Mood Stabilizer Prescribing Guidelines

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Policy

It is the policy of the San Bernardino County (County) of Department of Behavioral Health to establish practice guidelines for the use of mood stabilizers in client treatment.

Purpose

The DBH Mood Stabilizer Prescribing Guidelines are intended to provide guidance for providers, to increase the effectiveness and safety of mood stabilizer use. These Guidelines are not intended to be comprehensive in scope and are not a substitute for clinical judgment. In making decisions about client care physicians must carefully consider the clinical characteristics and circumstances of each individual.

Introduction

The San Bernardino County Department of Behavioral Health Mood Stabilizer Prescribing Guidelines for Adults offers guidance for providers to maximize the effectiveness and safety of medications used primarily for mood-stabilizing of symptoms and conditions, especially those related to bipolar spectrum disorder. This policy provides practical information and guidance for prescribing providers to improve treatment and quality of life in people diagnosed with bipolar spectrum disorders and related diagnoses. These guidelines are not intended to be comprehensive in scope. Furthermore, these recommendations are meant to inform and guide clinical decision-making but are not a substitute for prudent clinical judgment. Clinical decisions must carefully consider and incorporate the unique clinical characteristics and circumstances of each individual patient, with paramount importance given to the best interests and safety of each individual patient. The selection of a specific mood stabilizer, form of administration, dose, and duration of treatment is a complex decision-making process, involving multiple factors. These factors often include individualized treatment goals, patient choice, past medication trials, family history, side effect profile and other factors.

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Background

Mood stabilizers are a heterogeneous group of medications. For the purpose of this document, mood stabilizers include lithium and various anticonvulsant medications. Antipsychotic medications are also used for their mood stabilizing properties. Consult the San Bernardino County Antipsychotic Prescribing Guidelines (MDS2039) for further details on antipsychotic medications. Mood stabilizers may be prescribed for multiple psychiatric conditions. They are most often used for the treatment of bipolar spectrum disorders; however, mood stabilizers may also be used to treat other conditions. For example, lithium has anti-suicidal properties that are independent of its mood stabilizing effects in bipolar illness. Thus, it may sometimes be clinically appropriate to prescribe lithium to a patient struggling with suicidality, even if they do not have a diagnosis of a bipolar spectrum disorder.

The primary use of most mood stabilizers that are anticonvulsants is in the treatment of seizure disorders, although many carry FDA-approval for various bipolar spectrum disorders. Mood stabilizers are also used for the treatment of impulsive aggression, although they are not currently FDA approved for this purpose. As with other medication classes utilized in psychiatric practice, since mood stabilizers can be used clinically for non-FDA approved diagnoses ("off-label use"), prescribing providers should always ensure patients are informed they are being given medication for off-label use, and document patient's consent accordingly. The following sections discuss mood stabilizers currently being prescribed.

Lithium

A naturally occurring element, lithium is FDA-approved for the treatment of bipolar I disorder during an acute manic or mixed episode, as well as for maintenance therapy. The exact mechanism of action is not understood, but it has been thought to enhance neuronal resilience, plasticity and proliferation; alter levels of neurotransmitters; alter receptor sensitivities; modulate second messenger systems; and/or alter calcium cellular function. Lithium is exclusively excreted by the kidneys. Its onset of action for acute mania is approximately 6-10 days and full resolution of symptoms may take up to 3 weeks. When used for treatment of depression, it can take up to 1 month for maximal improvement. Lithium has a protective benefit against suicide and can reduce overall mortality when used in the treatment of depression, bipolar disorder, and other mood disorders.

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Mood Stabilizer Prescribing Guidelines, Continued

