The Evolving Paradigm for Bipolar Disorder

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Bipolar disorder is a recurrent illness, and treatment of bipolar disorder is challenging. Although no cure exists, effective acute and maintenance management of the illness can reduce morbidity and mortality associated with the illness. The following presentations by experts in the field address the selection of appropriate treatment for the acute and long-term management of bipolar disorder based on trial data for atypical antipsychotics and mood stabilizers.

Differential Pharmacology of Atypical Antipsychotics: Impact on Patient Functionality, Adherence, and Overall Health

Eduard Vieta, M.D., Ph.D., began by stating that conventional and atypical antipsychotics exert their actions over several receptors in the brain. The most important receptors for antipsychotic, and probably also antidepressant and antimanic, action are those related to dopamine.

Dopamine Pathways

Four dopamine pathways that are relevant to antipsychotic pharmacology are the mesolimbic, mesocortical, nigrostriatal, and tuberoinfundibular pathways.[1,2] The therapeutic mechanism of action for conventional antipsychotics is found in the mesolimbic pathway, where their actions as dopamine antagonists reduce the production of dopamine, which decreases positive symptoms and manic symptoms. Unfortunately, their mechanisms of action are not isolated in the mesolimbic pathway, and their actions on the other 3 dopamine pathways create the major side effects commonly associated with conventional antipsychotics. When conventional antipsychotics block dopamine receptors in the mesocortical pathway, it can increase negative symptoms, cognitive dysfunction, and depressive symptoms. The reduction of dopamine release by conventional antipsychotics over the postsynaptic receptors in the nigrostriatal pathway produces motor activity side effects such as extrapyramidal symptoms (EPS) and tardive dyskinesia. Finally, reducing dopamine production in the tuberoinfundibular pathway induces an increase of prolactin and a number of side effects related to hyperprolactinemia.

Conversely, atypical antipsychotics are antagonists of both dopamine and serotonin.[3] Serotonin inhibits the production of dopamine and is therefore important in allowing the atypical antipsychotics more variability in controlling dopamine increase among the various pathways. Atypical antipsychotics bind better to pathways responsible for psychosis than to pathways that control motor functioning.[3] While the exact mechanism of action is unknown, atypicals are thought to simultaneously block serotonin and dopamine receptors or to block dopamine receptors for only a short time. Serotonin in the mesocortical pathway allows some dopamine release, which may decrease negative and depressive symptoms.[1] Atypical antipsychotics do not have as much action as the conventional antipsychotics in the nigrostriatal pathway, and therefore EPS and tardive dyskinesia are not as common and severe as with conventional antipsychotics. In the mesolimbic pathway, atypical antipsychotics have the same palliative effects as do conventional antipsychotics for improving psychotic symptoms and manic symptoms. Finally, in

the tuberoinfundibular pathway, the simultaneous inhibition of serotonin prevents the production of prolactin, which mitigates hyperprolactinemia caused by the blocking of dopamine, although there may be relevant differences between atypicals with regards to the tuberoinfundibular dopamine pathway liability. For example, risperidone and amisulpride, which heavily block dopamine in the tuberoinfundibular pathway, carry the risk of problems due to hyperprolactinemia. Other problems associated with the antagonistic properties of some atypical antipsychotics include weight gain, sedation, seizures, and agranulocytosis.

Antipsychotic Action on Dopamine and Serotonin Pathways

An alternative to conventional antipsychotics and some of the older atypical antipsychotics is a newer antipsychotic, such as aripiprazole, that is a dopamine partial agonist.[1,4] Simply speaking, a partial agonist allows partial receptor activity. A full dopamine agonist allows full receptor activity. An antagonist such as haloperidol allows no receptor activity. Dopamine partial agonists act at the presynaptic and postsynaptic receptor sites, acting on the dopamine system as both agonists and antagonists. In fact, agents that are partial agonists are often called *dopamine system stabilizers*[3] because ideally they activate dopamine production in areas that have low output but inhibit dopamine production in areas with high output. Partial agonists act as functional antagonists in the mesolimbic pathway, which reduces positive symptoms, and at the same time act as functional agonists in the mesocortical pathways, which may reduce negative symptoms and cognitive impairment.[4] Aripiprazole is the first approved atypical antipsychotic agent having partial agonist activities at the dopamine-2 (D_2) receptor.[5,6] It demonstrates low intrinsic activity and partial agonist actions at the D_2 receptors and 5-hydroxytryptamine–1A (5-HT_{1A}) receptors, and it also acts as an antagonist at the 5-HT_{2A} receptors.[4,5,7]

The relationship between D_2 receptor occupancy and the therapeutic effect of an antipsychotic is statistically significant ($p = .02$).[8] Because haloperidol is a full antagonist of the D_2 receptor and not selective in its blockade activity, finding the right dose is difficult without inducing EPS and increasing prolactin levels.[9–12] The therapeutic window for an antagonist such as haloperidol occurs at 60% to 80% D_2 receptor occupancy, with incidences of EPS increasing above the 80% threshold.[13] The therapeutic dose of aripiprazole occupies up to 95% of the dopamine receptors with an incidence of side effects that is no higher than that of placebo.[13] Therefore, the therapeutic window is much wider for aripiprazole.

