Managing Bipolar Disorder From Urgent Situations to Maintenance Therapy, Part 2: Focus on Maintenance

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *presents the highlights of the planning teleconference series "Managing Bipolar Disorder From Urgent Situations to Maintenance Therapy, Part 2: Focus on Maintenance," which was held in March and April 2007. This report was prepared by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Eli Lilly and Company.*

The planning teleconference was chaired by ***Rakesh Jain****, M.D., M.P.H., R/D Clinical Research, Inc., Lake Jackson, Tex. The faculty were* ***W. Clay Jackson****, M.D., Dip.Th., Department of Psychiatry, University of Tennessee, Memphis;* ***Noel C. Gardner****, M.D., Department of Psychiatry, University of Utah School of Medicine, Salt Lake City; and* ***Vladimir Maletic****, M.D., Department of Neuropsychiatry and Behavioral Science, University of South Carolina School of Medicine, Columbia.*

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The Cardinal Importance of Long-Term Management in Bipolar Disorder

Almost a century ago, Emil Kraepelin,[1] the father of modern psychiatry, described bipolar disorder as having a prolonged course, with relapse being the rule rather than the exception. Rakesh Jain, M.D., M.P.H., explained that, despite the passage of time, relapse of bipolar disorder remains a critical problem for patients and clinicians. Presently, the importance of maintenance treatment is widely recognized among clinicians, and several pharmacologic and nonpharmacologic options are available that have demonstrated their effectiveness in randomized clinical trials.

When treating a patient with bipolar disorder, clinicians should first identify whether the patient is presenting with a manic, depressive, or mixed episode. The symptoms of the episode should be treated to full resolution, and the patient should be transitioned to an effective maintenance treatment. However, Dr. Jain emphasized that these steps are not always easily executed. Accurate identification of bipolar disorder is still suboptimal in both psychiatric and nonpsychiatric settings. A survey[2] found that 69% of patients with bipolar disorder who sought treatment within 1 year of symptom onset were initially misdiagnosed, by psychiatrists and nonpsychiatrists alike, with the usual misdiagnosis being unipolar depression.

Dr. Jain explained that, after the correct diagnosis is reached, complete remission of manic, depressive, or mixed symptoms should be the ultimate goal of treatment, but residual symptoms can still be far too common. The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)[3] found that not only do many patients have residual symptoms, but residual symptoms are associated with high rates of relapse. Therefore, clinicians should treat the symptoms as completely as possible in order to improve both short- and long-term outcomes. Monitoring is important during maintenance treatment because problems can arise when patients are noncompliant with treatment recommendations[4] or when treatments are ineffective for patients.[5]

Dr. Jain introduced 3 experts in the field of bipolar disorder: W. Clay Jackson, M.D., Dip.Th.; Noel C. Gardner, M.D.; and Vladimir Maletic, M.D. In the presentations below, these experts will explain why maintenance treatment is important and describe strategies to help clinicians provide optimum maintenance treatment for their patients with bipolar disorder.

The Importance of Facilitating Adherence During Maintenance Therapy for Bipolar Disorder

The goals of therapy vary according to the patient's phase of illness[6]: in the acute phase, syndromal recovery is the goal; in continuation treatment, functional recovery becomes the focus; and

in maintenance treatment, the goal is for the patient to attain stability and resume a normal lifestyle. During the maintenance phase of treatment, nonadherence presents one of the most significant barriers to effectively controlling bipolar disorder. Dr. Jackson described *adherence* as how well a patient's actions correlate with the treatment regimen that is recommended by the clinician. According to a recent study,[7] 45% of patients with bipolar disorder do not adhere to their prescribed pharmacotherapy or psychotherapy.

Impact of Treatment Adherence

A large burden of disability and subsequent medical costs accompanies bipolar disorder. For example, bipolar disorder is the fifth leading cause of years lost to disability among persons aged 15 to 44 years.[8] Expenses include both the direct costs of medical care and indirect costs such as work lost or incarceration.[9] Nonadherence to mood stabilizers predicts higher utilization of health care resources, including psychiatric emergency department visits and psychiatric hospitalizations.[10] However, with proper adherence to therapy, direct costs can be halved and indirect costs consequently lessened,[9] making treatment adherence an important goal for patients with bipolar disorder and the clinicians who treat them.

Factors Influencing Adherence

Many factors influence a patient's treatment adherence, explained Dr. Jackson.[11] A key component of adherence is the therapeutic alliance between the clinician and the patient. Factors related to the treatment itself—the cost of the treatment, the possible adverse effects of the treatment, and the patient's understanding about how to use the treatment—can also greatly impact treatment adherence. Another determinant of treatment adherence is the patient's level of insight into his or her illness: does the patient regard himself or herself as being mentally ill, and does he or she view treatment as important in overcoming mental illness? In some segments of society, a disease stigma may cause patients to receive negative feedback about being mentally ill or using mental health treatment. Additionally, the socioeconomic environment can present logistical challenges for patients who are trying to adhere to treatment, including obtaining reliable transportation to appointments and getting private or public insurance coverage for prescribed treatments.