Lithium - Dosing	Lithium dosing is generally based on the indication of usage (i.e., acute or maintenance therapy) and should be guided by lithium serum levels and the patient's response to treatment. FDA-approved dosing ranges from 300mg-1800 mg/day, divided into twice daily or three times daily dosing. However, due to variability in renal clearance in the patient population, sometimes doses lower or higher than this range may be clinically indicated. Once-daily dosing may be considered to improve adherence and may reduce the occurrence of adverse effects to the kidney. Dose changes have a predictable and linear effect on serum levels. For example, increasing lithium dose by 300mg/day should lead to an increase of approximately 0.3mEq/L in the serum lithium level.
Lithium – Special Consideration for Geriatric Patients	Geriatric patients often respond to lower doses and may exhibit signs of toxicity at doses and serum concentrations ordinarily tolerated by other patients. The use of mood stabilizers in older adults necessitates ongoing evaluations to consider the confounding presence of delirium/dementia, drug-drug interactions, and/or medical illness. Because renal and hepatic clearance of drugs can decline with age, dosages may need to be decreased or more slowly titrated in older individuals in order to reduce the risks of accumulation and toxicity.
Lithium – Special Consideration for Children and Adolescents	The safety and effectiveness of lithium for monotherapy treatment of acute manic or mixed episodes of bipolar I disorder and maintenance monotherapy of bipolar I disorder in patients ages 7 to 17 years of age has been established. The safety and effectiveness of lithium has not been established in pediatric patients less than 7 years of age with bipolar I disorder, nor for any other psychiatric diagnoses.

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Lithium - Monitoring

Target serum lithium levels for acute bipolar I disorder, acute/mixed episodes are between 0.8-1.2mEq/L and between 0.6-1.0mEq/L for maintenance therapy in bipolar I disorder. Lithium levels should be checked after steady-state concentration is achieved: Approximately 3-6 days in healthy adults, 3-5 days in children, and 4-8 days in the elderly. Levels should be checked even sooner, if there is suspicion of toxicity, drug-drug interactions, or electrolyte/renal abnormalities. Levels should be drawn 12 hours post-dose to obtain a 'trough' level of the medication. Maintenance levels should be checked at least once per year. In general, lithium toxicity can occur at levels ≥1.5mEq/L (adults and children) and ≥0.8mEq/L (elderly) and can have severe consequences. Prescribing lithium and lithium serum level monitoring are conjoined prescriber responsibilities. Prior to initiating lithium therapy, prescribers should ensure that the requisite screening labs and evaluations have been completed, and that a reliable system for routine, ongoing monitoring is in place. In situations where a patient is unable or unwilling to have initial and ongoing monitoring evaluations dose, consideration of an alternative mood stabilizer should be considered.

The following screening exams are generally recommended before initiating lithium treatment ("at baseline"):

A. Estimated glomerular filtration rate (eGFR)
B. Creatinine
C. Thyroid Function Tests (TFTs)
D. Calcium
E. Complete Blood Count with differential (CBC w/differential)
F. Complete Metabolic Panel (CMP)
G. Pregnancy test (in females of childbearing age)
H. EKG (in patients with cardiovascular disease risk factors and/or family history)
I. Body mass index (BMI)
J. Pulse and Blood pressure
K. Urinalysis
L. Electrocardiogram (EKG), if >40 years old or if patient has cardiovascular disease)

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Lithium - Monitoring, continued

Table 1 - ONGOING LITHIUM MONITORING

When	What
A. 1 week after initiation *OR* B. After a dose/formulation change *OR* C. After introduction of interacting medication, *AND* D. weekly until levels are stable*	**Plasma lithium levels:** • Aim for trough levels of: 0.8-1.2 mEq/ L (acute phase of bipolar I treatment), 0.8-1.0 mEq/L (maintenance phase of bipolar I treatment). Lower trough levels than these may be effective in some patients. • Elderly are more sensitive to lithium and side effects, so lower levels than those listed above may be more appropriate. • Monitor for signs of neurotoxicity, blurred vision, muscle weakness, tremor, slurred speech, polyuria, polydipsia, impaired coordination, and confusion.
At 3 months	**Urinary albumin creatinine ratio** (ACR): • NORMAL - no further regular ACR monitoring required (unless eGFR <60 ml/min, then re-check annually) • PROTEINURIA (ACR >30 mg/mmol) – re-check annually • HEAVY PROTEINURIA (ACR >70 mg/mmol) – refer to nephrology; consider stopping lithium
Every 2 months (until chronic steady dose achieved) **Every 6-12 months (after patient achieves steady dose AND is clinically stable)**	**Plasma lithium levels** – as above • Monitor for signs of neurotoxicity, blurred vision, muscle weakness, tremor, slurred speech, polyuria, polydipsia, impaired coordination, and confusion.