Nondopamine Pathways and Associated Side Effects

Dr. Vieta acknowledged that antipsychotic action on other receptors is also responsible for a variety of clinically relevant issues.[14,15] For example, antipsychotics that are potent antagonists at α_1-adrenergic receptors, such as risperidone, are associated with hypotension.[15,16]

Blockade of muscarinic and cholinergic receptors is related to dry mouth, constipation, tachycardia, blurred vision, urinary retention, and decreased cognition.[1] The affinity for histamine-1 (H_1) receptors varies across the different compounds, and there is a clear correlation between the receptor affinity for H_1 of an antipsychotic and weight gain.[17] Although weight gain is associated with antipsychotic action at several of the neurotransmitter receptors, it is most closely associated with H_1 receptors. For example, clozapine and olanzapine both have a high H_1 liability, and these agents cause more weight gain than the other atypical antipsychotics.[15] The Clinical Antipsychotic Trials of Intervention Effectiveness study in schizophrenia[18] found that olanzapine, compared with quetiapine, risperidone, perphenazine, and ziprasidone, had the highest rate of discontinuation associated with weight gain or metabolic effects. The American Diabetes Association published information that indicated which drugs carry the greater risk for metabolic effects.[19] Consistent with their H_1 receptor activity profiles, clozapine and olanzapine have the highest risk of weight gain, risperidone and quetiapine an intermediate risk, and ziprasidone and aripiprazole the least risk.

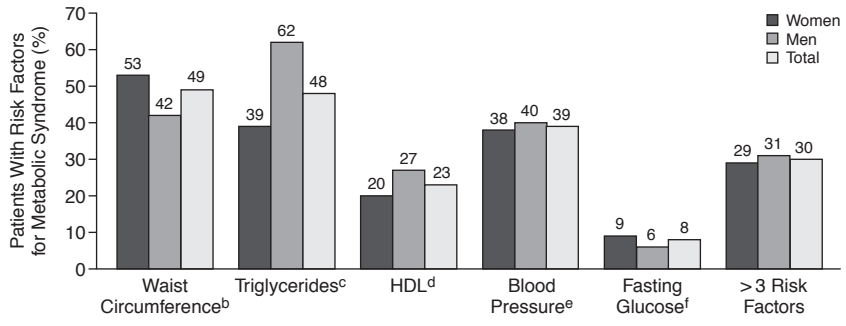
Patients with bipolar disorder are at particular risk for metabolic syndrome. One study found that 30% of patients with bipolar disorder met the criteria for metabolic syndrome.[20] Waist circumference and triglyceride, cholesterol, blood pressure, and fasting glucose levels were increased in both women and men with bipolar disorder compared with the general population (Figure 1).[20] Patients with bipolar disorder who met the criteria for obesity and metabolic syndrome were significantly ($p = .004$ and $p = .05$, respectively) more likely to report a lifetime history of suicide attempts; therefore, these patients should be closely monitored.

Histamine H_1 receptor blockade is also associated with sedation,[15] which is another reason that patients discontinue or switch antipsychotic treatment.[18] Sedation is not essential for the therapeutic effects of antipsychotics,[21] but especially in manic patients, the use of benzodiazepines for short-term, controlled sedation may be necessary to calm the agitated patient.[22] However, continuing a sedative drug long term can cause interference in the performance and intellectual functioning of the patient. Therefore, short-term benzodiazepine use for calming an agitated or insomniac patient would be a reasonable option in combination with nonsedating medications. Dr. Vieta concluded his discussion of nondopamine pathways and associated side effects by stating that all of these side effects may impact treatment adherence in bipolar patients.

Enhancing Treatment Adherence

Dr. Vieta stated that the main reason for poor treatment adherence is illness denial. Patients who deny

Figure 1. Patients With Bipolar Disorder at Risk for Metabolic Syndrome[a]



[a]Data from Fagiolini et al.[20]
[b]Defining level = > 102 cm (> 40 in) for men or > 88 cm (> 35 in) for women.
[c]Defining level = > 150 mg/dL or being on cholesterol lowering medication.
[d]Defining level = < 40 mg/dL (men) or < 50 mg/dL (women).
[e]Defining level = systolic blood pressure ≥ 130 mm Hg and diastolic blood pressure ≥ 85 mm Hg or being on blood pressure medication.
[f]Defining level = ≥ 110 mg/dL or being on a glucose-lowering drug.
Abbreviation: HDL = high density lipoprotein.

having an illness or do not believe that they suffer from a mental condition will most likely not take their medication properly.

One study[23] showed that only 60.5% of patients with bipolar disorder were fully compliant with their treatment program. In a careful assessment with each patient separately, then with a partner or a relative, and then checking blood medication levels, Dr. Vieta and his colleagues found that up to 13% of the patients were not taking medication and around 27% were taking some of the medication but not all.

What can the clinician do to enhance adherence in bipolar disorder? Dr. Vieta suggested that combating problems with treatment adherence involves providing information about bipolar disorder to the patient—not just a book, Web site, or leaflet, but true interaction. Psychoeducation encourages involvement of the family and caregivers, which fosters additional support for the patient. Psychoeducational programs have proven to be effective at enhancing adherence and improving outcome.[24,25] Enhancing adherence also involves treating the side effects of medication, making the medication more user-friendly, and developing medication regimens that are individualized to the patient.

