Clinical understanding and treatment of bipolar disorder: a review of the literature

Anthony Christopher Hamilton

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Clinical understanding and treatment of bipolar disorder:

A review of the literature

Anthony Christopher Hamilton

The University of Toledo

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Dedication

I dedicate this paper to all the people trying to lead normal and productive lives while living with a mental illness.

I would like to thank my family and friends for all their support throughout my educational career.
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Introduction

Approximately 5.7 million people in the United States have been diagnosed with bipolar disorder, according to the National Institute of Mental Health (2007). Typically, the disorder first manifests itself during late adolescence and early adulthood, affecting gender and race almost equally. Those affected can experience abnormal mood states, often going unrecognized early on as a true mental disorder and consequently left untreated for years. The abnormal mood states can greatly impair daily tasks and personal relationships, often making life very difficult. Early onset of symptoms in life is generally associated with a more severe disease course (Perlis et al., 2004). Years of research, better public awareness and knowledge of the disorder, the utilization of mental screening tools by clinicians, and the implementation of effective treatment plans has allowed many people with bipolar disorder to lead very productive lives.

The understanding and treatment of psychological disorders has undergone monumental transitions throughout history. Physicians and researchers have devoted entire careers to building the foundation and structure of the modern day medical approach to psychological illness. Beginning around the time of Hippocrates, bipolar disorder has shown active periods of research over time. Though many researchers have worked with the disorder, only a handful have played key roles in shaping bipolar disorder into its modern day understanding.

Hippocrates was the first to systematically describe and classify many mental disorders, including mania and depression. He believed the two mental states were separate from each other, though. It was not until the 1st century AD that the two were linked together by Aretaeus of Cappadocia, who described the two states as, “two different images of one single disease” (Angst & Marneros, 2001). His work proved essential as building blocks for 19th and 20th century researchers.
Works by Wilhelm Griesinger, Jean-Pierre Falret, and Emil Kraepelin during the mid to late 1800’s were very important in shaping the modern day understanding of the disorder. They built upon each other’s works to describe a circular type of mental disorder characterized by periods of mania and depression with balanced mental states in between. Falret, who suggested heredity played a role in the disorder’s etiology, called it ‘circular insanity’. Kraepelin, known by many as ‘the father of modern psychiatry’, called it ‘manic-depressive insanity’. Kraepelin was not so distinct in describing the disorder, though, grouping many other affective disorders into his ‘manic-depressive insanity’ (Angst & Marneros, 2001). His views were widely accepted until the 1960’s when bipolarity once again became a highly active area of research.

With researchers Jules Angst and Carlo Perris leading the way, bipolar disorder was more clearly defined in the *DSM-III* and in the current *DSM-IV-TR*. Distinctions between types of bipolarity were made during this time. Based on symptomology, bipolarity was broken down into bipolar I, bipolar II, and cyclothymia, with other affective disorders being excluded from bipolar disorder in the *DSM-IV-TR*. Research is still continuing to redefine affective mood disorders into more distinct classifications, hopefully leading more accurate clinical diagnoses and treatments (Pichot, 2006).
Diagnosis of Bipolar Disorder

The *DSM-IV-TR* (2000) lists the criteria/symptoms of the bipolar spectrum. Bipolar I disorder is described clinically as the occurrence of one or more manic or mixed episodes, often with the history of at least one major depressive episode. A mixed episode is one in which a person meets *DSM-IV-TR* criteria for mania and major depression simultaneously for a one-week period. Bipolar II disorder is described clinically as the occurrence of one or more major depressive episodes along with at least one hypomanic episode. Hypomania is a less intense version of mania that does not impair social or occupational function. Hypomania should not be confused with the balanced mental state experienced between depressive episodes, psychosis, or mixed episodes. Episodes of substance-induced mood disorder or of mood disorder due to a general medical condition do not count toward a diagnosis of bipolar I or bipolar II disorder. In addition, the episodes cannot be accounted for by schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder.

A major depressive episode includes a set of at least five symptoms being present over a two-week period that causes a noticeable functional impairment in an individual’s life. Symptoms include: depressed mood most of the day or nearly every day, loss of interest or pleasure in most or all activities nearly every day, change in eating habits with significant weight loss or weight gain (10% of body weight) without trying, change in sleep pattern-insomnia or hypersomnia nearly every day, fatigue nearly every day, feelings of worthlessness or inappropriate guilt, decrease in concentration, psychomotor agitation or retardation, and recurrent thoughts of death and suicide. Dysthymia is a less intense form of depression, lasting for at least two years. The symptoms of major depression and dysthymia cannot be accounted for by bereavement, i.e., the loss of a loved one, and must persist for at least two weeks or cause
marked functional impairment, thoughts of self worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation (*DSM-IV-TR, 2000*).

A manic episode consists of an abnormally and consistently elevated, extroverted, or irritable mood, lasting at least one week (or any duration if hospitalization is necessary). During the period of mood disturbance, three or more of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree. Symptoms include: inflated self-esteem or grandeur, decreased need for sleep, pressure to speak (very talkative), racing thoughts or flight of ideas, easily distracted, increased goal-oriented activity, and excessive involvement in pleasurable or dangerous activities such as buying sprees, indiscriminate sexual activity, or other risky behaviors. Symptoms of a manic episode do not meet criteria for a mixed episode, and they are severe enough to cause marked impairment in occupational and social functioning, or hospitalization (*DSM-IV-TR, 2000*).

A hypomanic episode also consists of a period of persistently elevated, extroverted, or irritable mood that is clearly different from the usual nondepressed mood. During this period of mood disturbance, three or more manic symptoms persist (four if the mood is only irritable) for at least four days and are present to a significant degree. The episode is associated with changes in functioning uncharacteristic of the individual when not symptomatic but not severe enough to cause perceptible impairment in one’s daily activities and responsibilities. It also does not necessitate hospitalization and there are no psychotic features present. The symptoms are also not due to the direct physiological effects of a substance or a general medical condition. A patient is considered cyclothymic when he/she experiences multiple episodes of hypomania and dysthymia (*DSM-IV-TR, 2000*).
DSM-IV-TR (2000) minimum criterion episode length for hypomania is four days. Some researchers have proposed changing the episode length to a shorter time period (Bauer et al., 2006). Using a daily self-reported mood ratings system, Bauer et al. looked at the impact of changing the hypomanic criterion episode length to two days. The sample included 135 bipolar I patients and 68 bipolar II patients by DSM-IV-TR criteria who recorded their mood daily. Criterion length change doubled the amount of patients with a hypomanic episode and increased the number of hypomanic episodes three-fold. By changing the criterion length of the episodes, the results suggest inadequate symptom control through the sample’s current treatment regimen. The change in hypomanic episode length has treatment implications, suggesting a need for a more stringent treatment regimen for patients continually going in and out of hypomania. Future research along the lines of this study in larger samples could indicate a need to officially change the time length of a hypomanic episode.

A bipolar patient is considered rapid cycling when he or she experiences at least four or more episodes of mania, hypomania, or major depression within a one-year time period, often switching from one polarity to the other. A patient can also experience ultra rapid cycling, which is four or more episodes in one month, and ultra-ultra rapid cycling, which is four or more changes in polarity in one day. Rapid cycling occurs in approximately ten to thirty percent of bipolar patients, with women making up about seventy percent of those patients (Papadimitriou, Calabrese, Dikeos, & Christodoulou, 2005). Rapid cycling patients often represent a population sub-set that does not easily respond adequately to standard pharmacological treatment.

