

THE PHARMA INNOVATION - JOURNAL

Bipolar Affective Disorder and Advancement in Mood Stabilization

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The development of bipolar disorder and subsequent mood stabilization with treatment interventions can consist of both pharmacological and nonpharmacological approaches. There may be challenges that are experienced with treatment but Effective treatment has the ability to improve an individual's quality of life.

Keyword: Mood Disorders, Off-Label, Bipolar Affective Disorder, Pharmacological Interventions, Psychotherapy

1. Introduction

Over the last two decades there has been the resurgence of interest in bipolar affective disorder and has been largely attributed to the availability of new pharmacological agents, disorder-specific psychosocial treatments, and emerging data on the genetic mechanism and neurophysiological and neuroanatomical correlates relating to the mental illness (Hersen, Turner, & Beidel, 2007). Bipolar disorder are generally subdivided into bipolar I disorder (mixed, manic, or depressed) , bipolar II disorder, cyclothymic disorder, and bipolar disorder not otherwise specified but diagnosis is generally based on the use of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (Schatzberg, Cole, & DeBattista, 2010). In order to be diagnosed with bipolar disorder (manic-depressive illness) an individual must meet the criteria for hypomania or mania having a prior episode that meet the clinical features of the illness (Schatzberg, Cole, & DeBattista, 2010).

In general, the first mood episode in bipolar disorder that is often identified in women is depression whereas males are more likely to experience manic episodes (Hahn, Albers, & Reist, 2008). Along with the distinguishing clinical features of either depression or manic, it has been shown that 90% of patients will experience a single manic episode will tend to have a recurrence of the mood disorder with manic episodes generally resulting in violence, job loss, recklessness, or social/occupational dysfunction in the lives of the sufferers (Hersen, Turner, & Reist, 2008). The symptoms of mania can include a pronounced mood of euphoria, grandiosity, decreased need for sleep, or racing thoughts, the symptoms of dysphonic mania can include severe agitation or anxiety, significant suicide risk, and the symptoms of hypomania can consist of increased energy and mental productivity or talkativeness (Preston & Johnson, 2011).

Additionally, the illness is commonly associated with substance-related disorders, eating disorders, and attention deficit hyperactivity disorder and in some cases it can prove to be challenging for clinician to discern bipolar disorder from attention deficit hyperactivity disorder given the similar clinical presentations and features (Hahn, Albers, & Reist, 2008).

When it comes to the differential diagnoses of bipolar disorders it is important one to have a clinical picture of the illness in order to effectively rule out other potential diagnoses and the data generally comes from a person's current clinical picture (whether depression or mania) and a comprehensive history of both manic or depressive episodes (Preston & Johnson, 2011). If the history is not available and the individual is experiencing an initial episode it may be necessary to observe the patient over time in order to make an accurate diagnosis. Also, a family history of either a mood disorder can be suggestive of a diagnosis of bipolar disorder (Hahn, Albers, & Reist, 2008). In terms of differential diagnoses, it is important to assess for the presence of a substance-induced mood disorder as the effects of medications of drugs such as amphetamines, steroids, stimulants, or cocaine, H2 blockers, or sympathomimetics can lead to or cause mania. Also one must also exclude the present of a mood disorder that is due to a general medical condition with common disorders such as central nervous system syphilis, AIDS, hyperthyroidism, brain tumors, or multiple sclerosis can cause mania (Hahn, Albers, & Reist, 2008).

The presence of cyclothymic disorder can cause manic-like episodes that do not meet the criteria for a manic episode, depressive episode, or major depression so careful consideration must be given for this disorder as well as the clinical presentation of an individual at the height of a manic episode can make it difficult to distinguish this from an acute exacerbation of paranoid schizophrenia but this is where a thorough assessment comes into play to rule out or confirm the presence of a bipolar disorder (Hahn, Albers, & Reist, 2008).