For example, Dr. Vieta explained that a patient could be switched to a different medication if the current medication were causing intolerable side effects. Physicians can also decide to switch a patient's antipsychotic medication when symptoms persist.[26] Adverse effects that lead to treatment intolerance, and, ultimately, switching antipsychotic medications, include acute effects such as akathisia and orthostatic hypotension and long-term events such as weight gain, sedation, and diabetes.[27]

Treatment withdrawal is a potential problem that may arise when switching medications. Atypical antipsychotics with minimal potential for sedation may create short-term insomnia when a patient is switched to them from a more sedating antipsychotic.[26,28] Antipsychotics with a high affinity for H_1, such as clozapine and olanzapine, are more likely to be sedating.[29] High-dose, low-potency antipsychotics, such as quetiapine and clozapine, may also be sedating. These short-term insomnia effects can be overcome by slowly tapering off the previous sedating antipsychotic to the new nonsedating medication.[26,28]

Other potential problems and withdrawal effects when switching antipsychotics are akathisia and anxiety, which can occur within the first few days after switching antipsychotics, especially with the discontinuation of a drug with sedative effects.[30] Rebound akathisia may be indistinguishable from psychosis or anxiety.

Nausea, vomiting, diarrhea, and malaise may also occur within a few days after switching, and some of these may be related to anticholinergic withdrawal, which is a result of discontinuing a potent antimuscarinic antipsychotic such as clozapine or olanzapine.[26] This anticholinergic rebound is an increased sensitivity in the mesolimbic dopamine system and an increased response to endogenous acetylcholine if the agent is fully withdrawn or replaced with one that has low affinity for the receptors.[31–34] Atypical antipsychotics have different affinities for muscarinic receptors, and slow cross-titration may minimize anticholinergic rebound when switching from an atypical antipsychotic with a high affinity for muscarinic receptors like olanzapine to an agent with a low affinity such as ziprasidone.[33] According to Dr. Vieta, however, it would be better to introduce the new drug before stopping the previous treatment if the cause for discontinuation is not urgent or life-threatening. During cross-titration, often the 2 drugs are below the therapeutic levels at some point. Therefore, a patient who is between 2 therapies can experience side effects from both drugs but no therapeutic effects. Providing information and psychoeducation in addition to adding the second drug is important. Dr. Vieta advised increasing the second drug slowly until a therapeutic dose is achieved, and then starting to taper off the previous drug.[30,33]

Dr. Vieta went on to explain that prolonged therapy with D_2 blockers may cause an increase in the number of D_2 receptors[1] and supersensitivity in the mesolimbic region.[35] Increased intrinsic activity in the presence of a sensitive D_2 system may cause rebound symptoms in some patients.[32,33] Again, slow cross-titration may minimize dopaminergic rebound when

switching from a high-affinity dopamine antagonist like risperidone to a lower-affinity dopamine antagonist or to a high-affinity dopamine partial agonist like aripiprazole. Potential problems of withdrawal can be addressed with adjunctive pharmacotherapy to manage short-term adverse effects during medication switching. β-Blockers such as propranolol can be used for akathisia,[36] while benzodiazepines such as lorazepam can be used for situational anxiety and agitation,[30] as well as for insomnia. Insomnia can also be treated with an anticholinergic agent such as diphenhydramine.[28] However, the best strategy, as described above, is adding the new drug to the previous one before tapering.

Dr. Vieta reiterated that improving treatment adherence in response to adverse events associated with medication and switching medications can best be done through psychoeducation.[30,37] Dr. Vieta suggested that psychoeducation may provide long-term, positive outcomes.

Conclusion

Dr. Vieta concluded that, although often grouped as a class, atypical antipsychotics have distinct pharmacologic profiles. Differences between agents have clinically meaningful implications. Sedation for some patients is a problem that can be resolved by using benzodiazepines, which can be tapered off after sedation is no longer necessary (such as in acute mania treatment). Weight gain and metabolic abnormalities can cause potential problems with nonadherence and subsequent treatment withdrawal. Addressing the potential for cholinergic and dopaminergic rebound when switching agents is important. Understanding the pharmacologic profiles of these drugs may help to address those side effects before they become a problem. Anticipating and managing adverse effects, switching to new medications carefully, and enhancing adherence through psychoeducation may improve long-term patient outcomes.

Management of Acute Mania: Clinical Strategies for Improving Long-Term Outcomes

Gary S. Sachs, M.D., reviewed some of the long-standing data regarding acute mania in bipolar disorder and focused on some principles for managing acute mania that are present across different studies. These principles can guide clinical strategies and may help to improve long-term outcomes.

Use Effective Treatments

Dr. Sachs stated that one principle of managing acute mania is to recognize the relationship between efficacious acute treatment and long-term effectiveness. Lithium, for example, has been the standard of care since the 1920s and has been effective in treating acute manic and depressive episodes and has also been effective in prophylaxis. Yet, despite its proven efficacy, lithium is underused and often prematurely discontinued. Data from a 6-year study of lithium use in a large health maintenance organization[38] showed that of the 74 patients with mental illness who were taking lithium, only 8% took lithium for 90% or more of their days of eligibility.

Treat to Recovery

Using data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) for acute episodes,[39] Dr. Sachs stressed another principle of improving long-term outcomes: treat patients to recovery. Of the 1469 participants who were in an acute episode, 58.4% recovered from the acute episode and were well for 8 consecutive weeks. These results are remarkable because patients in this study population would typically have been excluded from studies because of comorbid anxiety disorders, substance abuse, rapid cycling, or other reasons, and yet with the use of published pharmacotherapy guidelines and evidence-based treatments, and an iterative approach to treatment at every decision point, a majority of these patients responded.

Reduce the Risk of Recurrence

Another principle illustrated by STEP-BD[39] is that the long-term use of effective medications yielded better results than expected. In the first year after recovery, approximately 71% of patients had no recurrence, and almost 52% had avoided a recurrence in the second year. Slightly more than half stayed well for more than 2 years.