Clinical diagnosis is solely based on the patient’s history. Since the primary care provider has to rely on the patient’s ability to describe symptoms and feelings, a clear-cut diagnosis is not always easy to make. Screening tools such as the Mood Disorder Questionnaire
and Bipolar Disorder Questionnaire are often utilized to help the primary care provider make a diagnosis. If the diagnosis is still unclear, referral to a psychiatrist for expert opinion and care is often made.

Making a clear and accurate diagnosis is not always easy, so Parker, Hazdi-Pavlovic, and Tully (2006) conducted a study in which a self-report questionnaire of mood “highs” was completed by 157 outpatients who presented with a major depressive episode and been clinically diagnosed as either bipolar I, bipolar II, or unipolar depression. The purpose was to distinguish true bipolar disorder from unipolar depression with elevated mood states, and to sharpen the distinction between bipolar I and bipolar II disorder. The Mood Swing Survey (MSS), a 46-item questionnaire developed to assess lifetime “highs” in bipolar patients, was used to measure and distinguish true manic or hypomanic episodes from periods of normal happiness. The survey accurately distinguished between bipolar and unipolar depressive patients with a positive predictive value of 0.95. Bipolar I and bipolar II patients answered the questionnaire similarly, possibly indicating core mood state differs little in severity between the two. This possible indication is soft, though, since the sample population had already been receiving treatment for the disorder. The survey could prove more useful in making the primary diagnosis, which in turn would be important for treatment purposes.

Initial presentation and follow-up of patients who are experiencing unipolar or bipolar depressive symptoms is critical to making the correct diagnosis and developing an effective treatment regimen. Research, such as that of Parker et al. (2006) and that of Bauer et al. (2006), indicates and reminds clinicians to fully investigate each patient’s case. Patients do not always present as written in books, and patients sometimes leave out key details unless asked the right
questions. By using the *DSM-IV-TR* and available mood questionnaires as a guide, clinicians can make the correct diagnosis and employ treatment accordingly.
Pathophysiology of Bipolar Disorder

Multiple factors play a role in both the development and severity of bipolar disorder. Factors to consider are anatomical/physiological abnormalities of specific brain structures, life events/stressors, personal coping mechanisms, and genetics/heredity. Each plays a role in one’s mood stability to a certain degree. For bipolar patients, a dysfunction in one or more of these areas can cause an abnormal mood states and life instability.

Though there are no physiological tests to identify bipolar disorder, physiologic processes among specific anatomical brain structures are known to mediate a person’s mood and feelings. These structures together are known as the limbic system. The limbic system is the center for mediating one’s emotions, sleep cycle, appetite, sexual urges, memory, and energy, all of which become abnormal in bipolar patients. It also plays a role in cognitive function, which is also impaired in bipolar patients. The limbic system includes the amygdala, hippocampus, parahippocampal gyrus, hypothalamus, thalamus, cingulate gyrus, mammilary body, nucleus accumbens, orbitalfrontal cortex, and olfactory bulb. Together, these structures work to mediate mental and physical responses to various stimuli, affecting a person’s feelings, mood, decision-making, memory, endocrine system and autonomic nervous system (Adler, DelBello, & Strakowski, 2006).

Specifically, the amygdala is involved in signaling the cerebral cortex of motivationally significant stimuli. The hippocampus is the center of long-term memory formation, with the parahippocampal gyrus (spatial memory formation) and mammilary body also playing roles in memory formation. The hypothalamus regulates the autonomic nervous system, affecting heart rate, thirst, hunger, sexual arousal, and the sleep cycle through the production and release of hormones. The cingulate gyrus also affects the autonomic nervous system, while the nucleus
accumbens is involved in reward, pleasure, and addiction. The olfactory bulb interprets sensory input through the sense of smell. The orbitalfrontal cortex is required for decision-making, and the thalamus is the great relay center to the cerebral cortex (Adler et al., 2006).

With the limbic system greatly influencing one’s response to external stimuli, abnormalities in one or more of the anatomical structures and/or signaling between the structures has been hypothesized as the primary cause of bipolar disorder. Modern imaging, such as magnetic resonance imaging (MRI) and positron emission tomography (PET), has been used to study the structures and signaling of the limbic system in patients with bipolar disorder (Monkul et al., 2006, Rosso et al., 2007). Though some imaging and biochemical studies have implicated defects in specific areas of this system, none of the defects are universal to the entire bipolar population (Adler et al., 2006). The dysfunction of the entire system as a whole is most likely of more functional importance than a single anatomical defect.

One study compared the thalamus volume of 16 bipolar adolescents to that of 21 healthy adolescents via MRI. Thalamic gray matter volume was measured in the individuals of each group. The findings suggested there was no significant difference in thalamus size between adolescents with bipolar disorder and the healthy comparison subjects. One shortcoming of the study was the small sample size. A larger sample size may have revealed a more significant difference in thalamus size or a constant small difference in size (Monkul et al., 2006). Thalamic volume measurements of patients whose bipolar illness started later in life may yield different results, therefore testing across different age groups with bipolar disorder may yield interesting results. It would also be interesting to conduct a longitudinal study, measuring and comparing the thalamic volumes of a bipolar group and a healthy control group over time. If a change in
thalamic volume would show to be statistically significant among those in the bipolar group, it
could indicate the source of the disorder or at least a potential target for pharmacological therapy.

Other imaging studies have also measured the volume and neural responses of other
important limbic structures, especially that of the amygdala. Rosso et al. (2007) indicated a
deficit in amygdala volume and a reduced volume of white matter in the frontal and temporal
cerebral cortex in first-episode bipolar patients with psychotic features. If these findings are true
throughout this population sub-set, early screening of those who are at high risk for developing
bipolar disorder could theoretically be done. Early detection and treatment initiation in those
with a positive screening could prove to be very important in decreasing the severity and lifetime
effects of the disorder. Although the amygdala has been implicated in playing an important
causal role in bipolar disorder, a definitive structural abnormality has not been identifiable
throughout the entire bipolar population thus far (Rosso et al.).

Abnormalities in biochemical pathways of the central nervous system, especially that of
the limbic structures, have been identified in causing depression and other mood disorders.
These pathways involve the chemicals glutamate, gama-aminobutyric acid, histamine, serotonin,
dopamine, and norepinephrine, each playing different roles in neuronal signaling (Shastry,
2005). While antidepressant drugs have been formulated to correct the abnormal concentrations
of serotonin and norepinephrine present in depression, specific drugs for the treatment of bipolar
disorder have not been easy to develop since the specific physiologic cause of the disorder has
not been determined. The most effective drugs used to treat bipolar disorder have been
discovered on a trial-and-error type basis, and it is still not exactly known how or why many of
them work in treating the disorder. Researchers now believe mood-stabilizing drugs work by
modifying signaling cascades involved in neural plasticity. Four of the major proteins involved
in these signaling cascades are brain-derived neurotrophic factor (BDNF), extracellular signal-regulated kinase (ERK), glycogen synthase kinase (GSK)-3, and Bcl-2. The interaction of these proteins with others along signaling cascades involved in mediating neural plasticity goes beyond the scope of this paper, but they do offer promise as potential targets for further research and pharmacological treatments (Shaltiel, Chen, & Manji, 2007).

Genetic inheritability also plays a role in the development of bipolar disorder. First-degree relatives of those with bipolar disorder are six times more likely to develop bipolar disorder than the general population (Klaning et al., 2004). Also, monozygotic twins show a concordance rate of nearly eighty percent as compared to nearly twenty percent in dizygotic twins. Genomic studies have identified many genes involved in contributing to the disorder, but so far have been unable to identify a specific bipolar susceptibility gene/s that is universal to the bipolar population (Shastry, 2005). Though genetic inheritance plays a strong role in the development of the disorder, it may not be the deciding factor in many cases (Klaning et al.).