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Lithium - Monitoring, continued

When	What
Every 6-12 months	**CBC w/diff, CMP, pregnancy test (in females of childbearing age), EKG (if indicated at baseline), urinalysis, pulse, blood pressure, BMI** **Thyroid function tests (TFTs)** – risk of hypothyroidism increase up to five-fold and is particularly high in women 40-59 years old. Consider thyroid replacement early. **Renal function (e-GFR)** – consider more frequent checks in the elderly or established CKD. Monitoring trend in function is more useful than absolute value of test result. Consecutive results indicating reduction of renal function (especially if e-GFR is <60 ml/min, decreasing dose adjustment to maintain safe lithium level or increase in creatinine level) should prompt consideration of lithium review. If lithium is discontinued due to concerns about lithium related decline in renal function, continue to monitor renal function for at least one year after lithium is stopped. **Calcium** (tick bone box on path lab form) - long-term treatment is associated with hyperparathyroidism and hypercalcaemia. Clinical consequences of raised serum calcium include renal stones, osteoporosis, dyspepsia, hypertension and renal impairment.

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Lithium - Monitoring, continued

Table 1 - LITHIUM TREATMENT RENAL MONITORING

Stage of Chronic Kidney Disease	eGFR	Proteinuria	Action
Normal kidney function **Stage 1** **Stage 2**	> 60	3 months after starting lithium check urinary albumin creatinine ratio (ACR)	• Normal: no regular albumin creatinine ratio monitoring required • Proteinuria (ACR >30 mg/mmol): monitor albumin creatinine ratio annually • Heavy proteinuria (ACR >70 mg/mmol): refer to nephrology
Stage 3A **Stage 3B**	59 - 45 30 – 44	Check urinary albumin creatinine ratio (ACR) Confirm abnormal result with early morning sample. If proteinuria confirmed do reagent strip for hematuria	• Check eGFR every 3 months • Monitor ACR annually • Complete cardiovascular risk profile, consider antiplatelet drugs & cholesterol lowering therapy • Control BP (<140 mm systolic & 90 mm diastolic; lower in diabetes or ACR >30 mg/mmol) • Stage 3B: measure hemoglobin annually • Refer to nephrology and discuss discontinuation if: ○ At stage 3B ○ ACR >70 mg/mmol ○ ACR >30 mg/mmol + hematuria ○ Decline in GFR of >5ml/min over 1 year or >10ml/min in 5 years
Stage 4 **Stage 5**	15 – 29 < 15	As for stages 3A & 3B	Refer to nephrology. Lithium normally contraindicated

Lithium - Toxicity

Lithium may take up to 24 hours to distribute into brain tissue, so occurrence of acute toxicity symptoms may be delayed. Patients abnormally sensitive to lithium may exhibit toxic signs at serum concentrations that are considered within the therapeutic range.

Mild Lithium Toxicity: Typically occurs at lithium levels between 1.5-2.0 mEq/L with symptoms of nausea, vomiting, diarrhea, lethargy, coarse hand tremor and muscle weakness.

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Lithium - Toxicity, continued

Moderate Lithium Toxicity: Typically occurs at levels between 2.0-2.5 mEq/L with severe nausea, vomiting, diarrhea, confusion, slurred speech, nystagmus (abnormal eye movements), ataxia (unsteady gait), myoclonic twitches (abnormal muscle movements) and EKG changes (flat or inverted T waves).

Severe Lithium Toxicity: Typically occurs at levels >2.5 mEq/L with the same symptoms as moderate toxicity, and addition of grossly impaired consciousness, increased deep tendon reflexes, seizures, syncope, and coma.

No specific antidote for lithium poisoning is known.

Mild lithium toxicity can usually be treated by reduction in dose or cessation of the drug. Signs and symptoms of moderate or severe lithium toxicity may be considered a medical emergency and should be managed as such.

Additional information on the management of lithium poisoning or overdosage may be obtained from the National Poison Control Center at 1-800-222-1222 or via www.poison.org.

Lithium – Drug Interactions

Drug interactions can alter serum lithium levels. See Table 3 for information about drug interactions with lithium. Lithium clearance can be altered by changes in sodium intake; a significant decrease in sodium intake can increase lithium levels, whereas an increase in sodium intake can decrease lithium levels.