Data from STEP-BD[39] also showed that the presence of residual mood symptoms at initial recovery was predictive of shorter time to recurrence. Patients with more residual mania symptoms and a greater percentage of days depressed or anxious in the past year had a greater risk of getting ill again (Table 1). Dr. Sachs suggested that targeting residual symptoms in maintenance treatment may reduce the risk of recurrence and is another principle of improving long-term outcomes.

Grade the Evidence

Dr. Sachs explained the importance of what he referred to as "Category A" evidence, studies with sufficient methodologic rigor to support valid causal inferences. He cited double-blind, placebo-controlled trials with adequate sample size ($N \geq 100$) as an example of this kind of evidence—a study that would have enough statistical power to have an 80% chance of detecting a meaningful difference ($p < .05$). Positive, placebo-controlled trials in acute mania that fit these criteria support the use of lithium,[40] divalproex,[41] and carbamazepine,[42,43] as well as 6 dopamine-blocking agents: olanzapine,[44,45] ziprasidone,[46] risperidone,[47–50] haloperidol,[51] quetiapine,[51,52] and aripiprazole.[53] Negative or failed Category A trials have been reported for lamotrigine,[54] gabapentin,[55] and

Table 1. Clinical Features Independently Associated With Time to Recurrence in Subjects With Bipolar Disorder Over 2 Years[a,b]

Feature	p Value	Hazard Ratio	95% CI
Depressive recurrence			
Number of residual mania symptoms, clinical monitoring form	< .01	1.217	1.049 to 1.412
Percent days of depression, past year	< .05	1.007	1.000 to 1.014
Percent days of anxiety, past year	< .008	1.008	1.002 to 1.014
Hypomanic/manic/mixed symptom recurrence			
Number of episodes depression, past year	< .005	1.068	1.021 to 1.118
Percent days of depression, past year	< .05	0.985	0.972 to 1.000
Percent days of elevated mood, past year	.0005	1.024	1.010 to 1.038

[a]Reprinted with permission from Perlis et al.[39]
[b]Significance level for entering/removing an explanatory variable into/from the model in the stepwise method is .05.

Table 2. Comparing Effect Size for Acute Mania Trials of Atypical Antipsychotics

Study	Response Rate, %	NNT
Tohen et al.[44]		
Olanzapine	49	4.0
Placebo	24	
Tohen et al.[45]		
Olanzapine	65	4.5
Placebo	43	
Khanna et al.[49]		
Risperidone	73	2.7
Placebo	36	
Hirschfeld et al.[50]		
Risperidone	43	5.3
Placebo	24	
Vieta et al.[52]		
Quetiapine	48	5.9
Placebo	31	
Keck et al.[46]		
Ziprasidone	50	6.7
Placebo	35	
Keck et al.[53]		
Aripiprazole	40	4.8
Placebo	19	
Sachs et al.[57]		
Aripiprazole	53	4.8
Placebo	32	

Abbreviation: NNT = number needed to treat [1/(Active Treatment Response Rate – Placebo Response Rate)].

topiramate.[56] This evidence suggests that dopamine-blocking drugs as a class may have antimanic effect for dopamine but does not suggest a class effect for anticonvulsants.

Using number needed to treat (NNT), a simple metric for effect size, Dr. Sachs examined trials of olanzapine,[44,45] risperidone,[49,50] quetiapine,[52] ziprasidone,[46] and aripiprazole[53,57] (Table 2). The formula for determining the NNT is 1 divided by the difference between the response rate to active treatment minus the response rate to placebo.

Because the data for the medications shown in Table 2 were derived from different studies, direct comparisons are not valid. To illustrate this point, Dr. Sachs discussed the 2 risperidone studies.[49,50] Both studies enrolled patients with acute mania. One study was done in India[49] and the other in the United States,[50] but the protocols were essentially the same. The India study showed that it was only necessary to treat 2.7 patients with risperidone treatment to produce 1 extra responder than would have been seen with placebo treatment. In the U.S. study it was necessary to treat 5.3 patients with risperidone treatment to produce 1 extra responder than would have been seen with placebo treatment. This NNT analysis suggests that risperidone was about half as effective in the U.S. as it was in India and reminds us that comparisons made across studies with different populations are precarious. The key difference between these 2 trials was that the patients in the India study were more severely ill at baseline and were treated more aggressively than those in the U.S. study. Greater severity at baseline in India probably reflects the impact of allowing family consent for patient entry. This comparison would then indicate that if patients were aggressively dosed and required to stay on their treatment, the effect could be twice as robust. Dr. Sachs emphasized that all of the antipsychotic medications that have FDA approval for the treatment of mania, if dosed properly and used over a long enough duration, are likely to be adequate treatment to provide long-term benefit. The proper use of FDA-approved medications is another treatment principle that clinicians can take away from these controlled trials.

Continue to Treat

Dr. Sachs pointed out that most studies that are labeled as being maintenance trials are actually continuation phase studies because patients are still at an early phase in their recovery. Again, the grading of the evidence plays a role. Positive, double-blind, placebo-controlled continuation trials with adequate sample sizes have been published for lithium,[58–60] divalproex,[58] lamotrigine,[59,60] olanzapine,[61] and aripiprazole.[62] None of these agents works for every aspect of continuation maintenance phase treatment; however, continuing treatment with the same medication that worked in the acute phase is another principle to be gleaned from these trial data. Some medications work better for mania or depressive recurrence, but all are effective for some aspects of long-term care. Dr. Sachs reiterated that the principle that NNT analysis does not allow confident comparisons across studies also applies in these continuation studies. Therefore, head-to-head, double-blind, placebo-controlled trials are needed.