According to Dr. Jackson, chronicity and recurrence of bipolar disorder can predict nonadherence. The symptom domains grandiosity, irrationality, and depression are also associated with nonadherence, although some contradiction exists among studies.[7,12,13] Research has postulated that polypharmacy may contribute to nonadherence,[7] but one retrospective study[12] demonstrated that polypharmacy was not an independent predictor of nonadherence. Lack of psychotherapy may also affect adherence; several types of psychotherapy have been found to increase adherence to medication regimens when used as adjunctive treatment for bipolar disorder.[14] Patient characteristics, including young age,[13] African-American ethnicity,[13] lack of disease-state knowledge,[7] poor attitudes toward treatment,[7] low socioeconomic status,[12,13] and comorbid substance abuse,[13] may also predict nonadherence.

Dr. Jackson explained that patients experience internal and external negotiations in coming to terms with their need for medication treatment, and these negotiations also affect their willingness to adhere to treatment recommendations.[15] Internal negotiations relate to the patient's self-identity and include fears of dependency on the medication and views of the medication as a symbol of mental illness, both of which may be particularly common among African-American patients.[16] Patients may also view medication as a way of experimenting on them.[15] The external negotiations involve the clinical identity and include concerns about the type of medication, the dosing of the medication, and the method by which medication is administered. Given these potential psychological conflicts in the patient, Dr. Jackson asserted that nonadherence may be better framed by the clinician as a developmental phase that can be worked through rather than as a static categorical response.

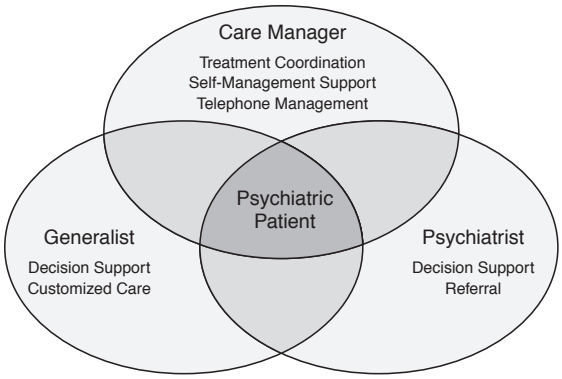
Adherence and Concordance

Dr. Jackson then described the relationship between adherence and *concordance*—the degree to which the patient and the clinician view the illness and the treatment plan in the same way—and how that relationship affects the clinician's treatment strategy.[17] If a patient is both concordant and adherent, which is the best-case scenario, the clinician should maintain concordance by recognizing collaborative therapeutic outcomes and building external support. If a patient is concordant but nonadherent, the patient believes what the clinician is telling him or her about the illness, but he or she is not capable of adhering to treatment for some reason. The clinician should then examine the patient's individual barriers to adherence and work to overcome those barriers if possible. If the patient is adherent but discordant, the clinician should improve concordance by recognizing the patient's own self-interest and his or her options for improved therapeutic outcomes, which will help the patient take charge of his or her own care. If the patient is nonadherent and discordant, the clinician must start by establishing the therapeutic alliance, clarifying the areas of agreement between clinician and patient, and recognizing that a lack of collaboration results in negative treatment outcomes.

The Therapeutic Alliance in Relation to Adherence

Dr. Jackson emphasized the importance of the therapeutic alliance between patient and clinician in effective maintenance treatment. For treatment to be effective, not only do the treatments have to be safe and efficacious,

Figure 1. Bipolar Disorder Coordinated Care Model[a]



[a]Adapted with permission from Kilbourne.[23]

but the patient must also be willing to take the medicine or participate in the treatment. The patient's willingness to initiate and continue adhering to treatment is influenced by his or her relationship with the clinician. Dr. Jackson suggested that the patient does not believe in the doctor because of the medicine; rather, the patient believes in the medicine because of the doctor. While a poor therapeutic alliance predicts nonadherence to therapy,[7] trust is a strong predictor of adherence. In a study[18] of illness concept, the greater a patient's trust in his or her medication and clinician, in the absence of negative treatment expectations, the longer he or she adhered to lithium treatment.

Dr. Jackson proceeded to describe various models of the therapeutic alliance. In the premodern, paternalistic conception[19,20] of the therapeutic relationship, clinicians used their power and authority over patients to give them instructions and expertise, and patients were expected to have confidence in the clinicians and to comply with their instructions.

The consumerism model[21] is the modern conception of the therapeutic relationship, in which patients control the therapeutic alliance and demonstrate knowledge, choice, and direction, and clinicians are expected to acquiesce and to provide prescription of certain therapies requested by the patients. Dr. Jackson asserted that this model is overly idealistic for use with patients with bipolar disorder because their ability to make informed decisions and give direction to their own care may be compromised by their illness.