As it currently stands there have been recent advances in mood stabilization with a movement towards the use of combination of pharmacological and psychosocial interventions but in the era of managed care cost containment, drug treatments are generally the only treatments that are provided but with clinical trials demonstrating the efficacy of combination therapy more and more people are moving towards this more holistic approach to treating mood disorders (Hersen, Turner, & Beidel, 2008). The goal of treating bipolar disorder is intended to meet two goals which is to achieve a reduction in current symptoms and to prevent relapse and current therapeutic approaches are largely focused on finding effective methods to reach this desired outcome (Preston & Johnson, 2011). The use of various of pharmacotherapy for bipolar disorder have demonstrated clear effectiveness with minimizing or alleviating symptoms and preventing relapse but sufferers of mood disorders can be prone to discontinuing their medications with as many as 60% being fully or partially compliant after a major episode so this discontinuation can make individuals susceptible to high risk of recurrent or suicide attempts which is the reason why psychotherapy can help to promote medication adherence, providing coping skills with stress triggers, and delay relapse (Hersen, Turner, Beidel, 2008). Empirically supported adjunctive psychotherapy interventions for bipolar disorder such as individual or group psychoeducation, cognitive behavioral therapy, and interpersonal therapy have been shown to delay relapse or recurrence of symptoms which has led to greater emphasis being placed on their initiation psychotherapy along with pharmacotherapy.

While there are still some gaps in the research on psychosocial treatment such as the mechanism by which they can improve medication adherence or increase self-efficacy, systematic investigations are being performed to determine the underlying root for mood stabilization.

Furthermore, mood stabilizers are generally considered to be the drugs of choice for bipolar disorder and this term was initially applied to lithium salts when it became recognized that they were not only effective in treating mania but could also be used prophylactically against both mania and depressive cycles ((Schatzberg, Cole, & DeBattista, 2010). Other antimanic agents that can be used alone or in combination with lithium include mood-stabilizing anticonvulsants (e.g.oxcarbazepine, topiramate, tiagabine, or levetiracetam, divalproex, carbamazepine), lamotrigine, or antipsychotics with antimanic effects (Preston & Johnson, 2011).

First of all the pharmacokinetic properties of lithium (the first mood stabilizer) is that it can be readily and nearly absorbed completing in the gastrointestinal tract with its peak concentrations occurring within 2-4 hours of the administration of the immediate release formulation with the slow release formulation showing lower peak concentrations (Keck, & McElroy, 2002). It is available as lithium carbonate capsules and tablets in slow release tablets and lithium citrate syrup.

Lithium does not undergo hepatic metabolism but rather it is renally excreted and the elimination half-life is about 24 hours with a time to steady state concentration in 4-5 days (Dirprio et al., 2005). Given the fact that lithium has a low therapeutic window it does not take much to move from a therapeutic range to a toxic range so cautions must be exercised when it is administered with medications that can lead to toxicity such as diuretic and angiotensin-converting enzyme inhibitors (Keck & McElroy, 2002). For the pharmacodynamics properties of lithium, it is considered to be a monovalent cation whose exact mechanism is unknown but it is has been proposed that it causes depolarization-provoked and calcium-dependent release of dopamine and norepinephrine from the nerve terminals of the central nervous system, allows for the distribution of sodium, calcium, and magnesium across the neuronal membranes to produce its therapeutic effects (Keck & McElroy, 2002).

Valproate is available in five oral formulations (valproic acid, sodium valproate, divalproex sodium, divalproex sodium sprinkle capsules, and divalproex sodium-extended release tablets).

The peak plasma concentration of valproate are achieved within 2 hours for valproic acid and sodium valproate and it takes about 3-8 hours for the divalproex and divalproex extended release formulation. The absorption of the oral formulation of valproate can be reduced when administered with food, it is highly protein bound to serum albumin with the unbounded aspects of the drug exerting the pharmacologic activity (Keck & McElroy, 2002). Unlike lithium, valproate undergoes hepatic metabolism though 3 pathways: mitochondrial B-oxidation to 3-OH-valproate, 3-oxo-valproate, and 2-en-valproate; cytochrome -450 metabolism to the toxic 4-en- and 2, 4,-en-valproate metabolites. In terms of the pharmacodynamics properties of valproate it is indicated for the treatment of acute manic episodes of bipolar disorder that is a simple branched-chain carboxylic acid that possess antikingling properties and neuroprotective properties that is proposed to be associated with its antimanic and mood-stabilizing properties (Diprio et al., 2005).