Studies have also shown people with certain personality traits and coping mechanisms to be prone to developing mood disorders. Blatt, Quinlan, Chevron, McDonald, and Zuroff (1982) described two separate personality types more prone to developing depressive symptoms secondary to negative life events. This became known as the ‘events congruency theory’. One of the personality types is dependent on others and he/she bases his/her self worth on social relationships. Blatt et al. called it ‘dependent’. They found this personality type was more prone to depression when hurt or rejected by close relationships. The second personality type bases his/her self worth around personal success. Blatt et al. called it ‘self-critical’. This personality group tends to be very critical of one’s self and set very high standards, therefore being more prone to depression when failing to meet personal or professional goals. These findings
consequently brought up the question of whether the ‘events congruency theory’ could be applied to bipolar disorder.

Francis-Raniere et al. (2006) put together a study to test the ‘events congruency theory’ among individuals diagnosed as bipolar II, cyclothymic, or bipolar disorder not otherwise specified (NOS). The subjects were separated into the ‘dependent’ personality group and the ‘self-critical’ personality group. The study was to determine if negative life events sensitive to the personality type correlated with greater depressive symptoms and if positive life events sensitive to the personality type would produce greater hypomantic symptoms. Over a four-month time period, 106 participants filled out questionnaires and had short interviews pertaining to his/her mood and life events. Participants had a previous diagnosis of either bipolar II (n=67) or cyclothymia/bipolar NOS (n=39). The number of depressive and hypomantic episodes, the severity of symptoms, the duration of symptoms, and life event occurring just prior to each episode was recorded. Results showed those with the ‘self-critical’ personality style experienced statistically significant increases in hypomantic symptoms secondary to personality congruent positive life events (p = 0.009), as well as statistically significant increases in depressive symptoms secondary to personality congruent negative life events (p = 0.03). These results support the ‘events congruency theory’ in bipolar patients with the ‘self-critical’ personality type. The ‘dependent’ personality type showed significant increases in depressive symptoms secondary to both personality congruent and non-congruent negative life events (p = 0.004, and p < 0.02). These results do not support the ‘events congruency theory’ in the ‘dependent’ personality type. What is not clear from the study is whether the mood disorder started first and dictated response style, if response styles dictated change in mood, or if the two interact equally to induce manic/hypomantic and depressive symptoms. Clinically, it may be useful for a
clinician to be able to identify a patient’s personality type so that the patient can be counseled on how life events and his/her response to those events can affect symptom severity.

The relationship between depressive and hypomanic personality traits with personal response styles have also been examined. Using the Beck Depression Inventory (BDI), Eckblad and Chapman’s Hypomanic Personality Scale, and a revised version of Nolen-Hoeksema’s Response Styles Questionnaire (RSQ), response styles secondary to depression or hypomania were analyzed. Results indicated those with hypomanic traits were more likely to get involved in dangerous activities and respond to depressive situations by doing distraction activities that are pleasurable, and that a ruminative response style was associated with depressive symptoms. The ruminative response style was more closely associated with depressive symptoms, accounting for 40 percent of the variance, while response styles secondary to hypomanic traits only accounted for 17 percent of the variance. This proposes that other processes not measured by this study contribute to the development of hypomanic traits (Thomas, & Bentall, 2002). One’s personality traits and response styles to life events can put him/her at a higher risk of developing an abnormal mood state. Those with bipolar disorder consistently respond to outside stimuli in abnormal ways. By identifying a bipolar patient’s response style, a clinician can work on changing the patient’s response style as a part of improving treatment.

Understanding and recognizing events that set off depressive or manic/hypomanic symptoms in individuals can be very helpful in devising treatment strategies. Learning how to properly respond to and manage trigger events could be key to handling breakthrough symptoms. Also, developing accurate screening tools based on personality traits, coping mechanisms, and response styles could prove important in the early detection of adolescents and young adults at high risk of developing bipolar disorder, reducing the time to diagnosis and treatment.
New research has given clinicians some insight into the pathophysiology of bipolar disorder, but it is still not well understood. It involves a complex and intricate balance of many factors and variables. Genetics, specific brain structures and networks, chemical signaling, and response styles/coping mechanisms to life events are all believed to play important roles in the development of bipolar disorder. With so many factors on hand, no research to date has been able to pinpoint the explicit physiologic process of bipolar disorder. With new advances in technology and the study of the human genome, researchers may one day be able to implicate specific genomic or physiologic actions that can be targeted by treatments.
Treatment of Bipolar Disorder: Pharmacologic Options

Treatment of bipolar disorder is a life-long process. Depending on the type and severity of symptoms, treatment may be implemented by a primary care provider, psychologist, psychiatrist, or a combination of providers. Just as the etiology of the disorder is multifaceted, treating bipolar disorder may also require a multifaceted approach. The mainstay of treatment is pharmacological therapy, often involving more than one drug.

Mono-Drug Treatment

Four drugs have been approved by the United States Food and Drug Administration (US FDA) for maintenance treatment of bipolar disorder: lithium carbonate, lamotrigine (Lamictal), olanzapine (Zyprexa), and aripiprazole (Abilify). Each of these drugs is considered a first-line mood-stabilizer: a clinician’s first choice in attempting to achieve mood stabilization in a bipolar patient. While not yet approved by the FDA for maintenance treatment, divalproex (Depakote) and carbamazepine (Tegretol) are commonly used as both short-term and long-term treatments for bipolar disorder. Lithium carbonate is the oldest of the mood stabilizers, with the anticonvulsant drug lamotrigine, and atypical antipsychotics olanzapine and aripiprazole gaining approval and popularity in recent years (Nasrallah, Ketter, & Kalali, 2006). Patients often require multi-drug treatment with the use of multiple mood stabilizing drugs.

Lithium Carbonate

Lithium carbonate was established as an anti-manic agent in the late 1940’s, but it was not approved for use in the United States until 1970. It has proven to be a valuable mood-stabilizing agent in bipolar individuals. Lithium’s specific mechanism of action in producing
mood-stabilization is still unknown, although it is believed lithium affects the concentration and activity of important neurotransmitters, second-messengers, and other intra-cellular processes important in dictating mood. Lithium is mostly absorbed through the gastrointestinal tract and almost completely eliminated by the kidneys (Brunton, Lazo, & Parker, 2007).

Lithium is also known for its narrow therapeutic range, adverse side effects, and the psychotropic effects of sedation and mental dulling. Common side effects include increased thirst, polyuria, abdominal discomfort, nausea, diarrhea, muscle weakness, fatigue, impaired memory, and weight gain. As plasma levels of lithium go above the therapeutic range, symptoms of lithium intoxication set in. Symptoms of mild intoxication include nausea, diarrhea, blurred vision, polyuria, dizziness, fine resting tremor, increased muscle weakness, and drowsiness. As intoxication increases, one can experience ataxia, decreased consciousness, seizures, coma, and even death. Long-term lithium treatment can also cause hypothyroidism. Due to the narrow therapeutic window and array of side effects, it is important to monitor blood plasma levels on a regular basis and make adjustments to the medication dosage as needed (Brunton et al., 2007).