Dr. Sachs explained that successful continuation trials also use a so-called enriched design, which means patients first enter an open-treatment phase and are only randomized to continuation treatment if they meet the criteria for getting well while treated openly with the study medication. He noted that failed continuation/maintenance studies of divalproex and lithium randomized a higher percentage of patients who entered the open treatment phase than the successful studies. The take-home message was that successful continuation maintenance studies started with a sample enriched with patients who had already demonstrated benefits from the study drug during the acute phase. This observation is

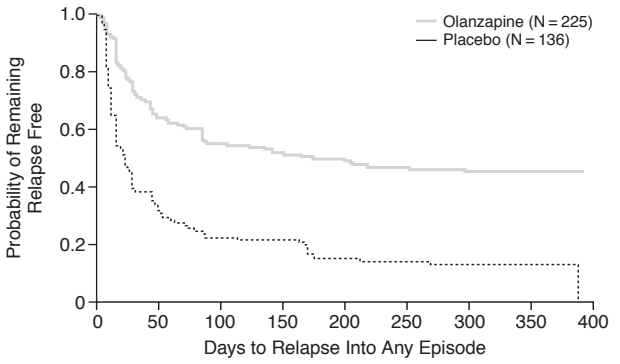
compatible with a clinical strategy of continuing the same medication that had acute efficacy.

Another principle that applies to clinical practice is not to disrupt treatment after patients have been well only a short period of time because this has a negative effect on recovery. Tohen and colleagues[61] conducted a study of olanzapine versus placebo in which patients who had achieved symptomatic remission from an acute manic or mixed episode of bipolar I disorder after 6 to 12 weeks of open-label treatment with olanzapine (5 to 20 mg/day) were then randomly assigned to double-blind maintenance treatment with either olanzapine or placebo for up to 48 weeks. The patients who were switched from olanzapine to placebo experienced a statistically significantly ($p < .001$) shorter time to relapse than those who continued taking olanzapine (Figure 2).

In a similar study,[62] patients who were manic were first treated with aripiprazole monotherapy (15 or 30 mg/day) until they were well and then switched to placebo or aripiprazole for an additional 26 weeks or until relapse. However, in this study, unlike the olanzapine discontinuation study,[61] patients had to remain stable for 6 weeks before they were randomized. The difference in relapse between aripiprazole and placebo did not appear until about 100 days after randomization (Figure 3). Dr. Sachs interpreted the data as recommending that if the patient has had successful acute phase treatment (typically with an FDA-approved drug), continue the medication that works.

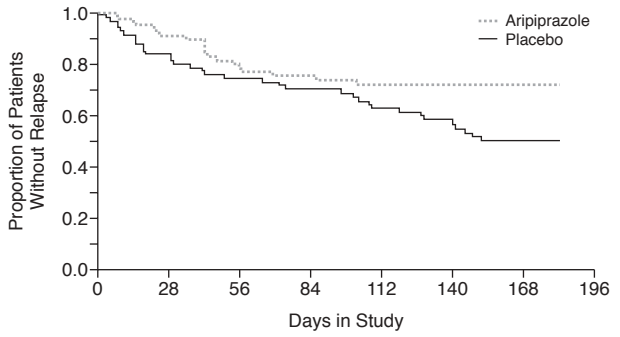
The final principle is that, if a decision is made to discontinue an acute phase treatment, any transition ought to be made gradually and preferably after patients have achieved durable remission. Tohen and colleagues[63] conducted a study that demonstrates this principle. Patients first received open-label cotreatment with both olanzapine and lithium for 6 to 12 weeks, underwent double-blind taper for 4 weeks, and then received double-blind monotherapy for 48 weeks. Olanzapine and lithium did not statistically differ in time until mood episode recurrence (Figure 4). The gradual, steady slope for both agents in Figure 4 illustrates the principle that gradual discontinuation over several weeks may minimize recurrence compared with no treatment or abrupt cessation of acute treatment.

Figure 2. Time to Symptomatic Relapse (olanzapine and placebo)[a]



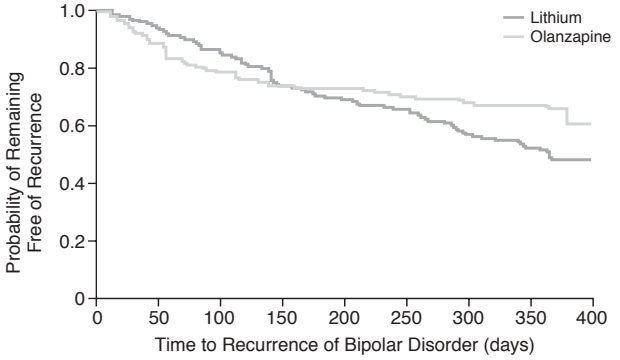
[a]Reprinted with permission from Tohen et al.[61]

Figure 3. Time to Symptomatic Relapse (aripiprazole and placebo)[a]



[a]Reprinted with permission from Keck et al.[62]

Figure 4. Time to Symptomatic Recurrence (olanzapine and lithium)[a]



[a]Reprinted with permission from Tohen et al.[63]

Conclusion

Dr. Sachs concluded that the following principles can be learned from acute mania treatment trials.

