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General pharmacokinetic/pharmacodynamic concepts of mood stabilizers in the treatment of bipolar disorder

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Abstract

Introduction: Mood stabilizers are the recommended treatment for patients who receive a diagnosis of bipolar disorder. Because of the necessity of mood stabilizer treatment in patients with bipolar disorder and the extent of pharmacokinetic and pharmacodynamic principles involved, the purpose of this review is to summarize the pharmacokinetic principles of lithium in addition to the pharmacodynamics of lithium, carbamazepine, lamotrigine, and valproic acid/valproate.

Methods: Practice guidelines, review articles, and clinical trials were located using online databases PubMed, CINAHL, IDIS, and Medline. Search terms included at least one of the following: *bipolar disorder*, *carbamazepine*, *lamotrigine*, *lithium*, *mood stabilizers*, *pharmacokinetics*, *pharmacodynamics*, *valproate*, and *valproic acid*. Online clinical databases Dynamed® and Lexicomp® were also used in the study.

Results: Mood stabilizers collectively possess distinct qualities that are closely regarded before, during, and after therapeutic initiation. Individual patient characteristics, coupled with these observed traits, add to the complexity of selecting the most optimal neurologic agent. Each medication discussed uniquely contributes to both the maintenance and restoration of overall patient well-being.

Discussion: Introduction of mood stabilizers into drug regimens is often done in the presence of an array of mitigating factors. Safety and efficacy measures are commonly used to gauge desired results. Careful monitoring of patients' responses to selected therapies is paramount for arriving at appropriate clinical outcomes.

Keywords: mood stabilizers, pharmacodynamics, pharmacokinetics, bipolar disorder

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Introduction

Mood stabilizers are commonly prescribed for patients with various mental health disorders, such as bipolar disorder, depression, and schizophrenia.[1] Second-generation antipsychotics are noted to possess mood-stabilizing properties. These agents are often dubbed *nontraditional mood stabilizers* in an attempt to better describe their evolving roles in this capacity. The review provided here captures the functionalities of traditional mood stabilizers while omitting contributions from second-generation antipsychotics. The intent of this paper is to provide an overview of pertinent pharmacokinetic/pharmacodynamic concepts ascribed to commonly encountered traditional mood stabilizers.

Patients who receive a diagnosis of bipolar disorder often have intense emotional states that are characterized by either manic or depressive episodes (*Diagnostic and*

TABLE 1: Summary of treatment for acute mania (adapted from the Canadian Network for Mood and Anxiety Treatments)[3]

First line	
Monotherapy	Lithium, antipsychotic,[a] valproate[b]
Combination therapies	Lithium or valproate + antipsychotic[a]
Second line	
Monotherapy	Carbamazepine, haloperidol
Combination therapy	Lithium + valproate[b]
Third line	
Monotherapy	Oxcarbazepine, antipsychotic[a]
Combination therapy	Lithium or valproate + haloperidol

[a]Second-generation antipsychotics, such as olanzapine and risperidone, are preferred over first-generation antipsychotics, such as haloperidol, because of benign side effect profiles.

[b]For mixed episodes, valproate may be preferred over lithium.

TABLE 2: Summary of treatment for acute depressive episodes in bipolar disorder (adapted from the Canadian Network for Mood and Anxiety Treatments)[3,a]

First line	
Monotherapy	Lithium, lamotrigine, quetiapine
Combination therapy	Lithium or divalproex + SSRI, lithium or divalproex + bupropion, olanzapine + SSRI, lithium + divalproex
Second line	
Monotherapy	Valproate, lurasidone
Combination therapy	Quetiapine + SSRI, lithium or valproate + lamotrigine, lithium or valproate + lurasidone
Third line	
Monotherapy	Carbamazepine, olanzapine, ECT
Combination therapy	Lithium + carbamazepine, lithium or valproate + SSRI, quetiapine + lamotrigine

ECT = electroconvulsive therapy; SSRI = selective serotonin reuptake inhibitor.

[a]When acute depressive episodes of bipolar disorder do not respond to first-line medications at optimal doses, consider add-on therapies. Alternative add-on therapy includes SSRIs or venlafaxine or monoamine oxidase inhibitors.