The postmodern conception of a therapeutic relationship is a collaborative model,[22] in which clinicians and patients have overlapping areas of power and responsibility. Clinicians are expected to provide knowledge and make recommendations regarding treatment; patients are expected to be engaged in their own disease management and remain adherent. In contrast to *compliance*, which is strictly following directions, *adherence* means that patients are cleaving to the clinicians' recommendations. Additionally, patients are expected to keep appointments and share all care-related information. For the collaborative model to work well, clinicians should listen to their patients and provide up-to-date, expert knowledge about effective maintenance treatment options. Trust is the central driver to this therapeutic interaction, and mutual reliance between patients and clinicians can facilitate recovery.

Dr. Jackson suggested following a coordinated care model for bipolar disorder to meet psychiatric, medical, and social needs of patients and thereby improve adherence and outcomes (Figure 1).[23] This model uses 3 main care providers for the patient: a psychiatrist, a generalist, and a care manager. The psychiatrist implements psychiatric treatment, offers decision-making support, and gives referrals for medical problems. The generalist also helps with decision-making support and attends to medical comorbidities and adverse effects that may co-occur with bipolar illness. The care manager coordinates treatment and encourages patient autonomy through self-management support as well as telephone management.

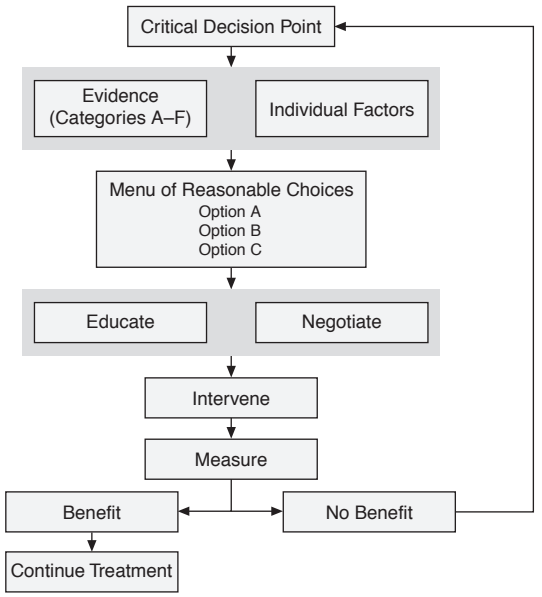
Conclusion

A strong therapeutic alliance has many benefits, including a negative correlation with key characteristics and complications of bipolar disorder,[24] concluded Dr. Jackson. For example, depressive symptoms and manic symptoms occur less frequently in patients who have a strong therapeutic alliance with their practitioner. Additionally, patients who have a strong therapeutic alliance tend to have positive attitudes about medication; have increased adherence, which results in improved outcomes; and have a mitigated perception of the stigma of their bipolar disorder diagnosis. Building a strong therapeutic alliance with patients, and thereby encouraging enhanced adherence to recommended interventions, remains the cornerstone of promoting robust and sustained recovery in bipolar patients.

Individualizing Evidence-Based Medicine in the Maintenance Treatment of Bipolar Disorder

Bipolar disorder is a disabling illness that often has an early onset[25] and is characterized by chronic, episodic relapses and recurrent syndromal and subsyndromal symptoms.[26–28] As a result, treating bipolar disorder requires more than just stabilizing an acute manic or depressive episode; treating bipolar disorder also requires opti-

Figure 2. An Iterative Approach to Treating Patients[a]



[a]Reprinted with permission from Sachs.[39]

mizing treatment across the lifespan of the patient, explained Dr. Gardner. The goal of effective maintenance treatment would be to prevent relapse,[29–31] reduce subsyndromal symptoms, decrease hospitalizations, decrease morbidity and mortality, and improve functioning and quality of life.

Limited Maintenance Data

According to Dr. Gardner, the problem with using evidence-based treatments for maintenance therapy of bipolar disorder is that few data exist on which to base optimal pharmacotherapeutic treatment on an individual basis. The available data[32] are largely limited to bipolar I patients, but the majority of patients who fall in the bipolar spectrum do not meet all of the criteria for a DSM-IV diagnosis of bipolar I disorder. Data[33] from studies are also largely limited to acute phases of the illness with a majority focusing on manic and mixed states, although a few studies are now available on acute bipolar depression.[34,35] The available maintenance studies often have limited generalizability because they exclude children, adolescents, or patients with comorbid psychiatric conditions, medical illnesses, or substance use disorders, which substantially limits the ability to interpret that data in relation to a specific individual patient in treatment.