- Efficacious acute treatment is the first stage of long-term effectiveness.
- Initiate treatment based on the highest quality evidence available. The best evidence comes from double-blind, placebo-controlled trials with adequate sample size and a statistical power great enough to detect meaningful differences.
- Treat patients to full recovery. After a durable remission is achieved, transition to maintenance.
- Target residual symptoms in maintenance treatment to reduce the risk of recurrence.
- Use FDA-approved medications at proper doses over a long enough duration.
- Use the medication in the continuation phase that has already been effective for the patient in the acute phase.
- Maintenance treatment is recommended. If treatment discontinuation is, however, required, do so gradually after the patient has achieved a durable recovery (> 8 weeks well).

These principles should be applied to improve long-term outcomes in the clinical setting.

Evidence-Based Pharmacologic Treatment of Bipolar Disorder: Translating the Evidence on Maintenance Treatment Into Best Practices

Paul E. Keck, Jr., M.D., suggested that the most important phase in the treatment of bipolar disorder is maintenance treatment. The goal of maintenance treatment is to prevent recurrent manic and depressive episodes and ameliorate subclinical symptoms of hypomania and depression. Therefore maintenance treatment is, in essence, relapse prevention.

FDA-Approved Medications for Maintenance Treatment in Bipolar Disorder

Dr. Keck stated that the FDA has approved several medications that have been studied in well-designed placebo-controlled trials and have shown evidence of efficacy in relapse prevention.

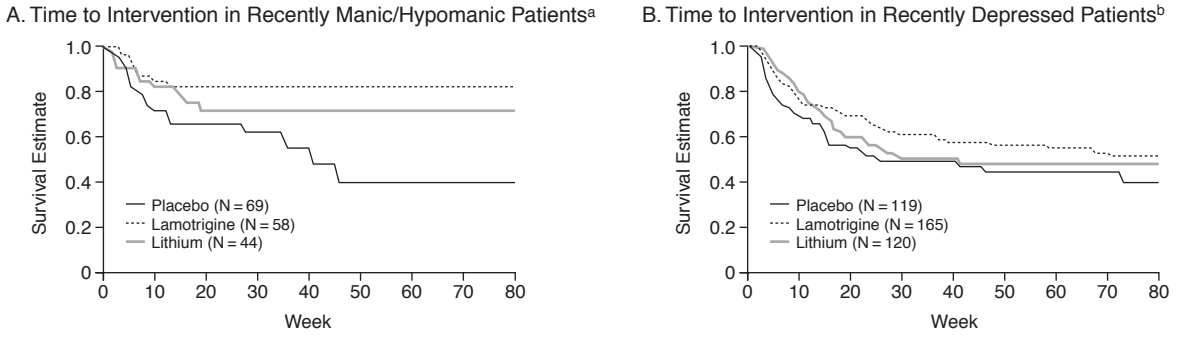
Lithium. Lithium is the most well-studied medication for bipolar illness. A pooled data analysis[64] of 7 maintenance studies examined the efficacy of lithium in preventing relapse of bipolar illness. One of the largest maintenance studies (N = 205) in this analysis provided data at 1 year and found that 36% of patients taking lithium relapsed compared with 68% of patients taking placebo. The odds ratio for relapse (4.1) favored the placebo group at 20 to 24 weeks and 48 to 60 weeks. Dr. Keck also pointed out that the beneficial effect of lithium was evident within the first 6 months of these studies. In fact, the protective effect of lithium remained consistent compared with the effect of placebo between 6 and 12 months. Dr. Keck offered a reminder that discussing the odds of remaining well versus remaining sick or relapsing is an important part of educating patients about relapse prevention.

Dr. Keck then described a 1-year, placebo-controlled study comparing lithium with divalproex, in which Bowden et al.[58] found that neither lithium nor divalproex were significantly superior to placebo in time to relapse to any mood episode, although divalproex tended to perform more favorably than placebo. Divalproex had the lowest termination rates among the treatment arms. Lithium had significantly higher termination rates ($p = .001$) than placebo when patients discontinued for intolerance and noncompliance. However, the study results suggest that lithium's unexpectedly poor response could be due in part to the inadvertent inclusion of a number of patients who were relatively mildly ill and had a low risk of relapse. A post hoc analysis in the study[58] found that patients who remained on divalproex treatment for the duration of the study had a 46% longer duration of prophylaxis than patients who were stabilized with divalproex and then switched to placebo. This analysis suggests that divalproex does have relapse prevention efficacy.

An open-label study conducted in Europe[65] was one of the few controlled trials examining carbamazepine in relapse prevention. The study compared lithium and carbamazepine over a $2^1/_2$-year period, and patients could receive additional treatments, such as an antipsychotic if manic symptoms were occurring or an antidepressant if depressive symptoms were occurring. The study found that lithium was slightly superior to carbamazepine on most outcome measures. Recurrences occurred in fewer patients treated with lithium (28%) versus carbamazepine (47%). However, in the context of clinical practice, the overall rates of relapse were high on monotherapy with either drug over the $2^1/_2$-year time frame.