Statistical Manual of Mental Disorders, fifth edition [DSM-5]). Although the exact etiology of bipolar disorder is not completely understood, neurochemical theories propose that a dysregulation of serotonin (5-HT), dopamine, and norepinephrine occurs in hyperactive and depressive states.[2] A diagnosis of bipolar disorder is further categorized as either bipolar I or bipolar II. According to the DSM-5, patients with bipolar I experience manic or mixed episodes that last for a duration of at least 1 week or manic symptoms that require immediate hospitalization because of the severity of symptoms.[2] Bipolar II can be differentiated by the lack of severe manic or mixed episodes but is similar in the fact that these patients often develop depressive episodes that fluctuate with hypomanic episodes.[2]

The practice guidelines published by the Canadian Network for Mood and Anxiety Treatments and the International Society for Bipolar Disorders indicate that the treatment of bipolar disorder relieves symptoms, prevents recurrence and relapses, improves quality of life, and decreases mortality associated with acute episodes.[3] Maintenance treatment with medication should be continued following a single manic episode and should be strongly considered in patients with bipolar II disorder.[3] Table 1 summarizes the treatment of acute manic conditions. Table 2 summarizes the treatment of acute depressive episodes in bipolar disorder. Table 3 summarizes dosing recommendations for mood stabilizers used in bipolar disorder.

Methods

A search using electronic databases PubMed, CINAHL, IDIS, and Medline was conducted limiting date ranges to 1990-November 2014. Search terms included at least one of the following: *bipolar disorder*, *carbamazepine*, *lamotrigine*, *lithium*, *mood stabilizers*, *pharmacokinetics*, *pharmacodynamics*, *valproate*, and *valproic acid*. Published research, clinical trials, and other review articles were reviewed to ensure validity and remove potential bias when appropriate. Practice guidelines from the American Psychiatric Association, National Institutes of Health, and Veterans Affairs were also included to demonstrate relevance of the study. Online clinical databases Dynamed™ and Lexicomp® were also referenced to identify the mechanism of action and recommended doses for each of the drugs of interest.

A complementary search was employed obtaining exposure to multiple article databases, primarily via the Summon federated search software (Proquest), which searches 120 subscription databases. Databases accessed included Elsevier Science Direct and ProQuest Science Journals, as well as the IDIS Drug Database (University of Iowa) and open access databases, such as PubMed Central and Freely Accessible Science/Medical Journals (NPG). PubMed was used to identify citations that could then be located in full text through library resources. Search strategies included the use of Boolean operators (AND, OR, NOT) and key terms related to pharmacokinetics and pharmacodynamics, including *metabolism*, *action*, *absorption*, etc. Other forms and derivatives of these terms were included through the use of wildcard operators. Date and

TABLE 3: Dosing for mood stabilizers in bipolar disorder[2,8,36,40]

Drug	Dose/Drug Concentration
Lithium (Lithobid®, Eskalith®)	900-2400 mg/d in 2-4 divided doses
	IR: 300 mg/d in 3 divided doses
	ER: 450 mg/d in 2 divided doses
	Plasma concentration: 0.6-1.2 mEq/L
Valproate/valproic acid/ divalproex sodium (Depakene®, Depakote®)	700-1050 mg/d in divided doses
	IR/DR: 750 mg/d in 2 divided doses
	ER: 25 mg/kg/d once daily
	Maximum: 60 mg/kg/d
	Plasma concentration: 50-125 µg/mL
Lamotrigine (Lamictal®)	12.5-25 mg/d increase biweekly to average dose: 200 mg/d
	Maximum: 400 mg/d
	Plasma concentration: n/a
Carbamazepine (Tegretol®, Equetro®)	800-1200 mg/d
	ER: 400 mg/d in 2 divided doses
	IR: 400 mg/d in 4 divided doses
	Maximum: 1600 mg/d
	Plasma concentration: 4-12 µg/mL

DR = delayed release; ER = extended release; IR = immediate release; n/a = not applicable.

location limiters were not used, in order to broaden the scope of the resulting articles.