Table 3 -SERIOUS ADVERSE LITHIUM AND OTHER MEDICATION INTERACTIONS

Medicine/Group	Magnitude of Effect	Timescale	Precaution
ACE inhibitors Angiotensin-2 receptor antagonists	• Unpredictable • Up to 4-fold increase in lithium levels	Develops over several weeks	7-fold increased risk of hospitalization for lithium toxicity in the elderly
Thiazide diuretics	• Unpredictable • Up to 4-fold increase in lithium levels	Usually apparent in first 10 days	Loop diuretics are safer but caution still required. Any effect will be apparent in the first month
NSAIDs (OTC anti-inflammatories)	• Unpredictable • From 10% to >4-fold increase in lithium levels	Variable; few days to several months	NSAIDs are widely used on a PRN basis – this is potentially more problematic
These medications reduce the excretion of lithium resulting in an increase in lithium plasma levels. Try to avoid combinations of these drugs. If they *must* be used, lithium levels must be monitored more frequently (weekly x 1 month, then monthly until stable).			

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Lithium – Drug Interactions, continued

Table 4: MILD-MODERATE LITHIUM AND OTHER MEDICATIONS INTERACTIONS

Medicine/Group	Effect/Interaction
* **Loop diuretics & potassium-sparing diuretics (safer than thiazides)**	Reduced excretion of lithium - increase in levels & risk of toxicity
Tricyclic antidepressants	Risk of toxicity
Antipsychotics - clozapine, flupentixol, haloperidol, phenothiazines, quetiapine, risperidone, sulpiride, zuclopenthixol	Increased risk of extrapyramidal side effects
Antipsychotics - clozapine, flupentixol, haloperidol, phenothiazines, risperidone, zuclopenthixol	Possible neurotoxicity
Antipsychotics - amisulpride	Increased risk of adverse effects of amisulpride
Antipsychotics - olanzapine	Possible risk of lithium toxicity
Amiodarone	Risk of ventricular arrhythmias Increased risk of hypothyroidism
Methyldopa, Phenytoin and Carbamazepine	Concomitant use may increase risk of adverse reactions of these drugs. Possible neurotoxicity (without increased lithium levels).
Calcium channel blockers - diltiazem, verapamil	May cause neurotoxicity and psychosis.
Dapoxetine	Increased risk of serotonergic effects
Nitroimidazole Antibiotics - metronidazole	Concomitant use may increase serum lithium concentrations due to reduced renal clearance. More frequent monitoring of serum lithium concentration. Reduce lithium dosage based on serum lithium concentration and clinical response.
SSRIs	Concomitant use can precipitate serotonin syndrome.
*** Sodium containing antacids**	Lithium excretion increased – reduced lithium levels

Lithium – Contraindications / Warnings

Lithium is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients. Lithium is contraindicated in individuals with kidney failure, cardiovascular insufficiency, Addison's disease, and untreated hypothyroidism. Lithium has several warnings associated with its use. It can unmask Brugada syndrome which is abnormal potassium channel repolarization seen on an ECG. Brugada syndrome can lead to sudden cardiac death. Lithium can decrease the ability of the kidneys to concentrate urine in some individuals; acute and chronic reductions in glomerular filtration rates can occur. Long-term lithium treatment leads to morphological kidney changes in 15-20% of individuals. Significant fluid loss increases the risk of lithium toxicity.

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Mood Stabilizer Prescribing Guidelines, Continued

Lithium - Pregnancy	Lithium can cause fetal harm when administered to a pregnant patient. Cardiac malformations, including Ebstein's anomaly, are associated with the use of lithium during the first trimester of pregnancy. The use of lithium later in pregnancy may increase the risk of neonatal complications including preterm birth, hypotonia, cyanosis, hypoglycemia, low Apgar scores, macrosomia, neonatal goiter, bradycardia and nephrogenic diabetes insipidus. Lithium dose requirements change throughout pregnancy and delivery due to volume shifts, changes in glomerular filtration rates and changes in renal clearance. Decreases in serum lithium levels during pregnancy, compared to the pre-partum period. If lithium must be used, lithium levels should be monitored very closely throughout pregnancy and delivery, and close collaboration should be sought with the patient's OB/GYN.
Lithium - Lactation	Lithium is highly excreted in breastmilk, and infant serum levels are 1/3 to 1/2 of the patient's serum levels. Signs of infant toxicity include cyanosis, hypotonia and hypothermia. Breastfeeding should be avoided in patients taking lithium. If nursing while taking lithium, the lowest effective lithium dose should be used and infant lithium level, TSH, BUN and creatinine should be monitored frequently.