The Role of Treatment Guidelines

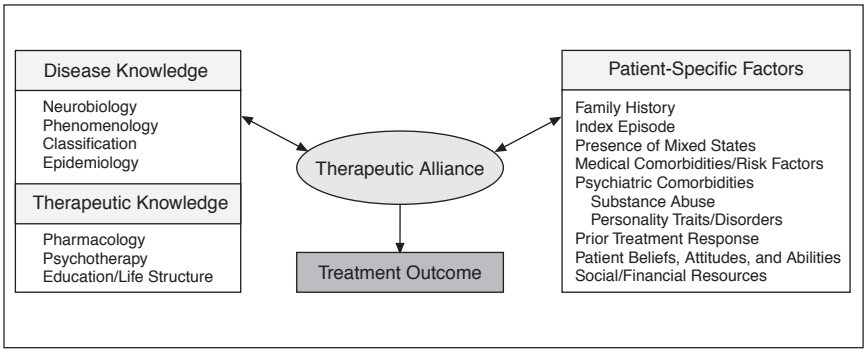
With a rapidly expanding number of pharmacologic treatment options, treatment guidelines have become increasingly helpful in assisting clinicians to treat their patients. Guideline committees examine the available evidence as well as widely accepted therapeutic principles within the practicing community and generate a summary of reasonable treatment options in an easily accessible format.[36] These treatment guidelines are designed to articulate expert opinions and general principles on optimal treatment approaches while considering the current best evidence. Dr. Gardner emphasized that treatment guidelines should not replace clinical judgment and individualized treatment. Rather, guidelines are a way of gathering the data and emphasizing where the strengths and the limitations in that data are. Currently, there are 2 prominent U.S. treatment guidelines: the Texas Implementation of Medication Algorithms[37] and the Expert Consensus Guideline Series.[38] Both guidelines support the importance of maintenance treatment, despite limited maintenance data.

The Art of Evidence-Based Practice for Patients With Bipolar Disorder

Treatment guidelines help clinicians organize and prioritize evidence-based practice therapeutic knowledge so that it can be applied to the individual needs of a specific patient, according to Dr. Gardner. A practical model for the acute treatment of bipolar disorder was developed by Sachs,[39] which was derived from the STEP-BD program[3,40]; this model suggests a systematic, iterative approach. This model (Figure 2) suggests that decisions in clinical practice derive from the immediate needs of the patient at a critical decision point (e.g., an acute manic or mixed state), in which clinicians should use their knowledge from clinical experience to examine both research-based evidence and individual patient factors. After synthesizing this information, the clinician develops a menu of reasonable choices, which includes information about medication safety, efficacy, and tolerability.[39] The clinician can then educate the patient and negotiate with him or her to find an appropriate treatment to which the patient can commit, and the intervention proceeds. The clinician must monitor and measure the patient's outcomes and weigh both benefits and potential problems to select ongoing treatment. Dr. Gardner noted that although this model[39] is limited to bipolar I acute manic and mixed states, it suggests that sequential treatment is an ongoing process that should transition into the maintenance phase.

In accordance with this STEP-BD–derived model for acute treatment,[39] Dr. Gardner stated that greater emphasis on individualized treatment is needed to refine bipolar maintenance treatment. Clinicians should therefore

Figure 3. The Importance of Therapeutic Alliance in Evidence-Based Clinical Practice



partner with the patient in personalizing treatment that will meet the unique needs of that patient. As emphasized by Dr. Jackson, the therapeutic alliance with the patient should be central to the art of evidence-based clinical practice; clinicians provide expert knowledge of the disorder and its treatment, which is then aligned with patient-specific factors.

Figure 3 illustrates how all clinically relevant information in the treatment process flows through the therapeutic alliance. A clinician's continuously advancing knowledge of a disease and current therapeutics, including evidence-based treatment guidelines, finds application only when it is integrated with patient-specific factors in a dynamic partnership and communication with a patient. This is not just a one-time engagement that occurs in the initial evaluation, but a continuous fine-tuning of treatment within a working partnership.

Dr. Gardner stated that treatment should be characterized by active listening and identifying the patient's life goals. If patients understand that the clinician is committed to their life goals, then patients will feel a genuine partnership and will not feel as though they are viewed as symptoms on a checklist. The clinician should state explicitly that, even though the patient may not experience a pharmacologic treatment in the same way that the "average patient" has experienced in clinical trials with that treatment, his or her treatment steps will be tailored to facilitate an individually optimal outcome. To maintain the quality of the patient-clinician alliance, Dr. Gardner stressed that constant attention and communication are required. Additionally, the clinician should engage the patient in an ongoing process of self-monitoring and self-management.

Maintenance Treatment of Bipolar Disorder

Currently, several medications have a U.S. Food and Drug Administration (FDA) indication for maintenance treatment of bipolar disorder, including lithium,[41] lamotrigine,[42] olanzapine,[43] and aripiprazole.[44] Maintenance medications that have not been approved by the FDA but are frequently used in clinical practice include divalproex,[45] carbamazepine,[45] and oxcarbazepine as well as other atypical antipsychotics[46,47] and even some typical antipsychotics.[48]

Effective maintenance treatment should help patients maintain the remission of symptoms and promote long-term robust wellness. Dr. Gardner stressed that mixed states; subsyndromal mixed, manic, and depressive symptoms; and depressive relapses are all barriers to achieving full remission for patients with bipolar disorder. For example, mixed states raise the risk of suicidal ideation in bipolar patients.[49,50] Subsyndromal mixed and manic symptoms often predict syndromal relapse.[27,28] Judd et al.[26] found that 74% of the weeks that patients with bipolar disorder spent symptomatic involved subsyndromal symptoms. Similarly, Altshuler et al.[51] showed that quality of life (including duties at work, school, and home and relationships with family and friends) was seriously impacted by subsyndromal depressive features in bipolar patients. Depressive relapses are also particularly associated with impaired function.[52] The depressive phase of the illness is an ongoing focus of treatment in which the role of antidepressants has not yet clearly been established.[6]