Lithium carbonate is used clinically for bipolar mania, depression, and mixed states. It is used both as an acute treatment for mania and as a maintenance therapy. Geddes et al. (2004) conducted a meta-analysis of five randomized controlled trials analyzing manic, mixed, and depressive relapses of patients on lithium versus placebo. Together the trials included 770 participants who were assessed over a one-to two-year time period. Lithium showed superiority over placebo in preventing manic relapse on average by 40%. It showed a lower effect on preventing depressive relapse, a 22% advantage over placebo. While lithium has shown effectiveness in preventing manic and to a lesser extent depressive relapses when compared to
placebo, studies comparing its effectiveness and tolerability to other maintenance drugs for bipolar disorder are of great importance clinically.

A major advantage for the use of lithium in bipolar patients is the associated lower risk of suicide. Gonzalez-Pinto et al. (2006) looked at 72 bipolar I patients on lithium therapy over a 10-year period, identifying suicide attempts and analyzing the adherence to drug therapy with the associated suicide attempts. Those with high adherence to lithium therapy over the 10 years showed a significantly lower amount of suicide attempts, suggesting adherence to the medication is an important factor in decreasing suicide risk. The sub-set of patients who demonstrated higher numbers of suicide attempts was less adherent to the drug regimen. Further analysis showed suicidal risk was associated with previous suicidal tendencies, younger age, more depressive episodes, and less treatment adherence (Gonzalez-Pinto et al.). Decreased suicidal risk with high adherence to lithium treatment is important, but more interestingly, comparing suicidal risk in patients with high adherence to lithium therapy to patients with high adherence to a different mood stabilizing drug could be of more importance clinically.

Lithium carbonate is the oldest of the mood-stabilizing agents and can be used clinically to treat bipolar mania, bipolar depression, and mixed states. While lithium can be very effective in achieving mood-stabilization in many patients and decrease suicidal risk, its therapeutic range is very narrow (blood plasma levels of lithium should be checked regularly), and it can cause many adverse side effects. Most adverse side effects are minor but can become bothersome for some patients. Lithium can also be used in combination with other mood-stabilizing drugs to achieve increased efficacy in symptom control.
Lamotrigine

Lamotrigine is an anti-convulsant drug with mood-stabilizing effects. It is used clinically to treat bipolar depression, mixed episodes, and rapid cycling. It can be used as maintenance therapy and as adjunctive therapy to another mood-stabilizer for uncontrolled depressive symptoms. As a maintenance therapy, lamotrigine has shown to be effective in controlling bipolar depressive symptoms (Muzina, Elhaj, Gajwani, Gao, & Calabrese, 2005). This has also been shown in an 18-month placebo-controlled trial conducted by Calabrese et al. (2003). Bipolar I patients (n=463) were randomly assigned to lamotrigine (n=221), lithium (n=121), and placebo (n=121). Efficacy was measured by time to recurrence of manic, hypomanic, depressed, or mixed episode. While lamotrigine and lithium showed almost equal superiority to placebo in time to recurrence of any of the mood episodes, lamotrigine outperformed lithium and placebo in time to recurrence of a depressive episode (p = 0.047), and lithium outperformed lamotrigine and placebo in time to recurrence of manic/hypomanic symptoms (p = 0.026) (Calabrese et al.).

Olanzapine

Olanzapine is an atypical antipsychotic drug that can be applied for maintenance therapy of bipolar disorder. Olanzapine has shown advantages over divalproex in long-term symptom control and in time to remission of an acute manic episode. Mean time to remission with olanzapine has shown to be 14 days, while mean time to remission with divalproex has shown to be 62 days (p = 0.05) (Tohen et al., 2003). Olanzapine has also showed effective results as monotherapy in prolonging time to episode relapse. A 47-week placebo-controlled, double-blind study indicated a mean time to episode relapse in bipolar I patients to be 174 days as compared
to 22 by placebo \( (p < 0.001) \) (Tohen et al., 2006). A longer time between manic episodes is very valuable to patients.

**Aripiprazole**

Aripiprazole is an antipsychotic drug with mood-stabilizing properties. A 100-week double-blind study conducted by Keck et al. (2007) determined aripiprazole to be effective in preventing relapse of manic symptoms in bipolar I patients who had experienced a recent manic or mixed episode. First, the patients were given open-label aripiprazole, either 15 or 30 mg/day for 6 to 18 weeks. Patients achieving stabilization \( (n=161) \), as depicted by a Young Mania Rating Scale (YMRS) score of 10 or less and Montgomery-Asberg Depression Rating Scale (MADRS) score of 13 or less for 6 consecutive weeks, were then assigned randomly to an aripiprazole \( (n=78) \) or placebo group \( (n=83) \) for 26 weeks. Patients who completed the 26 weeks \( (n=66) \) continued for 74 more weeks. Keck et al. monitored the patients for relapse (manic, mixed, or depressed), efficacy, and tolerability. The study indicated aripiprazole was superior to placebo in delaying manic relapse \( (p = 0.005) \), but did not show statistical significance in delaying depressive relapse \( (p = 0.602) \). Adverse side effects were minor and included tremor, akathisia, dry mouth, hypertension, weight gain, vaginitis, abnormal thinking, pharyngitis, and flu syndrome. Data from this study clearly shows that aripiprazole can provide relief from manic relapse in bipolar patients. As this study used a refined cohort to gather data, randomized trials are needed to clarify the efficacy of aripiprazole in preventing manic relapse.

**Divalproex and Carbamazepine**

While the anticonvulsant drugs divalproex and carbamazepine have been approved for acute manic or mixed episodes, they have not been approved for long-term maintenance therapy.
Carbamazepine has yet to gain FDA approval as maintenance therapy due to lack of large randomized trials and a high discontinuation rate among trial subjects. Their mood-stabilizing properties have led to off-label use for long-term maintenance treatment (Nasrallah et al., 2006). Continued research will determine its potential future approval by the US FDA as maintenance monotherapy.

Divalproex has had limited study as monotherapy in bipolar depressed patients. A pilot study by Winsberg, DeGolia, Strong, and Ketter (2001) has indicated positive effects in treating bipolar depression with divalproex. Twelve of nineteen patients adequately responded to divalproex monotherapy over the twelve-week trial period, which was measured as > 50% reduction in the Hamilton Depression ratings. The medication was well tolerated by the patients over the trial period as well. A similar study by Davis, Bartolucci, and Petty (2005) also examined divalproex’s efficacy in bipolar depression. Davis et al. conducted a double-blind, placebo-controlled, randomized study with bipolar depressed patients (n=25) over an 8-week period. Outcome measure for depression was the Hamilton Rating Scale for Depression. Patients receiving divalproex (n=13) showed significant improvement in depressive symptoms as compared to the patients receiving the placebo (n=12) (p = 0.0002). These studies are solid groundwork for larger double-blind placebo-controlled studies.

An earlier randomized study by Bowden et al. (2000) produced inconclusive results on the efficacy of divalproex as a long-term maintenance drug for bipolar disorder. Results showed no significant difference in episode relapse rate as compared to lithium and placebo (p = 0.26), but did show a decrease in depressive symptoms among the patients receiving divalproex.

Carbamazepine has been shown by Okuma et al. (1990) to be as effective as lithium in controlling manic states. During a four-week time period, 105 bipolar patients were given either
carbamazepine or lithium to combat manic symptoms. The final global improvement rate revealed similar results between the two groups. The percentage of patients taking carbamazepine with at least a moderate improvement in manic symptoms was 62% as compared to 59% of patients taking lithium.

A meta-analysis which included ten double-blind, randomized studies comparing carbamazepine to lithium in relapse prevention, showed similar results. The group receiving carbamazepine did not have a significantly statistical advantage over the lithium group on time to relapse. While carbamazepine did not show a statistically significant advantage over lithium, it did show it was just as effective as lithium for mood-stabilization (Davis, Janicak, and Hogan 1999).