Results

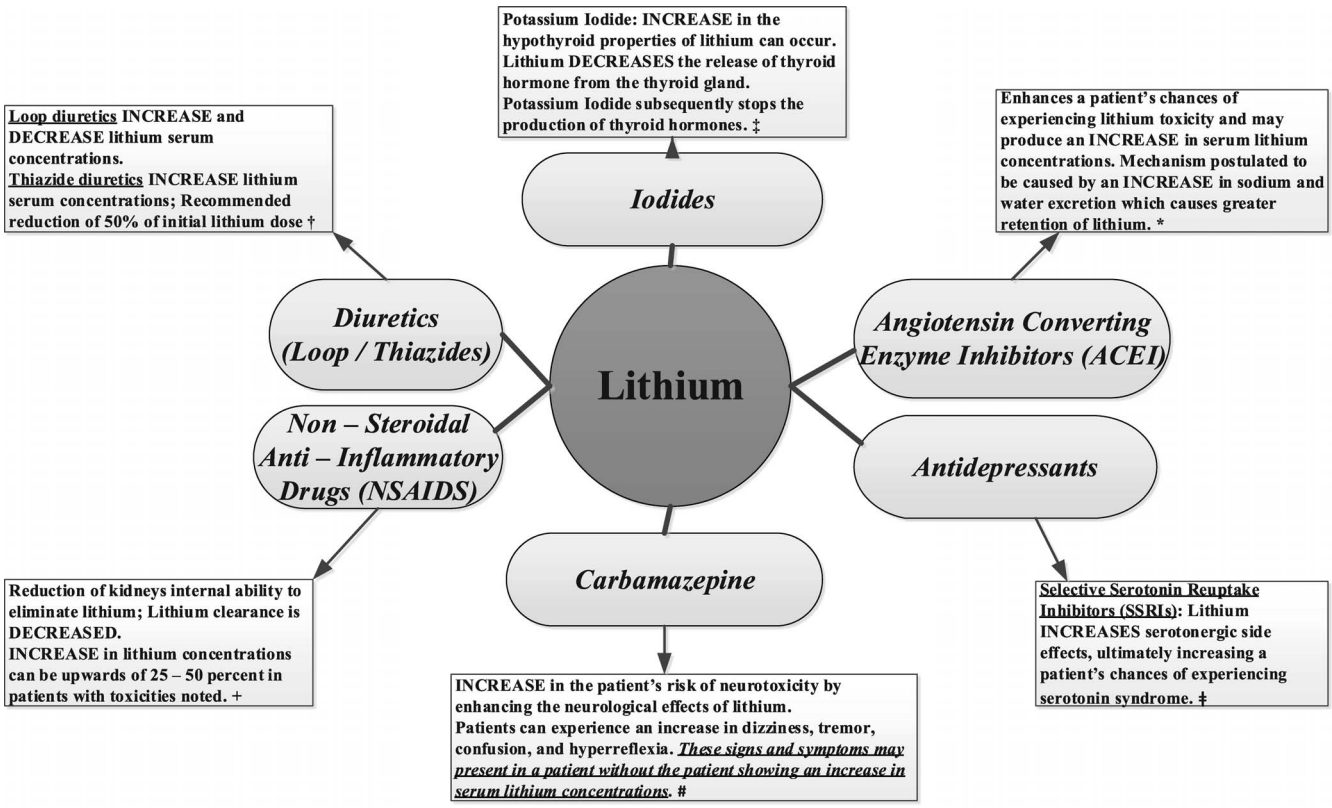
According to most guidelines, mood stabilizers are the initial drug class of choice for treatment of both bipolar I and II disorders.[3-5] Pharmacokinetic and pharmacodynamic issues are some of the most important considerations to keep in mind when treatment is being considered, especially in females. Data suggest that women naturally have a lower hepatic metabolism than that of men, and this metabolic rate can be altered by reproductive hormones, suggesting fluctuations in plasma drug concentrations, which may be of great importance.[6] Other studies have shown that during pregnancy there is an increase in renal blood flow of the mother as well as an increased glomerular filtration rate, further proving the need for careful drug monitoring to avoid toxicity in both mother and fetus.[6]

