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Maintenance Treatment of Bipolar Disorder: An Expert Interview With Trisha Suppes, MD, PhD

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Editor's Note:

Much research exists to provide guidance to clinicians who treat acute mania or depression. The pharmacologic options for treating acute episodes in patients with bipolar disorder continue to expand, but options for maintenance treatment are less well developed. Yet keeping patients well may be the most important long-term treatment goal. To learn the state of the art in maintenance therapy, Medscape's Randall F. White, MD, FRCPC, spoke with Trisha Suppes, MD, PhD, Professor of Psychiatry and Director of the Bipolar Disorders Research Program at University of Texas Southwestern Medical School in Dallas, Texas.

Medscape: You are the director of the Texas Medication Algorithm Project for bipolar disorder. Would you describe the process of developing the algorithms?

Trisha Suppes, MD, PhD: The algorithms that were developed during late spring of 2004 and published in 2005^[1] came from a panel of national physician experts along with pharmacists and employees of the state mental health system. Two consumers who were very helpful in informing the process also participated, rounding out a panel of about 15 people. All the funding was from within the state; no pharmaceutical funding was involved. During the day-and-a-half meeting, we looked at our previous version and all the new evidence available for treatment of bipolar I disorder, including mania, hypomania, and depression, and we also addressed maintenance therapy. We did not develop guidelines for bipolar II disorder because of the scarcity of data.

Even though the algorithms contain specific recommendations, particularly for acute treatment, they are not meant to be rigid or to limit what clinicians do. They are meant as a guide to be adapted to the individual situation.

Medscape: What is the goal of maintenance treatment for bipolar disorder?

Dr. Suppes: The goal is remission and return of full function, with all symptoms removed, and the prevention of new episodes.

Medscape: The consensus panel devised 2 maintenance algorithms, one for patients whose most recent episode was manic and one for patients whose most recent episode was depressed. Why is this distinction important?

Dr. Suppes: With bipolar disorder, in general, data show that the last episode may predict the next episode.^[2] So for example, if your last episode was manic, a slightly higher probability exists that you'll be manic in your next episode; if you've been depressed most recently, a higher chance exists of being depressed next. The group felt it would be helpful to provide guidelines based on last episode polarity.

Medscape: Can you briefly say what the levels of treatment are and why they are important?

Dr. Suppes: In the acute treatment algorithms, we created stage 1, stage 2, stage 3, and so on. The initial stages have more evidence than the later stages. For maintenance therapy, we provided levels of treatment because we felt the data were not strong enough to do a more specified kind of presentation.

Medscape: So interventions are ranked according to the quality of evidence.

Dr. Suppes: Right. I think that one of the main points is that too few studies of maintenance treatment for bipolar I disorder have been done. The industry studies are very important, they contribute to our knowledge base, but those studies are designed to meet US Food and Drug Administration (FDA) criteria for approval. And the majority of maintenance studies until recently have included monotherapy vs placebo, whereas the majority of patients are not on a single medication.^[3]

Medscape: That's an important caveat. Now, for patients who were recently manic or hypomanic, what does the evidence indicate is the most effective maintenance therapy?

Dr. Suppes: The studies, again, have been done with monotherapy. The drugs approved right now for maintenance phase are lithium, olanzapine, lamotrigine, and aripiprazole.^[1] And the approvals are all a little different from one another. Probably the largest body of evidence would be for lithium and olanzapine. Lamotrigine, of course, has strong data for preventing new depression.^[4] The point, though, isn't these individual medications. The point really is that we need more studies looking at these medications and how best to use them, particularly in combination.

Medscape: Many patients receive acute treatment with a second-generation antipsychotic in combination with a mood stabilizer. Should clinicians eventually attempt to discontinue the antipsychotic, or do specific situations exist in which it should be continued indefinitely in combination with the mood stabilizer?

Dr. Suppes: The Texas guidelines recommend that effective medication should be continued into the continuation phase.^[1] The acute phase is 0 to 2 months, and the continuation phase is 2 to 6 months after acute episode onset. The continuation phase is a vulnerable period for people who've had mania. The physician may need to decrease doses a bit during this phase because of side effects -- patients tolerate higher doses of antimanic medication when they're manic. It would seldom be recommended to change medication during the continuation period unless the patient developed more symptoms, in which case an initial approach might be increasing medication dose rather than adding another medication.

The maintenance phase would begin at about 6 months, and if a patient is doing very well, it may be reasonable to taper one of the medications depending on the available evidence for either one. Of course, another factor is the patient's history. For example, a patient may do well for extended periods on lithium alone but require lithium plus an anticonvulsant or an atypical antipsychotic during an acute episode. If the patient is subsequently stable for 6 months, it would be reasonable to taper the second medication slowly and monitor closely.

Medscape: Mixed episodes are included in the mania maintenance algorithm,^[1] but are there any data suggesting a more specific approach to maintenance for patients with mixed episodes?

Dr. Suppes: We know that patients with mixed episodes have a tendency for earlier recurrence or relapse.^[5] The main thing I would say about mixed episodes is that I hope in the future we'll have more research to be able to make more specific recommendations.