Mono-drug therapy is always a good start in treating patients with bipolar disorder. For some patients, it is all they will need to achieve mood-stabilization. Lithium has been then the standard for many years, but clinicians now have more drug options. Continued research of lamotrigine, olanzapine, aripiprazole, divalproex, and carbamazepine as long-term maintenance therapy will influence future treatment regimens for bipolar disorder. While mono-drug therapy is enough to attain a stable mood in a lot of bipolar patients, many still require further drug therapy.

Combination Drug Treatment

Many bipolar patients require more than one drug for long-term therapy due to breakthrough/residual episodes/symptoms. Depending on the symptoms reported by the patient, the clinician employs his or her judgment in selecting adjunctive drugs for further mood stabilization. Typical adjunctive pharmacological therapy consists of anticonvulsants, atypical
antipsychotics, antidepressants, or benzodiazepines added to a first-line mood stabilizer. With manic and hypomanic relapses being so common (Perry, Tarrier, Morriss, McCarthy, & Limb, 1999), it is essential for clinicians to understand and choose effective drug options for quelling breakthrough symptoms.

Breakthrough manic or hypomanic episodes are common among those with bipolar disorder despite what is considered adequate mono-drug therapy with lithium. Adding divalproex or olanzapine to the treatment regimen can be effective in calming the manic or hypomanic breakthrough symptoms. A study by Maina et al. (2007) showed significant improvement in breakthrough symptoms over an eight-week period in groups that added either divalproex or olanzapine to the maintenance lithium therapy (p < 0.001). Though both groups showed significant improvement over the entire 8-week study, the olanzapine group showed significant improvement over the divalproex group during weeks one through four (p < 0.05).

With manic and hypomanic relapses being so common, it is essential for clinicians to understand and choose effective drug options for quelling breakthrough symptoms.

Other adjunctive drug treatments to first-line mood stabilizers have been of discussion in recent years as well. Two such drugs, lamotrigine (anticonvulsant) and citalopram (Celexa-antidepressant), have been compared as to their effectiveness in further controlling bipolar symptoms in patients already on a mood-stabilizing drug. Both drugs showed to provide significant improvement in depressive symptoms (citalopram, p = 0.002; lamotrigine, p = 0.001). While antidepressants are not considered appropriate treatment due to the risk of switching the patient into a manic episode, this study suggests antidepressants may be efficacious as adjunctive therapy to a first-line mood stabilizer in controlling depressive symptoms. As this was a pilot trial with a small sample size (n=20), larger randomized, placebo-controlled trials are needed to
determine if improvements seen by patients in this study are statistically significant (Schaffer, Zuker, & Levitt, 2006). Also, though both drugs may be efficacious as adjunctive treatment, clinical judgment and experience must be used to choose the correct medication for the patient.

The effect of second-generation antidepressants, such as citalopram and fluoxetine, on manic and depressive-related doctor office visits for bipolar patients has shown good outcomes in some studies. One such study showed a decrease in depressive related visits without an increase in manic related visits over a one-year period. A retrospective study was conducted using a national managed-care claims database, identifying patients with bipolar disorder who received a new antidepressant prescription. The patients were then separated into three categories: second-generation antidepressant (AD) monotherapy (contraindicated in bipolar disorder), mood stabilizer (MS) monotherapy, and antidepressant-mood stabilizer (AD-MS) combination therapy. The number of office visits secondary to depressive or manic symptoms for each group over a one-year time period was then calculated. Results showed no statistically significant increase in manic related visits for the AD monotherapy and AD-MS combination group when compared to the MS monotherapy group. Also, AD monotherapy and AD-MS combination therapy showed a decrease in the number of depression related visits (Fu, Liu, Christensen, & Hansen, 2007). If long-term clinical trials show safe and positive outcomes of antidepressant use in patients with bipolar disorder, antidepressants may play a larger role in effective drug treatment of bipolar disorder.

Quetiapine (Seroquel), an anti-psychotic drug, has been studied to see how well it controls manic episodes in bipolar I patients. Studies by Buckley, Paulsson, and Brecher (2007); Ketter, Jones, and Paulsson (2007); McIntyre, Konarski, Jones, and Paulsson (2007); and Sussman, Mullen, Paulsson, and Vagero (2007) looked at the efficacy of quetiapine in
controlling manic symptoms. Each examined the effects of quetiapine by itself and in combination with lithium or divalproex as compared to placebo.

Both agitation and aggression are symptoms associated with bipolar mania and can cause serious harm to the patient and others. Buckley et al. (2007) studied how well quetiapine controlled these symptoms in patients with bipolar mania. They looked at its efficacy as monotherapy versus a placebo and as adjunctive therapy to lithium or divalproex versus placebo. The Positive and Negative Syndrome Scale (PANSS) Activation subscale, PANSS Supplemental Aggression Risk subscale, and items relevant to agitation form the Young Mania Rating Scale (YMRS) were used to assess patient symptoms throughout the trial periods. The trials showed quetiapine monotherapy (at high dosage) to be significantly more effective than placebo in controlling agitation and aggression (p < 0.001). Adjunctive quetiapine therapy to lithium or divalproex showed a decrease in agitation and aggression scores when compared to the placebo group, but it failed to be significant statistically (p = 0.637).

Similarly, a study by McIntyre et al. (2007) examined quetiapine’s efficacy in improving all bipolar mania symptoms. Again, quetiapine was used as either monotherapy or as combination therapy with lithium or divalproex. The YMRS and PANSS were applied to assess symptom control over the 84-day trial period. Quetiapine again showed efficacy in controlling manic symptoms. Quetiapine as monotherapy showed significant improvement in YMRS scores after just four days (p = 0.021), as well as at day 21 (p < 0.001) and day 84 (p < 0.001). The addition of quetiapine to lithium or divalproex produced significant improvement in YMRS scores after just one week (p < 0.05), and continued to show improvement at day 21 (p = 0.014). Quetiapine combination therapy also showed significant improvement in four of eleven categories of the YMRS as compared to lithium/divalproex monotherapy. Quetiapine as
monotherapy or in combination therapy also showed great improvements in the PANSS scores during the trial period (monotherapy, \( p < 0.001 \); combination, \( p < 0.05 \)).

Studies by Ketter et al. (2007) and Sussman et al. (2007) showed similar results with the use of quetiapine in acute manic situations. Each showed a statistically significant rate of remission among the sample taking quetiapine as compared to placebo. Ketter et al. conducted a 12-week double-blind, placebo-controlled study examining the efficacy of quetiapine versus placebo in quelling an acute manic episode. The YMRS and MADRS were applied in measuring response/remission among participants (\( n=403 \)). At days 21 and 84 of the study, patients receiving quetiapine monotherapy (\( n=208 \)) showed significant response as compared to placebo (day 21, \( p < 0.001 \); day 84, \( p < 0.001 \)). Sussman et al. analyzed results from one 3-week and one 6-week double-blind study of patients who were hospitalized with bipolar mania. Patients received quetiapine plus lithium/divalproex or placebo plus lithium/divalproex. Response/remission rates were calculated using the YMRS and MADRS. At day 21 of the pooled data, quetiapine plus lithium/divalproex showed a significantly higher rate of response/remission than placebo plus lithium/divalproex (\( p = 0.003 \)). At day 42 of the 6-week study, a significantly higher rate of response/remission was again seen in the quetiapine plus lithium/divalproex group as compared to placebo plus lithium/divalproex (\( p < 0.05 \)). The results of these studies clearly show quetiapine as being efficacious in quelling manic symptoms as both monotherapy and adjunctive therapy.