Lithium

Lithium was the first mood-stabilizing drug approved in the 1970s for the treatment of mania by the US Food and Drug Administration.[7] Lithium has proven efficacy in the treatment and management of both manic and depressive episodes of bipolar disorder, as well as prophylaxis therapy. The exact mechanism by which lithium works in bipolar disorder is not completely understood, but it is postulated that lithium can alter sodium transport within nerve cells and muscle cells and can affect intraneuronal catecholamine metabolism.[8-11] In order to have complete knowledge regarding lithium treatment, it is important to understand its clinical pharmacokinetic properties. The absorption and bioavailability of lithium differ based on the various formulations available. Lithium carbonate and lithium citrate are both employed in long-term maintenance.[11] An estimated 300 mg of lithium carbonate administered 3 or 4 times daily approximates 8 mEq of lithium citrate (5 mL) administered 3 or 4 times daily.[11] The absorption of lithium products occurs rapidly. The oral solution form has the quickest absorption rate of the formulations available: within 1 hour.[12,13] Absorption rates for the regular-release and extended-release preparations include 1 to 3 hours and 3 to 6 hours, respectively.[12,13] The bioavailability of lithium's regular release versus sustained release products varies widely, from 95% to 100% to 60% to 90%, respectively.[12,13] Peak effects of lithium can be divided into acute effects and maintenance effects; an acute decrease in manic symptoms can be seen within 5 to 7 days of beginning therapy, and complete therapeutic effect can be seen within 10 to 21 days.[10,12]

Lithium has been found to be widely distributed into most of the tissues and fluids of the body, such as bone, thyroid, brain, saliva, and erythrocytes, and it is not plasma protein bound. Lithium is excreted through the kidneys without undergoing in vivo metabolism.[10,12]

The pharmacokinetic properties of lithium can vary in special situations, such as pregnancy, advanced age, and renal disease. Lithium is listed as pregnancy category D and should only be used in pregnant women when the potential benefits outweigh potential risks to the fetus.[10] In the absence of harm to the mother, lithium should be withheld for at least the first trimester because of the increased risk of Ebstein anomaly (0.05%-0.1%) compared with the general population.[5] The renal clearance of lithium doubles and ultimately heightens the chances that a pregnant patient may experience a recurrence of previously controlled manic episodes.[13,14]



†#‡Lithium. Dynamed Web site. Last updated 2013 July 24. Available at: http://web.a.ebscohost.com.libproxy.presby.edu/dynamed/. Accessed July 9, 2015.
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+Phelan KM, Mosholder AD, and Lu S. Lithium Interaction With the Cyclooxygenase 2 Inhibitors Rofecoxib and Celecoxib and Other Nonsteroidal Anti-Inflammatory Drugs. *J Clin Psychiatry*, 2003, 64(11):1328-34

FIGURE: The description of selected drug interactions with lithium

In terms of the aging population who may be on lithium, specific guidance is lacking regarding dosage modifications in the elderly. In order to minimize the potential risk of adverse events, it is recommended that a lower starting dose and slower dose titrations be used because of a decrease in renal function.[10,15-17] Nevertheless, response to lithium has not been shown to be related to age. Specifically, bioavailability of lithium in the elderly will remain unchanged because of the lack of first-pass metabolism; however, because of a decrease in body water that occurs with an increase in age, less distribution of lithium throughout the body occurs and can expose the patient to a higher concentration in the serum; these same effects can also be caused by dehydration and decreased glomerular filtration rate.[10,18] The serum half-life reported in elderly patients is 36 hours; therefore, a dose reduction is recommended in patients older than 65 years.[16] The elimination half-life reported in patients with renal disease is increased from 24 hours up to 40 to 50 hours. It is recommended that patients' renal function be monitored every 2 to 3 months during the first 6 months of lithium therapy in order to monitor for changes in renal function.[13,18] Assessment of renal function may encompass urine analyses to monitor specific gravity, fluid states, and creatinine clearance estimations.