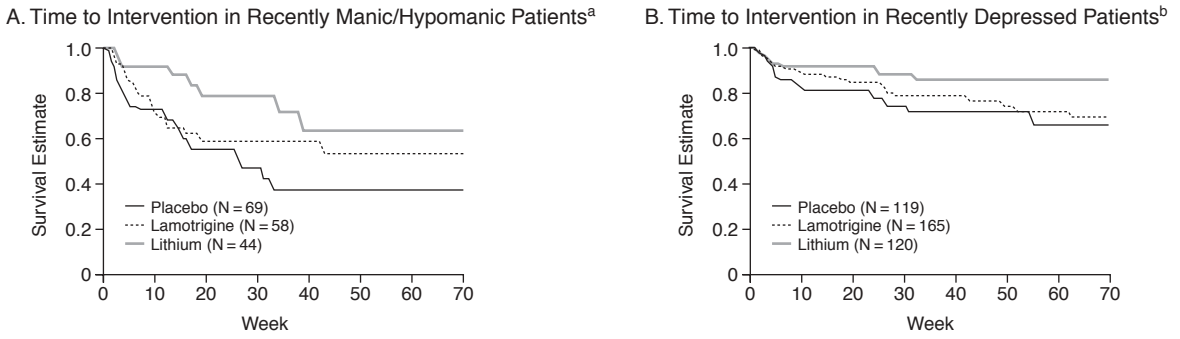
Lamotrigine. Dr. Keck stated that lamotrigine is another medication approved by the FDA specifically for relapse prevention in bipolar disorder. Two placebo-controlled studies comparing lamotrigine with lithium[59,60] over 18 months found similar results. The only difference between the 2 studies is that one study recruited patients emerging from a manic episode,[59] and the other study recruited patients emerging from a bipolar depressive episode.[60] Dr. Keck stated that these differences in design were relevant because immediate prior mood episodes tend to predict subsequent mood episode relapse, especially

Figure 5. Lamotrigine vs. Lithium for Prophylaxis Against Depressive Relapse



[a]Reprinted with permission from Bowden et al.[59] p = .015 lamotrigine vs. placebo, p = .167 lithium vs. placebo, p = .355 lamotrigine vs. lithium.
[b]Reprinted with permission from Calabrese et al.[60] p = .047 lamotrigine vs. placebo, p = .209 lithium vs. placebo, p = .434 lamotrigine vs. lithium.

Figure 6. Lamotrigine vs. Lithium for Prophylaxis Against Manic Relapse



[a]Reprinted with permission from Bowden et al.[59] p = .280 lamotrigine vs. placebo, p = .006 lithium vs. placebo, p = .092 lamotrigine vs. lithium.
[b]Reprinted with permission from Calabrese et al.[60] p = .339 lamotrigine vs. placebo, p = .026 lithium vs. placebo, p = .125 lamotrigine vs. lithium.

within the first 6 months. In other words, if a patient emerges from a depressive episode, the next most likely episode to occur is a depressive episode within the next 6 months. However, a patient emerging from a manic episode is more likely to have another manic episode as the next mood episode within 6 months.

Both studies[59,60] found that lamotrigine and lithium were superior to placebo in time to intervention for any mood episode. Some slight differences existed in the type of mood episode into which the patients relapsed. In patients who had been recently manic/hypomanic and in patients who had been recently depressed, lamotrigine was more effective than lithium at preventing depressive relapse (Figure 5).[59,60] In patients who had been recently manic/hypomanic and in patients who had been recently depressed, lithium was more effective than lamotrigine at preventing manic relapse (Figure 6).[59,60] Dr. Keck suggested that lamotrigine is the only medicine with a demonstrated greater efficacy at preventing bipolar depressive episodes compared with bipolar manic episodes.

Olanzapine. Olanzapine is also approved by the FDA for relapse prevention. Tohen et al.[61] conducted a double-blind, placebo-controlled study of olanzapine for relapse prevention in bipolar I disorder. The relapse rate in the placebo group (80.1%) was significantly higher ($p < .001$) than the relapse rate in the olanzapine group (46.7%).

Another study[63] compared olanzapine with lithium for 12 months. The patients who received olanzapine in this trial had a significantly lower rate of hospitalization ($p < .03$) than patients who received lithium during the double-blind treatment period. Two drugs with known efficacy seldom have a significant separation from each other on an efficacy measure, but in this trial, olanzapine was better than lithium at preventing manic relapse. No significant difference existed between the 2 treatments in the prevention of bipolar depressive episodes.

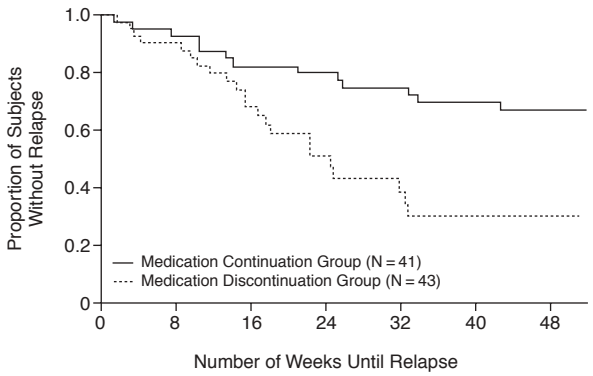
Aripiprazole. Another agent to receive FDA approval for relapse prevention as a monotherapeutic agent is aripiprazole. In a 26-week trial,[62] aripiprazole and placebo had a similar

rate of relapse into any mood for about the first 3 months; thereafter, the aripiprazole relapse rate remained steady, but the placebo group continued to have a greater percentage of patients relapsing. Aripiprazole was more efficacious than placebo in preventing manic episodes. During the 26-week period, only 8% of patients in the aripiprazole group had a recurrent manic episode compared with 23% of patients in the placebo group. No significant difference existed in the depressive relapse rates between patients who took aripiprazole or those who took placebo.

Dr. Keck reiterated that immediate prior mood episode tends to predict relapse into similar mood episode. All patients who entered this maintenance study[62] had responded to aripiprazole for a manic or a mixed episode. The overall likelihood of relapse in this treatment group would be toward a manic or a mixed episode rather than a depressive episode. Dr. Keck speculated that this may be why no significant difference existed between the aripiprazole and placebo groups in depressive relapse.