Additionally, carbamazepine is another mood stabilizer that is available as a solution, suspension, syrup, and chewable formulation that experiences slow and unpredictable absorption with oral administration and its peak plasma concentration is achieved in about 4-8 hours with bioavailability being about 85% (Keck & McElroy, 2002). Similar to valproate, carbamazepine undergoes hepatic metabolism to be converted to 10, 11-epoxide that has pharmacologic activity and further undergoes conversion to the inactive compound (Wilder, 1992). Carbamazepine is considered to be a potent inducer of the cytochrome P450 system so it has the potential to increase the metabolism of other drugs with concurrent administration. Carbamazepine's pharmacodynamics properties fall into its effects on neuronal ion channels and its effects on synaptic and postsynaptic transmission.

It is connected to various neurotransmitters that are associated with its treatment of mood disorders, and these include dopamine, norepinephrine, serotonin, acetylcholine, GABA, and glutamate to name a few.

While the exact mechanism of carbamazepine is not known clinical trials have demonstrated efficacy in the treatment of acute bipolar mania and depression (Keck & McElroy, 2002). For lamotrigine, it is quickly and completely absorbed after oral administration with minimal first pass metabolism and unlike valproate whose absorption is affected by food this is not the case with lamotrigine. It is able to achieve its peak plasma concentration at about 1.4-4, 8 hours after its administration. Since it is less bound to plasma proteins it is unlikely to cause significant drug interactions unlike the other mood stabilizers. Lamotrigine's elimination and excretion involves both renal and hepatic so significant impairments with these organs can affect its clearance (Diprio et al., 2005). The most significant issue affecting the lamotrigine is its concurrent administration with valproate which can increase lamotrigine levels causing a life-threatening rash called Stevens-Johnson syndrome so the dose of lamotrigine has to be reduced by half and undergo slow titration when it is administered with valproate (Hahn, Albers, & Reist, 2008). Lastly, as a class the antipsychotics can have display their antimanic activity through either D2 receptor activity and antidepressant activity can be display by serotonergic and alpha adrenergic effects. The effects on the alpha can cause orthostatic effects, H1 antagonism can cause sedation and increased appetite and M1 antagonism can cause anticholinergic effects (Keck & McElroy, 2002).

In general, mood stabilizers can be used for bipolar disorder as previously stated, schizoaffective disorders and cyclothymia and have demonstrated effectiveness for acute mania and for prophylaxis of mania and depression in bipolar disorder as well as for bipolar maintenance treatment (Hahn, Albers, & Reist, 2008). Most of the mood stabilizers are typically not abused or misused but inappropriate use can

lead to the development of significant side effects or adverse events. For example, lithium toxicity can develop if its level is not maintained within the therapeutic window of 0.80-1.20Meq/L and this can cause stupor, seizures, ataxia, or permanent irreversible neurological impairments ((Schatzberg, Cole, & DeBattista, 2010). Therapeutic drug levels also exist for valproate (50-125mg/ml) even as high as 150mcg/ml, and carbamazepine with a target level of (8-12mcg/ml) which are target levels that clinicians generally want to aim at when it comes to achieving desired treatment effects (Hahn, Albers, & Reist, 2010). The use of other anticonvulsants for the treatment of mood disorders have shown to be instrumental in serving as adjunctive therapy to lithium, valproate, carbamazepine, or lamotrigine and in some cases can help in cases where there is treatment-resistant bipolar disorder with their addition.

Lastly, mood stabilizers can be used off label with the most frequently identified off-label indications for mood stabilizers being, 1) prophylaxis of mood swings, 2) treatment of aggression, 3) manic symptoms, 4) antipsychotics augmentation in treatment-resistant schizophrenia, 4) post-traumatic stress disorder (Haw & Stubbs, 2005). Out of all of the mood stabilizer, lithium is generally the least likely to be prescribed off level as a result of its side effect profile and narrow therapeutic window (Hahn, Albers, & Reist, 2008). The off-label use of mood stabilizers are becoming more and more common in in psychiatry and this has been shown to be a benefit to most patients even there is the problem with fully understanding the off-label concept which generally does not have clinical trials or evidence to support the use of the medication for the particular indication (Haw & Stubbs, 2005). It is imperative the prescriber consider the evidence or lack thereof for the use of a particular mood stabilizer for an unauthorized indication and if there is little support for this indication the risk versus benefit of initiating therapy must be strongly analyzed. For mood stabilizers that are used off-label close clinical monitoring and

frequent assessment may necessary to quickly identify any potential adverse reactions or effects.

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