Because many patients will be taking lithium in combination with anticonvulsants, antipsychotics, or antidepressants, it is important to note any clinically relevant drug interactions. The description of what occurs when carbamazepine is used concomitantly with lithium is provided in the Figure.[17] When lithium is used in conjunction with other mood stabilizers—such as oxcarbazepine, valproic acid (VPA), and lamotrigine, respectively—no known clinically relevant drug-drug interactions occur.[10] Drug interactions noted when lithium is used in combination with medications other than mood stabilizers must also be addressed.[18-27] Examples of these interactions and the mechanisms underlying these clinically relevant scenarios are also featured in the Figure.

Lithium is classified as an agent with a narrow therapeutic index.[8] Steady-state serum concentrations accepted as normal are predicated upon whether acute mania or long-term control is the area of emphasis.[8] In general, acceptable lithium concentrations range from 1.0 to 1.5 mEq/L for acute mania and 0.6 to 1.2 mEq/L for

maintenance therapy.[8] Nonspecific symptoms of lithium toxicity include impaired coordination, emesis, diarrhea, and muscle weakness. Despite lithium's hydrophilic makeup, it has been shown to cause prompt neurologic disturbances, such as dizziness, vertigo, and pseudotumor cerebri. It is important to understand how lithium works within the body and to note the effects that lithium may have on patients of differing age, body composition, and disease states. Coupling these clinical insights with awareness of significant drug interactions aids in optimizing lithium management.

Carbamazepine

Discovered in Switzerland by a chemist more than 60 years ago, the highly lipid-soluble agent carbamazepine has been a reliable choice in epilepsy management.[28,29] Exerting its effectiveness in partial and generalized seizures, carbamazepine appears to combat epileptic events at the level of the sodium channels and through its impact on synaptic transmissions. Carbamazepine is also commonly used for bipolar disorder and trigeminal neuralgia.[28] Carbamazepine mechanistically potentiates the inhibitory activity of the neurotransmitter gamma-amino butyric acid while attenuating the excitatory activity of the neurotransmitter glutamate.[27] Chemically similar to the tricyclic antidepressants, inhibition of biogenic amine uptake has been linked to carbamazepine use. Carbamazepine has been shown to exhibit low solubility while undergoing extensive metabolism.[28] The rate of carbamazepine absorption is increased with a high-fat meal.[28]

Carbamazepine is a potent inducer of the cytochrome P450 (CYP450) enzymes, which often complicates patients' clinical conditions. Accelerated metabolism of therapeutic regimens in the presence of carbamazepine may lead to treatment failures and deleterious outcomes. Adrenal insufficiency has been shown to result from the inductive effect of carbamazepine on exogenous steroid therapies.[30,31] Carbamazepine increases the metabolism of oral contraceptives and sex hormones, such as estrogen.[31] Dose alterations to carbamazepine or the induced agent(s) are mechanisms for addressing expected plasma concentration deviations. Findings have also surfaced regarding alterations in blood pressure and heart rate in the setting of alcohol use and carbamazepine therapy.[32] Despite the cardiac aberrations identified, ethanol was not shown to have a reportable influence on the pharmacodynamics of carbamazepine.[32]

Carbamazepine is widely known to induce its own metabolism. Carbamazepine's ability to undergo auto-induction presents substantial challenges from a dosing perspective. The maintenance dose of carbamazepine if often adjusted in 1- to 2-week increments to account for the autoinduction observed.[33] Other potent inducers of CYP450 enzymes which increase the metabolism of carbamazepine are phenytoin and phenobarbital.[33] VPA has demonstrated the ability to decrease the metabolism of carbamazepine to the 10,11-epoxide metabolite, resulting in higher plasma concentrations of the parent compound.[33] Identifying the carbamazepine epoxide may lead to a lower risk of toxic reactions and increase the likelihood of reaching the therapeutic target.[33] In addition, possession of the HLA-B*1502 gene has been associated with the development of life-threatening reactions, such as Stevens Johnson Syndrome and Toxic Epidermal Necrolysis.[33] Carbamazepine maintains a reputable role in the management of an array of neurologic conditions. Increasing familiarity with its desired and untoward effects will continue to aid in the promotion of safe and effective outcomes.