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Lithium – Adverse Effects

Lithium is associated with a number of adverse effects; many of them can be easily managed. See Table 5 below for additional details.

Table 2 - LITHIUM ADVERSE EFFECTS AND THEIR MANAGEMENT

System Affected	Adverse Effect	Management
Gastrointestinal	Nausea	Use ER formulation; take with food
	Dry mouth/thirst	Adequate hydration, ice chips, sugarless gum, artificial saliva
Genitourinary	Polyuria	Use once daily dosing; target lower serum levels; treat with amilioride
	Acute kidney injury: generally, occurs with toxicity	Treat lithium toxicity; if moderate-severe, refer for emergency medical treatment
	Chronic kidney disease: 15-20% of patients develop slow decline in GFR	Monitor kidney function; <1% of patients develop end stage renal disease after 15 years of treatment
Dermatologic	Acne: may induce new acne or worsen existing acne; most common in ages 20-30; onset 2 weeks after initiation	Resolves 1 month after discontinuing or reducing lithium; if continuing lithium, consider treating acne
	Psoriasis: most common in >50 years; onset 1-10 months after initiation	Topical or systemic treatment for mild to moderate; refer to dermatology for severe; dose reduction may help
	Alopecia: more common in women	Check thyroid function as lithium-induced hypothyroidism causes hair changes
Cardiovascular- caution warranted in patients with *known* cardiac disease	Atrioventricular block or other conduction issue	Lithium can be safely continued unless a 3rd degree block is present
	Bradyarrythmia	May be exacerbated by hypercalcemia and hypothyroidism; monitor for severe bradycardia and syncopal events
	ECG changes- T wave flattening or inversion	Usually benign and reversible
Endocrine/metabolic	Hypothyroidism	Monitor thyroid levels yearly, treat with thyroid hormone if needed
	Weight gain (average 4-6 kg)	Healthy diet and exercise
Hematologic	Leukocytosis	None- generally benign
Neurologic	Fine tremor	Avoid caffeine; treat with propranolol

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Lithium Therapy Patient Counseling Points

Patients should be advised that lithium is most often prescribed to stabilize mood and should only be taken as directed by their prescribing medical provider. The importance of compliance with the prescribed treatment to maximize efficacy should be emphasized, while changing the dose of lithium without first consulting with the prescribing medical provider should be discouraged. Patients should also be encouraged to let their other prescribing medical providers that they are taking lithium, due to the potential for drug-drug interactions noted above.

Lithium should be taken at the same time(s) every day. Instruct patients not to double the dose if a dose is missed, due to the complexity of individualized dosing and potential for lithium toxicity.

Patients should be informed that they will need regular laboratory tests, including lithium levels, renal, and thyroid function tests, to verify that lithium is in the correct range as well as monitor for potential side effects.

Side effects of lithium include: nausea, dry mouth, acne, weight gain and fine hand tremors. Changes to kidney function and thyroid are possible as well.

Lithium may be taken with food if it causes dyspepsia. Use of a extended-release form of lithium may also reduce the likelihood of GI side effects.

Since lithium may cause somnolence particularly when initiating treatment, patients should be advised to avoid operating vehicles or hazardous machinery, until they are reasonably certain that lithium treatment does not affect them adversely.

Counsel patients on the adverse reactions related to lithium induced polyuria and educate patients on maintaining a normal diet with salt. Adequate hydration should be maintained, and dehydration avoided. Excessive thirst and/or significant urination should be reported to their healthcare provider.

Inform patients of the adverse reactions related to lithium toxicity that require medical attention. Counsel patients to discontinue lithium treatment and contact their healthcare provider if clinical signs of lithium toxicity such as diarrhea, vomiting, tremor, lack of muscle coordination, drowsiness, abnormal heart rhythm or muscular weakness occur.