If quetiapine is able to settle down manic symptoms, can it help to improve depressive symptoms as well? This was the focus of a study by Vieta et al. (2007), in which the effects of Quetiapine monotherapy in bipolar I and bipolar II patients who suffered from a rapid-cycling form of the disorder and was now experiencing an episode of major depression was studied. A
study involving 108 subjects, 31 receiving 600 mg/day of quetiapine, 42 receiving 300 mg/day, and 35 receiving placebo was conducted over an eight week period. The MADRS was the primary tool applied to monitor the severity of the patients’ depressive symptoms. Efficacy was measured by the average change in MADRS score from baseline to week eight. Change in MADRS score of greater than fifty percent was considered an adequate response. Results showed both groups taking quetiapine made significant improvement in average MADRS scores compared to placebo (p < 0.001). Though quetiapine has proven efficacious quelling manic and depressive symptoms in trials, it is of no use clinically if its side effects are not tolerable to patients.

Adler, Fleck, Brecher, and Strakowski (2007) examined the tolerability and safety of quetiapine in bipolar patients over a twelve-week trial period. It was a double blind, placebo-controlled study analyzing side effects experienced among patients on quetiapine monotherapy and in combination with lithium or divalproex. The Simpson Angus Scale (SAS) and Barnes Akathisia Rating Scale (BARS) were used, as well as reports of adverse events, in determining type and severity of side effects experienced throughout the trials. The most common side effects reported were somnolence, dry mouth, weight gain, dizziness, asthenia, pharyngitis, and postural hypotension. Discontinuation from the trial secondary to quetiapine treatment was not significantly different from the placebo groups, nor was the mean change in scores from the SAS and BARS significantly different between the quetiapine and placebo groups. Though the quetiapine groups gained almost two kilograms of weight on average, it was neither clinically significant nor significant enough for any patients to drop the trial secondary to weight gain.

Safety and tolerability has also been of secondary concern in other studies. In that done by Vieta et al. (2007), 15 out of 73 patients who received quetiapine dropped from the trial due to adverse
effects. The psychological benefits of quetiapine treatment in bipolar patients experiencing an acute manic or depressive episode most likely outweigh the risks associated with possible adverse side effects.

Another antipsychotic being studied for its mood stabilizing effects is aripiprazole (Abilify). To examine its antidepressant effects in bipolar disorder, McElroy et al. (2007) conducted a pilot study of 31 bipolar patients with clinically significant depressive symptoms without manic symptoms and who have not adequately responded to treatment with at least one mood stabilizer. It was an open-label, 8-week trial with a group of 13 patients receiving aripiprazole as monotherapy and a group of 18 receiving aripiprazole as adjunctive therapy to an initial mood stabilizer. The MADRS was used to assess depressive symptoms, while the Clinical Global Impression Scale Modified for Bipolar Illness (CGI-BP) was used to assess the degree of improvement in both depressive symptoms and overall illness. The YMRS was used to assess manic symptoms. While both groups reported significant improvement on the MADRS, CGI-BP, and no change on the YMRS, only 17 of the 31 patients completed the 8-week trial. The other 14 dropped from the trial secondary either to side effects, mood worsening, or no improvement. Side effects reported were bothersome but not life threatening. Side effects included: akathisia, insomnia, nausea, increased appetite, headache, tremor, anxiety, difficulty with concentration, fatigue, blurred vision, increased urinary frequency, muscle soreness, decreased appetite, and manic symptoms. Mean dosage of those who dropped the trial prematurely was 12.2 mg/day, while the mean dosage of those who completed the study was 15.8 mg/day. The use of aripiprazole in larger samples of bipolar depressed patients is needed to truly assess its safety and tolerability. Clinically, using aripiprazole may be of significant value
with some bipolar patients since the potential mental improvement is of greater significance than
the potential side effects, which can easily be monitored.

Mood stabilization in bipolar patients often includes multiple drug treatments. The use of
lithium carbonate, anticonvulsants, atypical antipsychotics, antidepressants, and benzodiazepines
alone or in combination provides relief from bipolar symptoms in most patients. Though most
bipolar patients receive great relief through polypharmacy, many still are still symptomatic.
Non-pharmacological therapies are becoming increasingly popular options in dealing with
breakthrough/residual symptoms.
Treatment of Bipolar Disorder: Non-Pharmacologic Options

While treatment of bipolar disorder tends to focus on pharmacological remedies, non-pharmacological treatments in conjunction with pharmacological treatments are showing to be of importance in improving overall treatment effectiveness and quality of life for many bipolar patients. Just as there are multiple drugs for treating bipolar disorder, there are multiple non-pharmacological treatments available. There is no one specific type of non-pharmacological treatment for all bipolar patients. The type of non-pharmacological treatment employed depends upon the patient and clinician involved.

Behavioral/Psychotherapy

One type of non-pharmacological treatment is psychoeducation, which addresses issues in a group therapy type setting. Main goals are to get bipolar patients to understand their condition, understand the importance of sticking to treatment regimens, and understand they are not alone. These psychological techniques include psychoeducation, cognitive behavioral therapy (CBT), interpersonal social rhythm therapy (IPSRT), and family focused therapy (FFT).

A pilot study by Goldner-Vukov, Moore, and Cupina (2007) looked at the effects of psychoeducation in a small group of ten bipolar patients over a two-year period. The outcomes showed to be very beneficial for all ten participants. No patients experienced any major relapses during the trial period, adherence to pharmacotherapy was one hundred percent, and each patient reported significant improvements in family and social function. Though proving very beneficial for those ten participants, many more trials of this type of small group therapy need to be done before truly knowing if most bipolar patients would also receive the same benefits.
Other patients may get more benefit out of a more focused intensive psychotherapy than group intervention. Miklowitz et al. (2007) examined the difference in recovery between a group of bipolar outpatients receiving intense psychotherapy and those receiving collaborative care over a one-year time period. Those receiving intense psychotherapy were separated into three types of psychotherapy: family-focused therapy, interpersonal and social rhythm therapy, and cognitive behavioral therapy. The collaborative care group focused on brief psychoeducational intervention. At year’s end, a significantly higher recovery rate was seen in the intensive psychotherapy group, as well as a faster recovery time (p = 0.01). The rate of recovery between the intensive psychotherapy subgroups was not statistically significant.

Family-focused therapy (FFT) has been shown to be beneficial in other studies as well. FFT has shown to lower the rates of relapse and hospitalizations in bipolar patients. In a study by Rea et al. (2003), patients who received FFT in conjunction with mood stabilizer drug therapy had a considerably lower rate (28%) of relapse during the twelve-month follow-up period than patients who received standard drug and individual psychiatric treatment (60%). Also, the FFT group showed a significantly lower rate of hospitalization (12%) than the individually based treatment (60%) during the follow-period. Both groups received 21 sessions of therapy which focused on psychoeducation, problem-solving, supportive care, and enhanced communication, with the addition of at least one family member in the FFT group being the primary difference. The results indicate the education, increased problem-solving ability, and enhanced communication skills of family members of bipolar patients help greatly in controlling bipolar symptoms (Rea et al.).

Cognitive-behavioral therapy (CBT) has been shown to produce positive results in decreasing depressive symptoms in unipolar depressed (UP) patients by changing personal
behaviors and thoughts of one’s self. It has also been demonstrated that individuals with UP and bipolar disorder (BP) exhibit similar ratings of self-esteem, dysfunctional attitudes, and personality style (Scott & Pope, 2003). Therefore, CBT represents a form of therapy that may also provide great relief in bipolar patients. CBT also showed positive results in a pilot study conducted by Feeny et al. (2006), which included bipolar adolescents who were already on standard drug therapy. Though a small sample size, each of the eight bipolar adolescents who received CBT weekly for two months scored better on the YMRS and General Behavioral Inventory (GBI) than the eight bipolar adolescents who only received drug therapy. It was determined that not only was the CBT beneficial, but it was also financially feasible for the participants. As this was a pilot study, larger studies looking at both efficacy and financial feasibility of CBT compared to other forms of therapy are needed. Also, the role of adjunctive CBT in decreasing the number of relapses in the bipolar patient is of interest.