Valproic Acid

VPA is classified as a fatty acid. It is employed primarily in epileptic events, with additional utility in migraines and bipolar, mood, and anxiety disorders.[34] The pharmacodynamics of VPA manifest particularly at the level of the brain via gamma-amino butyric acid activity and through antagonism of voltage-gated ion channels.[34] The reduction of high-frequency neurons through the sodium, calcium, and potassium blockade is also thought to be a possible mechanism of VPA therapy.

Depletion of carnitine stores has been linked to chronic VPA usage.[35] Carnitine is purported to be involved with energy production at the cellular level.[35] It appears to serve as a necessity for beta-oxidation of long-chain fatty acids in the mitochondria.[35] Carnitine also has been suggested to have antioxidant properties that seem to aid in decreasing oxidative stress and subsequently safeguarding against neurologic oxidative damage.[35] Several rationales for this resulting decrease in carnitine in the body have been proposed. At the level of the kidney, it has been suggested that VPA alters the reabsorption processes of carnitine.[35] Inhibition of biosynthetic enzymatic processes by VPA and a diminished ability to transport extracellular carnitine into the cell as a result of VPA inhibition of the organic cation transporter 2 (OCTN2) have also been implicated.[35] Depressed concentrations of carnitine typically presents as cardiomyopathy and generalized muscle weakness.[35]

Hepatotoxicity secondary to VPA therapy has been associated with manifestations such as Reye syndrome and hyperammonemia. The former predicament appears to arise from impaired fatty acid oxidation in this particular setting.[34] The latter state has been linked to urea cycle disorders often observed as a complication of VPA therapy.[34] The volume of distribution of VPA varies

because of physiologic considerations (eg, decreased serum albumin and renal impairment). Fluctuations in VPA's volume of distribution are also attributed to its nonlinear protein-binding capabilities. The clinical effectiveness of VPA is widely established with careful monitoring of the respective plasma concentrations.

The generally agreed-upon therapeutic plasma concentration range is 50 to 125 μg/mL.[36] VPA plasma concentrations are primarily monitored after therapy commencement, after alterations in the dosing schedule, or with the subsequent addition of other antiepileptic agents.[36] Patients should be converted from Depakote DR to Depakote ER using an increase in dose of 8% to 20% when transitioning to the ER product. An example of this conversion factor is that a patient receiving 1000 mg/d of the DR preparation could convert to 1250 mg/d of the ER equivalent.[36] Having knowledge of the interactions of VPA at the transporter/cellular level is likely to provide additional insights into advantages and disadvantages of VPA implementation.[37]