Maintenance treatment for patients with bipolar disorder also requires clinicians' constant attention to medication safety and tolerability, as well as treatment adherence. Safety and tolerability issues often lead to poor treatment adherence, which, in turn, leads to poorer outcomes.[53] While many of the newer agents used to treat bipolar disorder have better safety and tolerability profiles than older agents,[54] factors unique to each individual should be considered in the risk-benefit ratio for each treatment. Further, continued patient monitoring is essential for encouraging treatment adherence and ensuring optimal treatment outcomes.

Conclusion

The practice of evidence-based medicine blends the art and science of pharmacotherapy through a dynamic clinician-patient partnership, concluded Dr. Gardner. This blend of art and science is particularly important for the maintenance phase of bipolar disorder. Clear data on patient management are limited, and clinicians are constantly inferring treatment recommendations from data sets that may apply to patients different than those they are treating. The foundation of practicing evidence-based medicine relies on the partnership between patients and clinicians, which provides the best possible outcome for patients by individualizing their treatment and the greatest professional satisfaction for clinicians by ensuring optimal patient outcome.

Neuroprotective Issues in Bipolar Disorder

Bipolar disorder is a highly recurrent condition associated with significant functional deficits, began Dr. Maletic. Repeated mood episodes and even minor residual symptoms increase the risk of future recurrence.[3] Additionally, neuropsychological deficits may persist in the euthymic state,[55] and the risk of recurrence of bipolar episodes may increase over time.[56] Dr. Maletic briefly reviewed neurobiologic, neuroendocrinologic, pathohistological, and molecular-genetic research to examine whether bipolar disorder is a degenerative and progressive condition, whether past episodes increase the risk of future recurrence, and whether these changes in the brain are reversible.

Cortical Abnormalities in Patients With Bipolar Disorder

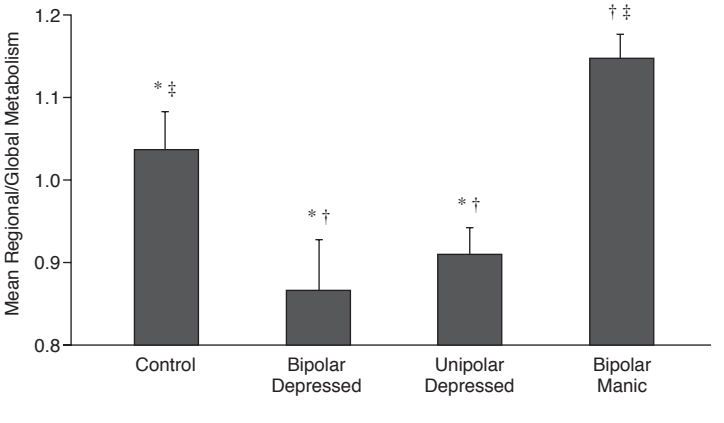
According to Dr. Maletic, manic patients are challenging subjects for structural and functional imaging. Variables, such as use of medication and current mood state, sometimes lack definition,[57,58] which makes interpretation of the results a daunting task. Because of these variables, neuroimaging studies of bipolar disorder are commonly characterized by vague findings and, in some instances, a lack of replication. But despite the difficulties associated with interpreting these results, many studies have found structural differences in the cortices of patients with bipolar disorder. For example, Strakowski et al.[59] used magnetic resonance imaging (MRI) to compare the ventricular volume of healthy volunteers versus the ventricular volume of first- or multiple-episode bipolar patients. Patients with multiple episodes were shown to have significantly larger lateral ventricles than first-episode patients or healthy subjects ($p < .05$), which was directly correlated with the number of previous manic episodes ($p < .02$). This association between ventricular volume and the number of previous affective episodes has also been found by Brambilla et al.[60]

The ventromedial prefrontal cortex (VMPFC)—together with the anterior cingulate cortex (ACC) and the amygdala—processes emotionally relevant information for the purpose of guiding behavior and orchestrating appropriate autonomic and endocrinologic responses.[61] Patients with unipolar[62] and bipolar[63] depression tend to have increased activity in the VMPFC. Blumberg et al.[63] found both functional and structural changes in the VMPFC of adolescent and young adult patients with bipolar disorder. These changes in the VMPFC may compromise patients' ability to adapt to changes in emotional and social circumstances. For example, manic patients tend to be excessively preoccupied by hedonic interests, whereas depressed patients demonstrate impaired mental flexibility.