A larger study by Lam, Hayward, Watkins, Wright, & Sham (2005) showed similar results in adults, addressing the problem of relapse in bipolar patients. In a randomized controlled trial, 103 bipolar patients were separated into a cognitive therapy plus drug therapy group or drug therapy only group. The cognitive therapy group had therapy sessions for the first 6 months of the study. After one year’s time, the cognitive therapy group showed a lower rate of relapse than the medication only group. Over the next 18 months there was not much difference in relapse rate between the two groups, though the cognitive therapy group routinely performed better on mood ratings, social functioning, coping with bipolar prodromes, and dysfunctional goal attainment. This indicates more therapy sessions beyond the 6 months received could be beneficial. Taking into account the entire 30 month time period, the cognitive group did show a significantly lower relapse rate (bipolar episode, p < 0.02), especially in depressive episodes (p <
This shows cognitive therapy could be very beneficial clinically in bipolar patients who predominantly suffer from depressive symptoms.

Lam, McCrone, Wright, & Kerr (2005) looked at the cost-effectiveness of CBT. They determined the cost of cognitive therapy to have offset costs occurred during the increased number of inpatient stays by the group receiving only medication. Also, if worth is applied to the extra bipolar-free days seen by the cognitive therapy group, it actually costs less than standard drug treatment alone. Therefore, the addition of cognitive therapy to prevent relapses in bipolar patients is a very practical and financially feasible choice.

In recent years psychological therapy as adjunctive treatment in bipolar disorder has been explored. Nine randomized controlled studies that employed these techniques as adjunctive therapy (5 CBT, 1 FFT, 1 IPSRT, 2 psychoeducation) were analyzed in a meta-analysis to determine relapse rates in bipolar individuals over a two-year time span. The results showed a significant decrease in relapse rate among bipolar patients receiving one of these forms of psychological treatment along with normal pharmacological care (p = 0.001). The differences seen between the groups did not vary significantly, suggesting the type of psychological intervention may not matter much in reducing the amount of bipolar relapses. What may be of more importance is clinical judgment in placing patients into a type of psychological care based on the patients’ needs and placing them early in the disease course (Scott, Colom, & Vieta, 2007).

Physical Activity

Physical activity, a simple and low-cost type of adjunctive therapy is also being explored for its possible positive effects in bipolar patients. Exercise has previously been documented in
improving anxiety and depression in clinical trials (Dunn et al., 2005). Depression can play a large role in bipolar patients, but anxiety disorders are also seen in a large percentage of bipolar patients. Simon et al. (2004) reported a lifetime prevalence rate of anxiety disorder in bipolar patients at roughly 51%. They also indicated that comorbid anxiety might increase the severity of bipolar symptoms in patients, reducing function quality of life, and most importantly increasing the chances of suicide.

Dunn et al. (2005) conducted a 12-week randomized trial studying the effects of exercise on improving symptoms in a sample of patients diagnosed with mild to moderate major depression. Using the Hamilton Rating Scale for Depression (HAM-D), depressive symptoms were assessed in five groups (n=80) over a twelve-week time period. Four of the groups took part in aerobic exercise programs of varying degree, while the fifth group acted as the placebo and only took part in flexibility exercise. The two groups who participated in the more rigorous exercise programs reported a significantly larger reduction in depressive symptoms, as indicated by a mean 47% reduction (p = 0.04, p = 0.03) in score from baseline on the HAM-D. Each of the other exercise groups also reported a reduction in score on the HAM-D after 12 weeks (p = 0.006, p = 0.02).

Another reason to explore exercise’s positive effects in bipolar patients is the large amount of bipolar patients who are overweight. Fagiolini et al. (2005) conducted a research study looking at the percentage of bipolar patients with metabolic syndrome, as defined by the National Cholesterol Education Program Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol (NCEP, ATP III). Sample included 171 men and women diagnosed with bipolar I, bipolar II, or bipolar NOS. While 30% of the sample met criteria for metabolic syndrome, 74% were either overweight or obese. These subgroups would definitely
benefit from a regular exercise program whether it directly affected their bipolar symptoms or not.

With exercise positively benefiting the unipolar aspects of the bipolar illness, exploring its possible use in bipolar patients makes sense. So Ng, Dodd, and Berk (2007) retrospectively looked at admissions to a private psychiatric unit of patients with the diagnosis of bipolar disorder over a two-month time period. During that time period patients were given the option to participate in a walking group with nurses. All patients were assessed by the clinician-rated Clinical Global Impression Severity (CGI-S) and Clinical Global Impression Improvement (CGI-I) scales, as well as a self-reported Depression Anxiety Stress Scales (DASS) upon admission and discharge from the psychiatric unit. The scores of the scales were then compared to each other based on those who were regular participants and those who were not. Differences seen in the CGI scales were nonsignificant upon discharge, but the self-reported DASS scores for the participating group showed significant improvement over the non-participating group (p = 0.005), thus showing a major decrease in depression, anxiety, and stress. A major downfall of this study was that there was not a direct measure for manic symptoms. Also, the amount of walking and speed of walking differed from patient to patient, based on his or her physical ability, so there was no controlled measure to the amount of exercise each of the participating patients had. Since the retrospective study did show positive outcomes in three major areas that affect the severity of the bipolar illness, large randomized studies are warranted to analyze the affects of regular exercise as adjunctive therapy in bipolar disorder.
Light Therapy and Sleep Deprivation

Light therapy (LT) is another interesting form of therapy that has been studied in conjunction with total sleep deprivation (TSD) to relieve depressive symptoms. While it has shown favorable results in unipolar depression and seasonal depression, its use for bipolar depressed patients has yet to be determined. LT is thought to work by shifting the circadian clock, which is often abnormal in patients with mood disorders. Though the exact association between circadian rhythms and mood disorders is still unclear, antidepressants and mood stabilizers appear to shift, reset, and stabilize these rhythms in achieving effective results. The primary molecular clock is located in the hypothalamus, but there are peripheral clocks throughout the rest of the body that respond to external stimuli, which in turn can offset the primary clock and affect mood. Through TSD and LT it is believed a patient’s circadian clock can be reset and stabilized, theoretically improving depressive symptoms and stabilizing one’s mood (McClung, 2007).