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Mood Stabilizer Prescribing Guidelines, Continued

Anticonvulsants

Many anticonvulsants have FDA indications for bipolar spectrum disorders due to their mood stabilizing properties, in addition to treatment of seizure disorders. Anticonvulsants have a variety of mechanisms of action, though most act to alter various voltage sensitive sodium channels or potassium channels, leading to lowered excitatory neurotransmission.

Valproic Acid (VPA) and Related Medications

In this guideline, "valproic acid" ("VPA") will be used to refer to all related medications (valproic acid, divalproex sodium, valproate sodium).

Valproic acid (VPA) is approved by the FDA for the treatment of acute manic or mixed episodes (with or without psychotic features) of bipolar disorder. Its exact mechanism of action in managing symptoms of bipolar disorder is not known. Theories include normalization of central GABA pathways and sodium/calcium channel activities, reduction of intracellular inositol and protein kinase C levels, presence of anti-kindling properties that are thought to decrease rapid cycling and mixed episodes, and modulation of gene expression.

VPA - Dosing

For valproic acid, a starting dose may be initiated at 250 mg TID, with rapid dose increase to lowest effective dose. For divalproex sodium, the recommended starting dose is 250-500 mg TID (delayed-release) and 500-750 mg daily (extended-release), with rapid dose increase to lowest effective dose. Regardless of formulation, the total maximum recommended dose is 60 mg/kg/day. For extended release, divaloproex sodium, initial doses of 20-25 mg/kg/day are sometimes used as a loading strategy when rapid symptom management is required. It can be given as a single dose, or in divided doses if tolerability issues arise. When changing to the extended-release (ER) formulation from the delayed-release (DR) formulation of divalproex sodium, the steady-state serum concentration could be expected to decrease by up to 20%; an increase of dose may be required.

VPA – Special Considerations for Geriatric Patients

Age affects many components of drug biotransformation. Absorption is often reduced. Body composition may affect the volume of distribution. Protein binding changes associated with age or concomitant declines in renal function as well as hepatic metabolism can result in a higher free fraction of VPA. Clearance of VPA may be reduced by up to 40% in geriatric patients. Clinical research suggests an increase in somnolence and fall risk in geriatric patients taking VPA. Dosing in this population should involve lower starting doses and be increased more slowly with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse reactions.

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VPA – Special Considerations for Children and Adolescents	It is important to note that while VPA is FDA-approved for some seizure disorders in children and adolescents, there are currently no FDA-approved indications for the use of VPA for any psychiatric disorders in pediatric populations. However, off-label use may be considered in some circumstances.
VPA - Hepatic Disease	Decreases in hepatic clearance may warrant decreased doses. **VPA should not be prescribed to individuals with significant hepatic disease or dysfunction.** Monitoring total concentrations may be misleading as free concentrations may be significantly elevated in individuals with hepatic disease even though total concentrations may appear to be normal.
VPA - Monitoring	Therapeutic serum VPA levels are 50-125 µg/mL. Higher levels are associated with more adverse effects, and toxicity can occur at levels >175 µg/mL. Levels should be drawn before AM dose. VPA levels should be obtained once steady-state is achieved, usually 3-5 days after initiation or dose change. If a patient has hypoalbuminemia (as may occur in renal failure), it is recommended to draw free VPA serum levels. See Table 6 below for divalproex monitoring parameters. For additional information about VPA monitoring, contact the pharmacy department. **The following screening exams are generally recommended before initiating VPA treatment:** A. Liver Function Tests (LFT) B. Complete Blood Count with diff. (CBC) C. Complete Metabolic Panel (CMP) D. Platelet Count and Coagulation Tests (bleeding time, PT, partial thromboplastin time, fibrinogen, von Willebrand factor level and/or a thromboelastogram.) E. Pregnancy Test (in females of childbearing age) at baseline and if there is a suspicion for pregnancy. F. Body mass index (BMI) G. Blood pressure

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VPA - Monitoring, continued

Table 3 - ONGOING VPA MONITORING

When	What
Every 2 - 4 weeks for the first two months of VPA treatment	VPA serum level
Every month for the first two months of VPA treatment	CBC with diff LFTs
Every 3 to 6 months	VPA serum level
Every 6 to 12 months	CBC with diff LFTs Weight
Additional monitoring considerations	VPA serum level after each change in dose. Consider obtaining free serum VPA concentration when altered protein binding might be expected (e.g., in patients with renal failure, elderly, malnourished, or medically ill individuals, or when clinically significant drug interactions are present). Pregnancy test (in patients of childbearing age)

VPA – Toxicity

Overdose may result in significant neurologic symptoms (e.g., ataxia, tremor, CNS) which may progress to cerebral edema, paradoxical seizures, coma, and death. There are also potential risks of heart block and hypernatremia. General supportive measures should be applied with maintenance of adequate urinary output. The efficacy of gastric lavage or emesis will depend on the time since ingestion. Hemodialysis/hemoperfusion may significantly remove VPA. Naloxone has been reported to reverse the CNS depression of VPA overdosage.