Changes in other parts of the prefrontal cortex (PFC) have also been found in neuroimaging studies of patients with bipolar disorder. The lateral orbital prefrontal cortex (LOPFC) regulates maladaptive and perseverative responses. Its activity appears to be decreased in manic patients and enhanced in the depressive state.[62] According to Dr. Maletic, impaired LOPFC function may result in disinhibition in manic patients.[64] The dorsolateral prefrontal cortex (DLPFC), together with the dorsal ACC and parts of the parietal cortex, is a component of the executive function network.[65] Decreased activity in DLPFC may be reflected in compromised working memory, sustained attention, and executive function.[57] Lastly, a review[66] of functional imaging studies of manic patients suggested that metabolism was increased and volume decreased in the subgenual ACC (sgACC) (Figure 4). The sgACC assesses emotional and motivational information, making necessary adjustments in behavior. It also modulates sympathetic and neuroendocrinologic responses. Alterations of the sgACC may lead to the disturbances in motivation and neuroendocrine function that often accompany bipolar disorder.[67]

Dr. Maletic explained that functional studies[62,68,69] have found increased activity in the limbic structures (i.e., the amygdala and hippocampus) of patients with bipolar disorder during manic and depressed states. The amygdala plays a role in rapidly assessing and assigning emotional value

Figure 4. Altered Glucose Metabolism in Subgenual Prefrontal Cortex of Bipolar and Unipolar Patients[a,b]



[a]Reprinted with permission from Drevets.[66]
[b]Bars denote standard deviation.
*$p < .025$, control vs. depressed.
†$p < .01$, depressed vs. manic.
‡$p < .05$, control vs. manic.

to surprising and ambiguous stimuli. Clinical evidence[69] suggests that patients with bipolar disorder have excessively intense responses to changes in circumstance and difficulty correctly identifying the emotional meaning of facial expressions. Structural studies of the amygdala show that children and adolescents with bipolar disorder tend to have decreased amygdala volume compared with controls,[70] while adults with bipolar disorder have greater amygdala volume than controls.[71] The hippocampus is involved in emotional modulation and also in memory and neuroendocrine control. A review[72] of neuroimaging studies noted inconsistent data in patients with bipolar disorder: the hippocampus was enlarged, decreased, or unchanged in volume. The amygdala and hippocampus have bidirectional connections with the hypothalamus. Dr. Maletic postulated that neuroendocrine and sympathetic dysregulation in bipolar patients may be a reflection of alterations in these limbic structures.

Several other brain structures may also be affected by bipolar illness. Some studies[73] have noted enlargement of caudate nucleus and putamen in bipolar patients, while others[74] have found either no difference[75] or a decreased volume.[76] A limited number of studies[77,78] have noted midline cerebellar atrophy in bipolar populations. Dr. Maletic suggested that vermal size appears to be associated with the number of previous affective episodes.[72,79] Alteration of the cerebellar vermis is of particular clinical interest since it has been implicated in generating automatic emotional responses, such as empathy to facial expressions.

Structural and functional changes in the cortices of patients with bipolar disorder suggest that the integrity of the fronto-subcortical and prefrontal-limbic circuits may be compromised. Additional involvement of fronto-cerebellar-thalamic circuitry is likely. Dr. Maletic suggested that structural and functional changes support an organic basis for emotional, cognitive, and neuroendocrine symptomatology of bipolar illness.[67] Prior manic and depressive episodes may have a cumulative impact on the brain structure.

Neuroendocrinologic Dysregulation in Bipolar Disorder

According to Dr. Maletic, disruption of the hypothalamic-pituitary-adrenal (HPA) axis regulation is well documented in bipolar disorder.[80] The combination of amygdala hyperactivity and compromised hippocampal modulation may contribute to HPA disregulation.[81] The increased release of corticotrophin-releasing factor (CRF) leads to greater adrenocorticotropic hormone (ACTH) secretion and the eventual elevation of circulating glucocorticoids.[80] As a result, glucocorticoid receptors appear to have diminished sensitivity in mood disorders, therefore disrupting physiological feedback regulation.[82] Additionally, elevated glucocorticoids have been associated with suppressed thyrotropin-stimulating hormone secretion and compromised enzymatic conversion of relatively inactive tetraiodothyronine to triiodothyronine.[82] Ensuing low-grade thyroid dysfunction has been noted in patients with bipolar disorder, which Dr. Maletic suggested might impact both the clinical presentation of the disorder and the treatment response.[83]

In addition to HPA axis dysregulation, bipolar disorder may be associated with excessive sympathetic nervous system (SNS) activation. Dr. Maletic stated that this SNS overactivity coupled with glucocorticoid receptor insufficiency may contribute to the increased release of inflammatory cytokines.[80] Cytokines diminish the sensitivity of glucocorticoid and insulin receptors. Inflammatory cytokines can interfere with the synthesis of brain-derived neurotrophic factors (BDNF) in the central nervous system and also compromise monoaminergic transmission.[84] Increased SNS activity, consequent inflammatory dysregulation, increased platelet/endothelial aggregation, and an unhealthy lifestyle may all contribute to the elevated risk of cerebrovascular and cardiovascular disease in patients with bipolar disorder.[80] Impaired HPA axis regulation combined with compromised glucocorticoid and insulin receptor activity (mediated by inflammatory cytokines) might explain the high rate of diabetes, dyslipidemia, and osteoporosis in the bipolar population.[84]