Medscape: And can you venture to say anything about maintenance therapy for rapid-cycling patients?

Dr. Suppes: We don't yet have specific treatment recommendations, but on divalproex or second-generation antipsychotics, rapid-cycling patients as a group don't do as well as nonrapid-cycling patients.^[6,7] Calabrese published a double-blind, 20-month maintenance study that found that lithium and divalproex as monotherapy performed equally poorly in rapid-cycling patients.^[8]

Medscape: Moving on, what is the evidence in favor of mood stabilizers for maintenance therapy for patients with a recent episode of depression?

Dr. Suppes: The strongest evidence I'm aware of is for lamotrigine. There was a very nice set of studies carried out by GlaxoSmithKline. In a pooled analysis of 2 placebo-controlled trials in bipolar I patients, the patients were randomized

to receive either lamotrigine, lithium, or placebo maintenance for 18 months.^[9] The study showed clear separation of lithium and lamotrigine from placebo for prevention of new episodes; lithium was particularly good for preventing mania, and lamotrigine was particularly good for preventing depression.

I think that lamotrigine has the best evidence for prevention of new depressive episodes. But the studies are with monotherapy, and we need more studies looking at drugs in combination.

Medscape: The US FDA has approved second-generation antipsychotics (SGAs) for the treatment of acute bipolar depression now. What do we know, if anything, about maintenance therapy with these agents for bipolar depression?

Dr. Suppes: We don't know as much. The maintenance studies on olanzapine have mostly, if my memory serves, been for patients who recovered from an acute manic episode,^[10] but more maintenance studies should be complete and presented for the first time at the spring meetings. So I think we'll soon have more information specific to prevention of depression.

The SGAs as a class are effective antimanic agents.^[11] But at this point, my own prediction is that we will see differences among them in their efficacy both for acute depression and for prophylaxis of depression.

Medscape: In the algorithm for acute bipolar depression, antidepressants are included as an option if other approaches fail. How long should a patient continue an antidepressant medication, and does the type of antidepressant matter?

Dr. Suppes: The Stanley Group has just finished some double-blind studies that showed differences among the antidepressants in likelihood of causing a mood switch.^[12] All of the patients were also on a mood stabilizer. Sertraline, a selective serotonin reuptake inhibitor (SSRI), and bupropion appeared to cause fewer switches relative to venlafaxine, a serotonin and norepinephrine reuptake inhibitor (SNRI).

Older data suggest that tricyclic antidepressants may be more likely to cause mood switching than SSRIs.^[13] Because an SNRI is, in some sense, a combination of a tricyclic and an SSRI, the study results may not be too surprising.

Whether people should remain on an antidepressant long term is an area of very active interest. Dr. Nassir Ghaemi is studying this question; his past data indicate that in some patients, antidepressants may do little good and may do harm.^[14]

Research clearly shows that antidepressants can cause some patients to develop a rapid-cycling course.^[15] Again, the bottom line is that we do not have enough data on the issue; we need prospective, controlled studies.

Medscape: The Texas Medication Algorithm addresses only bipolar I disorder. Is there anything that you could tell the readers about maintenance for bipolar II disorder?

Dr. Suppes: There are very few data on bipolar II. The quetiapine data set on treatment of acute depression in bipolar II patients is the largest controlled data set available for this disorder.^[16] The reason we did not include bipolar II in the Texas guidelines was a consensus that inadequate data in acute and maintenance treatment exist to develop an algorithm. Older data on lithium support its use in bipolar II patients, but good controlled trials are lacking.^[17]

The debate on bipolar II is extensive. For example, Dr. Jay Amsterdam asserts that some bipolar II patients can benefit from antidepressant monotherapy,^[18] but others believe that's the worse thing you could do. This will be resolved once we have clinical trial data in which medications are studied head-to-head.

In fact, I am involved in a National Institutes of Mental Health-sponsored clinical trial with Dr. Lori Altshuler in Los Angeles and Dr. Sue McElroy in Cincinnati for acute depression in bipolar II disorder. We're going to be looking at an

antidepressant vs lithium.

Medscape: Do psychosocial treatments have a role to play in maintenance therapy for bipolar disorder? And, if so, what does the scientific evidence indicate are the most cost-effective interventions?

Dr. Suppes: I think psychosocial interventions definitely have a role. In the short-term, 1-year time period, cognitive behavioral therapy can be helpful.^[19] Other interventions that show efficacy are interpersonal and social rhythm therapy, which Dr. Ellen Frank in Pittsburgh has pioneered^[20]; the psychoeducational approach, a structured program that Dr. Colom in Spain has presented^[21]; and the family-focused treatment studied by Dr. Miklowitz in Colorado.^[22] They're not a substitute for medication, but as adjuncts, psychosocial treatments can decrease the onset of new episodes, decrease hospitalization, and improve the management of the illness. I'm not sure which would be viewed as most cost-effective, and I'm not aware of studies in which they've been directly compared.

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