For current information on the management of poisoning or overdosage, contact the National Poison Control Center at 1-800-222-1222 or www.poison.org.

VPA – Drug Interactions

There are several drug interactions with VPA that can have serious consequences. See **Table 7** for information about drug interactions with VPA.

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VPA – Drug Interactions, continued

Table 4 - SERIOUS ADVERSE VPA AND OTHER MEDICATIONS INTERACTIONS

Medicine/ Group	Interaction	Precaution
Carbapenem antibiotics *(ex: imipenem / cilastatin, meropenem)*	Mechanism not known; may result in reductions of VPA levels within 24 hours	Avoid combination (administering additional VPA may not overcome this interaction)
Lamotrigine	VPA increases the availability of lamotrigine approximately 2-fold	When adding VPA to lamotrigine, dose of lamotrigine should be decreased by 50%; when adding lamotrigine to VPA, reduce the initial starting dose to 12.5 mg daily or 25 mg every other day.
Phenytoin	Complex interaction that may be unpredictable in outcome: VPA may cause an initial decrease in total phenytoin levels while free levels remain unchanged; phenytoin may double VPA clearance.	Monitor closely.
Warfarin	Potential increased effects of warfarin; VPA displaces warfarin from albumin-binding sites.	More frequent INR monitoring

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VPA – Drug Interactions, continued

Table 5 - POTENTIAL VPA AND OTHER MEDICATIONS ADVERSE INTERACTIONS

Drug	Interaction	Drug Interaction Management
Phenobarbital	Increased phenobarbital level	Reduce dosage
Magnesium- and aluminum-containing antacids	Increased valproic acid level	Monitor valproic acid level; reduce dosage
Carbamazepine (Tegretol)	Decreased valproic acid level; possible increased carbamazepine level	Monitor valproic acid level; adjust dosage
Aspirin and naproxen (Naprosyn)	Increased valproic acid level	Avoid salicylates or other drugs bound to plasma albumin
Clonazepam (Klonopin)	Increased sedation	Use with caution
Alprazolam (Xanax)	Increased alprazolam levels	Monitor; reduce dosage
TCAs	Increased TCA level	Monitor TCA level
Warfarin (Coumadin)	Increased warfarin level with fluvoxamine (Luvox)	Monitor prothrombin time (INR); reduce fluvoxamine dosage
MAOIs	Serotonin syndrome	Combination of MAOI and SSRI is contraindicated
Clozapine (Clozaril)	Increased clozapine level with fluvoxamine	Monitor clozapine level
l-Tryptophan	Serotonin syndrome	Combination of L-tryptophan and SSRI is contraindicated
Phenytoin (Dilantin)	Possible phenytoin toxicity	Monitor phenytoin level
Carbamazepine (Tegretol)	Increased carbamazepine level with fluvoxamine and fluoxetine (Prozac)	Monitor carbamazepine level
Tolbutamide	Possible increased hypoglycemia	Monitor blood glucose level
Theophylline	Increased theophylline level with fluvoxamine	Monitor theophylline level
Cimetidine (Tagamet)	Increased SSRI levels	Monitor clinically
Type Ic antiarrhythmics	Increased antiarrhythmic level with fluoxetine, paroxetine (Paxil) and sertraline (Zoloft)	Monitor antiarrhythmic drug levels
Beta-adrenergic blockers	Increased beta-blocker level and enhanced effects	Use lower beta-blocker dosage
Codeine	Inhibited metabolism from fluoxetine, paroxetine and sertraline	Use different SSRI
St. John's wort	Serotonin syndrome	Stop St. John's wort before beginning SSRI therapy

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Mood Stabilizer Prescribing Guidelines, Continued