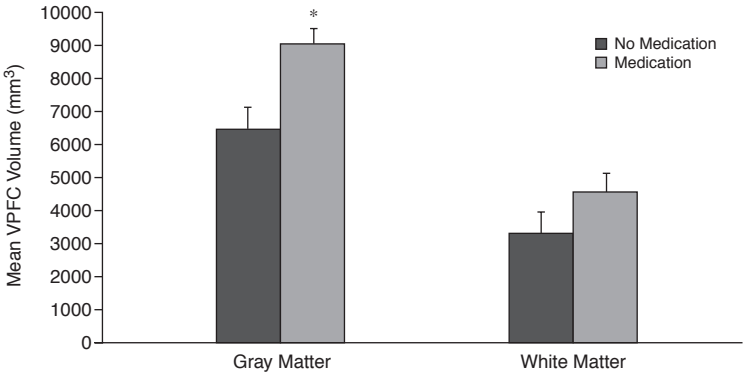
Pathohistologic and Genetic Alterations in Bipolar Disorder

Histologic evidence does not support the theory that bipolar disorder is a typical neurodegenerative disease, explained Dr. Maletic. Conventional neurodegenerative disorders are associated with neuronal loss and prominent gliosis. In contrast, bipolar disease tends to manifest glial loss[85] and a reduction of neuronal density,[86] possibly due to apoptosis and thinning of interneuronal neuropil.[87] Studies[63,88] have also noted accelerated aging in bipolar disorder, which is most likely due to oxidative stress. However, Dr. Maletic noted that the relationship between cell pathology and clinical manifestations of bipolar disorder has yet to be established. Bipolar disorder is most likely a genetically heterogeneous disease associated with alterations in approximately 100 polymorphic genes.[89] These genetic anomalies can negatively impact the integrated signaling networks that regulate the synthesis of growth and neuroprotective factors, stress-activated kinase pathways, circadian rhythms, and synaptic activity.

Dr. Maletic explained that manipulation of the glycogen-synthase-kinase-3 (GSK-3) pathway produces both antimanic and antidepressant effects. Many agents with mood stabilizing properties, such as lithium, valproate, and atypical antipsychotics, directly and indirectly modulate the phosphoinositide-3-kinase, GSK-3, and Wnt signaling pathways, which are the same pathways implicated in genetic studies of bipolar disorder.[89,90] Dr. Maletic was surprised that genetic research of bipolar disorder did not implicate neurotransmitter trafficking but rather shifted focus to oligoden-

droglia.[89] Since oligodendroglia are responsible for the myelination of central neuronal pathways, its dysfunction may lead to impaired connectivity. Recent functional neuroimaging studies of bipolar disorder have found a lack of "connectivity" between limbic and prefrontal structures possibly contributing to symptomatology.[87]

Figure 5. Medications May Have a Neuroprotective Effect in Bipolar Disorder[a,b]



[a]Reprinted with permission from Blumberg et al.[63]
[b]Bars denote standard deviation.
*Significantly larger volumes ventral prefrontal cortex (VPFC) gray matter were associated with medication use vs. no medication (p = .005).

Results of Pharmacotherapy Studies

If a relationship exists between clinical manifestations of bipolar disorder and functional changes observed in imaging studies, then successful treatment should normalize aberrant patterns of neuronal activity, according to Dr. Maletic. A recent magnetic resonance spectroscopy (MRS) study[91] of the ACC of patients with bipolar disorder found that risperidone use was associated with the normalization of glutaminergic transmission in the ACC of manic patients and a reduction of Young Mania Rating Scale scores. An additional MRS study[92] of olanzapine monotherapy in adolescents with bipolar disorder found increased ventral PFC neuronal viability and functioning. Further research with MRS[58] showed that valproate monotherapy and combination valproate and quetiapine treatment were associated with symptomatic improvement as well as normalization of hippocampal biochemical markers, but the combination therapy appeared to be more successful than valproate monotherapy.

In a functional MRI study by Blumberg et al.,[68] successful treatment with mood-stabilizing agents produced a reduction of amygdala activity and improvement in the rostral ACC activity. In a separate study by Blumberg et al.[63] using structural MRI, pharmacotherapy may have had a neurotrophic or neuroprotective effect on the ventral PFC of patients with bipolar disorder (Figure 5). A structural MRI study by Bearden et al.[93] suggested that lithium treatment resulted in a greater cortical gray matter density in portions of the anterior limbic-prefrontal network. Thus, evidence[63,93] has shown that mood-stabilizing agents may normalize aberrant patterns of neuronal activity in limbic and prefrontal areas of the brain, and preserve neural structure, thereby fostering clinical and functional improvement.