Recent studies tend to indicate TSD and LT along with antidepressants and/or lithium to have favorable short-term outcomes in relieving depressive symptoms in bipolar patients. Beneditti et al. (2005) looked at the clinical significance of TSD plus light therapy in addition to lithium and antidepressants in 60 bipolar I inpatients. Upon admission, 34 patients were drug-free, 10 were on antidepressant medication alone, and 16 were on a combination of an antidepressant and lithium. Patients who were not on drugs did not receive drugs during the trial, and the patients who were on drugs did not receive any change in their drug regimen. Patients were placed into three groups based on prior responsiveness/unresponsiveness to drug treatment. Group One consisted of 33 patients who had no history of unresponsiveness to drug treatment. Groups Two and Three, 27 patients in total, were made up of patients with a history of being
unresponsive to drug treatment. Group Two (n=10) was Stage 1 unresponsive by the Thase and Rush criteria, and Group Three (n=17) was Stage II or II+ unresponsive by the same criteria. Baseline depressive symptoms were assessed using the HAM-D rating scale for depression and response to treatment was considered a 50% reduction in score over the seven-day trial period. Each patient was administered three consecutive TSD cycles, composing periods of 36 hours of being awake. TSD was administered under 80-lux ambient light, and LT was administered under 400-lux green light for 30 minutes at set times over the seven-day trial. Results showed 70% (23/33) of group one achieved response and 44% (12/27) of groups two and three achieving response. Considering group one’s history of responding well to treatment, it was not surprising to see a higher response rate than groups two and three. Over the next nine months each of the patients’ clinical status was monitored to assess relapse. Group one had 39% of its patients euthymic after the nine months, with mean time to relapse being 18.6 weeks. Groups two and three only had 7% euthymic after nine months, with mean time to relapse 9.1 weeks. While TSD and LT was successful and safe in achieving short-term response, it did not show to have much long-term effect, though even a few weeks of euthymia after a major depressive episode can be very beneficial for bipolar patients. Aspects to consider in future trials include: type and strength of light used, length of time of each LT session and when to administer it, and if further LT sessions with TSD can produce positive long-term effects (Benedetti et al.). Larger randomized trials are needed to study the effects of LT and TSD on mood disorders.

An earlier study of LT and TSD with lithium therapy by Colombo et al. (2000) showed a similar positive short-term response. The sample included 115 bipolar depressed patients who were assessed over a seven-day period using the Visual Analogue Scale (VAS), which rates mood, and the Stanford Sleepiness Scale. Each of the patients included in the study scored
greater than 18 on the HAM-D. Forty-nine patients were on long-term lithium therapy (at least 6 months), while 66 patients were not on any long-term psychotropic medications. Each patient underwent three consecutive TSD cycles composed of 36 hours awake each cycle. TSD was administered under 80-lux ambient light. Patients were randomized into groups based on the type of light therapy administered and whether or not on lithium. Seven of the 115 patients did not complete the trial (n=108) due to switching polarity during the TSD treatment. One group (n=35) received no additional light therapy. Fifteen patients were on lithium therapy and 20 were not. A second group (n=33) received 150-lux red light for 30 minutes at set times. Fourteen patients were on lithium and 19 were not. The third group (n=40) received 30 minutes of 2500-lux red light at the same set times. Seventeen were on lithium and 23 were not. Analysis of VAS scores showed similar positive change between the lithium-free/light-treated patients and the lithium-treated/ambient light only (during TSD) patients. This indicates there was no additive affect of lithium plus LT with TSD. Therefore, either lithium or LT with TSD are both reasonable choices in reducing depressive symptoms in bipolar patients. Lithium with TSD may promote a more sustained antidepressant affect, while LT with TSD may be a more useful choice in the short term (Colombo et al.).

Though pharmacological treatment is the mainstay for bipolar patients, a growing amount of research is suggesting adjunctive non-pharmacological therapy can be very beneficial in controlling symptoms and improving quality of life. Types of non-pharmacological treatments include: psychoeducation, family-focused therapy, interpersonal social rhythm therapy, cognitive behavioral therapy, physical activity, and light therapy with total sleep deprivation. Each therapy has shown positive results and therefore it has been suggested that the type of non-pharmacological therapy employed may not be as important as the timing of adding the therapy.
to the treatment regimen. The earlier in the disease process non-pharmacological therapy is added to drug therapy the better the outcome. More research is needed to clearly depict non-pharmacological treatment guidelines for bipolar patients. Ultimately, the type of non-pharmacological therapy applied should be determined on clinical judgment.
Conclusions

Though symptoms of bipolar disorder have been recognized since the time of Hippocrates, the understanding of the illness continues to undergo change. Researchers of the 19th and 20th centuries have described the bipolar symptoms, thus defining bipolar disorder in the current DSM-IV-TR. Current and future research will continue to redefine the parameters of the illness in specific detail. This may help to produce a quicker and more specific diagnosis and highly effective treatment plans for individuals with bipolar disorder.

Current understanding of bipolar pathology is not well understood. A combination of many factors influences the development and severity of the disorder. Consequently, treatments have been based more on a trial and error type basis than pathophysiologic understanding. Unlike many diseases, current research has yet been able to pinpoint an exact cause throughout the bipolar population.

Pharmacological treatment has been and still is the standard in treating the disorder, but non-pharmacological treatments have shown increasing promise in improving symptom control. It has also shown to improve patients’ adherence to drug therapy, which is a major problem in treating mood disorders. Many times the patient feels better after a period of time and discontinues the drug treatment, leading to recurrence of symptoms. Approaching the illness from both the physiologic and mental aspect, the concurrent use of pharmacological and non-pharmacological therapies in bipolar patients is proving to be most beneficial for patients.

Implications for physician assistants in primary care revolve around the recognition and detection of bipolar disorder in patients. It is then important for the clinician to know his/her ability and limitations in treating the disorder. Patients with more severe forms of the disorder often need expertise treatment from a psychiatrist. As advances in modern technology continue
to propel research well into the 21st century, finding the specific physiologic cause/s will be of great importance in developing specific treatment regimens. This will allow all those with bipolar disorder a chance to lead a long and productive life.
References


## Appendix: Acronyms Used in the Paper

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>BARS</td>
<td>Barnes Akithisia Rating Scale</td>
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<td>BDI</td>
<td>Beck Depression Inventory</td>
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<tr>
<td>CBT</td>
<td>Cognitive Behavioral Therapy</td>
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<tr>
<td>CGI-BP</td>
<td>Clinical Global Impression Scale for Bipolar Illness</td>
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<td>CGI-I</td>
<td>Clinical Global Impression Improvement Scale</td>
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<td>CGI-S</td>
<td>Clinical Global Impression Severity Scale</td>
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<td>DASS</td>
<td>Depression Anxiety Stress Scales</td>
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<td>Family Focused Therapy</td>
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<tr>
<td>GBI</td>
<td>General Behavioral Inventory</td>
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<tr>
<td>HAM-D</td>
<td>Hamilton Rating Scale for Depression</td>
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<td>IPSRT</td>
<td>Interpersonal Social Rhythm Therapy</td>
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<td>LT</td>
<td>Light Therapy</td>
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<tr>
<td>MADRS</td>
<td>Montgomery-Asberg Depression Rating Scale</td>
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<td>MSS</td>
<td>Mood Swing Survey</td>
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<td>Response Styles Questionnaire</td>
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<td>Total Sleep Deprivation</td>
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<td>Young Mania Rating Scale</td>
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Abstract

Objective: The purpose of this paper is to explore bipolar disorder through a review of the literature, with the main focus on pharmacological and non-pharmacological treatment options.

Methods: MEDLINE, CINAHL, and PsycINFO were the databases used to research the literature. Pharmacological treatment options included in this review: lithium carbonate; anticonvulsant drugs lamotrigine, valproate/divalproex, and carbamazepine; atypical antipsychotic drugs olanzapine, quetiapine, and aripiprazole; and antidepressent citalopram.

Results: Typically, a combination of multiple drugs is employed to obtain mood stabilization, but in less severe bipolar cases a clinician may be able to obtain effective results with monotherapy. Non-pharmacological treatment options included in this review: behavioral/psychotherapy, physical activity, light therapy, and total sleep deprivation. Non-pharmacological therapies should always be employed as adjunctive treatment to pharmacological therapy. Conclusion: Treatments for bipolar disorder have gotten much better throughout the years, but much research into the exact physiologic cause of bipolar disorder is needed in order to develop more specific and effective treatments.