The reason that this study[62] used a 6-month time period to demonstrate efficacy is that 6 months was the minimum time it took for lithium to demonstrate efficacy in placebo-controlled trials.[64] The efficacy in relapse prevention of aripiprazole or any other agent compared with placebo should be evident within 6 months.

Figure 7. Time to Relapse for Subjects With Bipolar Disorder After Successful Antidepressant Response (1-year survival)[a]



[a]Adapted with permission from Altshuler et al.[71]

Combination Treatments

Dr. Keck noted that few studies have examined the evidence of efficacy for combination treatments for bipolar disorder and even fewer have examined combined medication treatments specifically. One study[66] compared the combination of lithium and divalproex against lithium and placebo. Another study[67] compared the combination of olanzapine and mood stabilizer versus placebo plus mood stabilizer.

The first study[66] compared the efficacy of lithium plus either divalproex or placebo for the continuation and maintenance treatment of patients with bipolar I disorder. None of the patients taking the combination of lithium and divalproex suffered a relapse, but 70% of patients treated with lithium and placebo relapsed or had a recurrence ($p = .014$). Dr. Keck noted that these results are not definitive because only 12 subjects were studied.

An initial study[67] of valproate or lithium combined with either placebo or olanzapine was only a 6-week trial in acute mania or mixed episodes. However, according to Dr. Keck, the research group has now completed a longer study,[68] which is the largest and most rigorous of the relapse prevention trials addressing combination pharmacotherapy. Patients in remission of bipolar I disorder after 6 weeks of acute-phase treatment with olanzapine plus either lithium or valproate were randomly reassigned to receive olanzapine plus lithium or valproate, or placebo plus lithium or valproate, and were followed for 18 months. The time to recurrence of symptomatic mania or depression was not significantly different between the olanzapine plus valproate or lithium group and the monotherapy group. However, among the 68 patients assessed also in symptomatic remission, time to recurrence of acute mania or depression was significantly longer for combination therapy ($p = .023$). Combination therapy extended time for recurrent mania but not for depressive relapse and was associated with significant weight gain compared to valproate or lithium alone. This is the only double-blind, placebo-controlled trial to definitively prove that 2 drugs with mood stabilizing properties were superior to 1.

Antidepressants for Relapse Prevention

Antidepressants are commonly used in the acute treatment of bipolar depression with an antimanic agent, but Dr. Keck posed the question, What about their role in maintenance treatment? A meta-analysis[69] examining the efficacy of antidepressants in relapse prevention of depressive disorders found that the odds of relapse in patients who were treated with an antidepressant versus placebo decreased by 70%. The average rate of relapse was 18% for antidepressants versus 41% for placebo.

Two retrospective, naturalistic studies[70,71] examined the impact of continuing or discontinuing antidepressant treatment on the risk for relapse of bipolar depression or a switch to a manic episode. Both studies found lower rates of emergent depression in those treated with antidepressants in combination with an antimanic agent. Those who discontinued antidepressant treatment had

an increased risk of relapse into bipolar depression.[70] After 1 year of antidepressant therapy, 70% of patients who discontinued antidepressant therapy relapsed to bipolar depression versus only 36% of those who continued on antidepressant therapy for the duration of the study (Figure 7).[71] No significant difference existed in switch rate into mania.[70,71] Dr. Keck pointed out that the patients included in the analyses were acute responders to combination therapy, did not switch during a 10-week acute treatment trial, and had no prior history of rapid cycling. Therefore, generalizing maintenance treatment for all patients with bipolar depression is problematic.

Conclusion

Dr. Keck reiterated that there are only 4 medications with FDA approval for bipolar disorder relapse prevention in the United States: lithium, lamotrigine, olanzapine, and aripiprazole. The profile of these agents suggests that lithium, olanzapine, and aripiprazole may be more beneficial in prevention of manic episodes, but slightly less beneficial in prevention of depressive episodes. Lamotrigine may be slightly more effective at preventing depressive episodes compared with manic episodes. Combination treatment, which is common for most patients with bipolar disorder in the United States, has not been well studied in randomized, controlled trials. The only large, well-conducted trial did find that the combination of olanzapine plus lithium or divalproex was more effective at preventing relapse than placebo plus lithium or divalproex.

Use of antidepressants for the treatment of bipolar disorder remains controversial, in part because of the risk of cycle induction and precipitation of hypomania, mania, or mixed states. However, studies have found that less risk of depressive relapse over time exists when patients continue antidepressant treatment following an acute combination trial with an antimanic agent.

To summarize, Dr. Keck listed the principles of maintenance treatment:

- First, optimize dose or plasma concentrations by titrating monotherapy agents to maximize response and minimize side effects before implementing combination therapy.
- Second, when a second agent is required for manic, hypomanic, or depressive symptoms or episodes, reassess the efficacy of and need for continuation of the primary agent.
- Third, in choosing among the widening array of treatment medications, consider side effects, pharmacokinetic interactions, and complementary mechanisms of action.

Drug names: aripiprazole (Abilify), carbamazepine (Equetro, Tegretol, and others), clozapine (Clozaril, FazaClo, and others), diphenhydramine (Benadryl and others), divalproex (Depakote), gabapentin (Neurontin and others), haloperidol (Haldol and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), propranolol (Inderal, Innopran, and others), quetiapine (Seroquel), risperidone (Risperdal), topiramate (Topamax), ziprasidone (Geodon).

Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, carbamazepine is not approved by the U.S. Food and Drug Administration for the maintenance treatment of bipolar disorder.

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