatment. Lastly, adjunctive quetiapine and adjunctive lurasidone, when the index phase of illness was depressed, may be an effective prophylactic strategy for bipolar depression, but again, much depends on acute responsivity. The past is not a guarantee of the future, bit it – it's not a bad guide as we're following patients over time. So thank you for joining us today.

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