Mood-stabilizing agents, including lithium and valproate as well as atypical antipsychotics, may modulate phosphoinositide-3-kinase (PI3K), protein kinase B (AKT), and GSK-3 signaling cascades, thereby supporting the synthesis of neurotrophic factors such as beta-catenin and bcl-2.[89] Mood-stabilizing agents may also aid neurogenesis and exercise neuroprotective effects. Two clinical studies[94,95] have demonstrated decreased levels of BDNF in untreated bipolar depressed and manic patients. Serum levels of BDNF were negatively correlated with clinical measures of depression (p = .033) and mania (p = .005).[94] Successfully treated, euthymic patients with bipolar disorder had normal levels of BDNF, suggesting a potential neurotrophic benefit of pharmacotherapy.

Since unrestrained limbic activation may precipitate neuroendocrine dysregulation, Dr. Maletic noted that the role of mood-stabilizing agents in correcting endocrinologic disturbances in bipolar disorder should be examined. Although pharmacotherapy may improve glucocorticoid receptor sensitivity,[96] study results have been equivocal and inconsistent. Lithium, mood-stabilizing anticonvulsants, and antipsychotics possibly modulate inflammatory cytokines,[97] which should theoretically improve immune response and endocrinologic function in patients with bipolar disorder. Unfortunately, the use of some mood-stabilizing medications, especially atypical antipsychotics, may also be associated with increased metabolic burden.

Conclusions

According to Dr. Maletic, minor structural brain changes may be associated with impaired function, and persistent functional alterations could lead to additional structural changes. Neurotrophic/neuroprotective factors may underlie this transformation. Additionally, bipolar disorder is an illness associated with neuroendocrine dysregulation,[67] metabolic syndrome,[80] cardiovascular and cerebrovascular disease,[98] accelerated aging,[88] and immune deficiency.[97] Because of the risk of developing these comorbid conditions, treatment should focus on preventing further structural changes in the brain. Successful treatment results in restored homeostasis, amelioration of endocrine function and immune response, and optimized neurotrophic/

neuroprotective support.[89,93,96] Complete and sustained remission is the optimal goal of treatment[97] since any residual symptoms may be a proxy of biologically active disease.[89,94,97] Dr. Maletic noted, however, that these conclusions are tentative and require systematic correlative studies establishing the connection between clinical improvement, normalization in imaging studies, neuroendocrine stabilization, and enhanced neurotrophic support.

Summary

Dr. Jain stressed that, to fully embrace the cause of maintenance treatment of bipolar disorder, clinicians must first acknowledge the dangers of less-than-optimum maintenance treatment. These dangers include high relapse and recurrence rates, reduced treatment adherence, and adverse neurobiological effects.

Several general rules apply to maintenance treatment of bipolar disorder. First, clinicians should routinely offer maintenance treatment because patients often relapse. Second, when selecting pharmacotherapy, multiple issues are important, including the patient's individual needs, the efficacy and side effect burden of individual medications, FDA-approved medications for bipolar maintenance therapy available in the patient's insurance formulary, and the quality of research data. Dr. Jain stated that antidepressants should usually be avoided, especially as monotherapy. While monotherapy mood stabilizer treatment is preferred, combination therapy is indicated if treatment response is suboptimum. A large number of pharmacologic treatment options are available for maintenance treatment, including the FDA-approved medications lithium, lamotrigine, olanzapine, and aripiprazole, as well as other agents such as divalproex, carbamazepine, oxcarbazepine, and atypical antipsychotics, which can be used as monotherapy or as part of combination therapy. Third, psychotherapy has become increasingly well-studied and can be used for the majority of patients as an adjunctive treatment strategy. Psychotherapy for bipolar disorder can delay recurrence, stabilize symptoms, and improve medication adherence.[99] Additionally, several types of psychotherapy are available that can be useful to augment the benefits of mood stabilizers, such as group psychoeducation, family-focused therapy, interpersonal and social rhythm therapy, and cognitive-behavioral therapy.[100]

Dr. Jain asserted that, while patient adherence is important for treatment to succeed, clinician adherence to treatment guidelines is also vital. A recent survey[101] of psychiatrists revealed that only 64% of clinicians reported routinely using any treatment guidelines in making clinical decisions, which leaves room for improvement. Dr. Jain also recommended the use of daily mood ratings to both psychiatrists and nonpsychiatrists to track the progress of patient treatment. Clinical experience and research data[102] show that maintaining daily mood ratings can be useful for both patients and clinicians to detect relapse earlier during treatment than without these ratings.

The need for maintenance treatment is now widely recognized, and clinicians now have access to multiple tools to ensure optimum maintenance outcomes for patients. Dr. Jain concluded that carefully matching a patient's unique needs with individual treatment interventions is the ideal path to achieving high rates of success.

Drug names: aripiprazole (Abilify), carbamazepine (Carbatrol, Tegretol, and others), divalproex (Depakote), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal), quetiapine (Seroquel), risperidone (Risperdal).

Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, carbamazepine, divalproex, oxcarbazepine, quetiapine, risperidone, and valproate are not approved by the U.S. Food and Drug Administration for maintenance treatment in bipolar disorder. If you have questions, contact the medical affairs department of the manufacturer for the most recent prescribing information.

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For the CME Posttest for this ACADEMIC HIGHLIGHTS, see pages 1314–1316.