Lamotrigine

Lamotrigine is an antiepileptic drug whose exact anticonvulsant mechanism of action in humans is widely unknown. In vitro pharmacologic studies of rats demonstrated that lamotrigine exhibits its mechanism of action through inhibition of voltage-sensitive sodium channels.[38,39] When lamotrigine was tested in vitro for activity at the *N*-Methyl-D-aspartate (NMDA) receptor, it did not show inhibition of the NMDA receptor in animal hosts.[38] The clinically significant findings often ascribed to aspects of lamotrigine's pharmacodynamics entail folate metabolism concerns, diminished renal excretion capacities, and cardiovascular complications. Because of the increasing prevalence of lamotrigine being used for such indications as bipolar disorder, cluster headaches, depersonalization disorder, peripheral neuropathy, and psychosis, in addition to the probability of combination therapy to treat and manage such disease states, the chances of pharmacokinetic/pharmacodynamic interactions will likely increase with more frequent use.[38] However, with lamotrigine, minimal drug interactions that are pharmacodynamic in nature have been reported in combination with nonepileptic agents. As it pertains to lamotrigine being used concomitantly with antiepileptic therapy, significant pharmacokinetic drug interactions have been noted. It has been shown that lamotrigine concentrations are elevated by valproate coadministration in excess of 2-fold.[40] Carbamazepine decreases the concentration of lamotrigine by approximately 40%.[38] The recommended maintenance dosage range for lamotrigine when coadministered with valproate is 100 to 200 mg/d. In concomitant VPA use, a defined lamotrigine titration schedule should be used. Lamotrigine is to be administered 25 mg every other day for the first 2 weeks. Lamotrigine administration should increase to 25 mg every day for the following 2 weeks. The dosing schedule for the fifth week of therapy extending into the maintenance phase encompasses an increase by 25 to 50 mg per day every 1 to 2 weeks. Guidance on coadministration of carbamazepine and lamotrigine stipulates that lamotrigine be administered at 300 to 500 mg/d in two divided doses.[38] Because of the lack of pharmacodynamic implications of lamotrigine, there is currently no recommended therapeutic dosing range to monitor efficacy and safety. Dose-escalation processes for patients taking lamotrigine in the absence of other antiepileptic agents is advised based on intricate interval considerations. During the first 2 weeks, the recommended dose is 25 mg daily.[39,40] The following 2 weeks calls for an increase to 50 mg daily. Upon arrival at the fifth week, guidance calls for increases of 50 mg/d every 1 to 2 weeks.[38] Lamotrigine's maintenance dose is typically divided into 2 doses ranging from 200 to 400 mg daily.[38-41] Prevention of Stevens Johnson Syndrome hinges on lamotrigine's titration schedule. The titration schedule needs to be modified in the presence of concomitant VPA therapy. The most common adverse effects observed when lamotrigine was used as monotherapy for bipolar disorder were nausea, insomnia, somnolence, fatigue, back pain, rash, and rhinitis.[38]

Discussion

Mood stabilizers are mainstay therapies instrumental in optimizing quality of life.[39-41] The agents presented here are unique in their modalities for bipolar management. Lithium concentrates in different tissues throughout the body, which allows its impact to be widespread. Its elimination is reliant upon adequate kidney function, which has noted implications in settings of renal compromise and the aging population. Strategies for lithium dose adjustments in the elderly are rather undefined. In addition to lithium's teratogenic potential, its clearance in the pregnant population is altered, exposing pregnant patients to risks of recurring manic episodes.

Lithium has a narrow therapeutic window that renders therapeutic drug monitoring a key component in optimizing individual responses to therapy.

Carbamazepine's contribution to mood stabilization has been attributed in part to its augmentation of inhibitory actions displayed by gamma-amino butyric acid neurotransmission. Having meal requirements associated with absorption rates, along with its inductive potential of CYP450 enzymes, carbamazepine dosing regimens often pose challenges to prescribing habits. Further complicat-

ing carbamazepine administration is its tendency to induce its own metabolism. Carbamazepine has been shown to significantly reduce the concentrations of concomitant drug therapies while in some instances having its own concentration reduced by potent CYP450 inducers. Hypersensitivity testing is customarily associated with carbamazepine therapy in an effort to limit serious adverse effects.

VPA has been implicated in the reduction of antioxidizing agents, such as carnitine. Additional observations of VPA's side effect profile reveal increases in ammonia concentrations in the blood and liver toxicities. Protein-binding features of VPA display nonlinear characteristics that warrant close monitoring when other highly protein-bound drugs are coadministered. Different dosage forms of VPA have evolved to bolster the ability to provide patient-specific care. Chronic monitoring of reported VPA concentrations remains a vital part of preventing subtherapeutic and supertherapeutic occurrences.

Lamotrigine has been evaluated for activity at the NMDA receptor level. Its prowess with regard to alleviating various neurologic conditions continues to expand. Lamotrigine's use in the presence of other antiepileptic agents may be prone to drug interactions, requiring alterations in prescribed regimens. Titration schedules for lamotrigine are often employed to assist with these clinical conundrums. In the absence of complementary agents used for bipolar disorder, lamotrigine's side effects appear to be regarded as conditions that are mostly dermatologic and neurologic in nature.

Patients and health care personnel are equipped with viable means for combatting bipolar disorder. The therapies discussed are each associated with advantages and disadvantages to subsequent implementation. Patient-specific considerations should remain at the forefront of deliberations surrounding initiation of these agents.

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