VPA – Contraindication and Warnings	VPA is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients. VPA is contraindicated in individuals with hepatic disease or significant hepatic dysfunction, urea cycle disorders, and mitochondrial disorders. Other VPA warnings include patients with: pancreatitis, hepatic failure, hyperammonemia, encephalopathy, and excessive bleeding.
VPA - Pregnancy	VPA can cause fetal harm when administered to a pregnant patient. VPA is associated with significant fetal malformation risks, particularly a 3-5% risk of neural tube defects, and it is not known whether folic acid supplementation is effective in reducing these risks. Furthermore, many pregnancies are unplanned. Both the American Academy of Neurology and American Epilepsy Society recommend against the use of VPA in patients of childbearing age. Therefore, in general, VPA should be avoided in patients of childbearing age, unless there are contraindications to alternative agents, or its use is essential for the management of the individual's illness.
VPA - Lactation	VPA is excreted in human milk, but in relatively low concentrations (~10% or less of maternal serum levels). Individuals taking VPA and breastfeeding should be advised of this and encouraged to monitor for any adverse events in their infant.

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VPA – Adverse Effects

VPA is associated with a number of adverse effects; some of them can be easily managed. See Table 9 below for additional details.

Table 6 - VPA ADVERSE EFFECTS AND THEIR MANAGEMENT

System Affected	Adverse Effect	Management
CNS	Ataxia, diplopia, dizziness, sedation, tremor	Sometimes self-limiting, may require dosage adjustment; older adults may be more susceptible to sedation; tremor may be treated with propranolol
Endocrine/ metabolic	Weight gain	Healthy diet and exercise
	Hyperammonemia	Close monitoring of levels and development of clinical symptoms; discontinuation if elevation is persistent or encephalopathy emerges
Gastrointestinal	Nausea, vomiting, diarrhea	Take with food
	Constipation	Adequate hydration, increase fiber in diet
	Transaminitis/hepatotoxicity, pancreatitis	Discontinuation of therapy
Endocrine/ metabolic	Weight gain	Healthy diet and exercise
	Hyperammonemia	Close monitoring of levels and development of clinical symptoms; discontinuation if elevation is persistent or encephalopathy emerges
Hematologic	Thrombocytopenia	Reduction of dose or discontinuation of therapy

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VPA – Patient Counseling Points

Advise patients, their caregivers, and families that VPA can be taken with or without food. Medication may be taken with food if it causes an upset stomach.

Divalproex sodium delayed-release and extended-release tablets should be swallowed whole. They should not be crushed, chewed, or split. Divalproex sodium delayed-release also has a capsule formulation, which can be opened up and mixed in food.

Blood levels should be measured periodically to check that the VPA is in a therapeutic range, to balance efficacy and risk of developing side effects.

When VPA is being considered for use in a patient of childbearing age, she should be counseled that use of VPA in pregnancy increases the risk of birth defects and may have adverse effects on neurobehavioral development, including lower IQ scores. Patients should be advised to use effective contraception while using VPA. If pregnancy occurs while a patient is taking VPA, they should be advised to contact their healthcare provider immediately. Patients of childbearing age should also be counseled that VPA is secreted in small concentrations into breast milk.

Patients, caregivers, and families should be advised that side effects of VPA may include: somnolence, dizziness, weight gain, weakness or unsteady gait, hand or arm tremors, and menstrual changes in females. Healthcare providers should be contacted if any of these adverse events occur.

VPA can potentially cause liver problems with serious side effects, including death. Patients, caregivers, and families should be advised that nausea, vomiting, abdominal pain, anorexia, diarrhea, asthenia, and/or jaundice can be symptoms of hepatotoxicity and, therefore, require further medical evaluation promptly. Patients should be counseled to contact a healthcare provider immediately, if any of these symptoms occur.

VPA can cause pancreatitis. Patients, caregivers, and families should be advised that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis and, therefore, require further medical evaluation promptly. Patients should be counseled to contact a healthcare provider immediately, if any of these symptoms occur.

VPA can cause hematological dysfunction. Patients, caregivers, and families should be advised to monitor for any indications of thrombocytopenia, such as petechiae, bruising, hematoma formation, epistaxis, or frank hemorrhage. Patients should be counseled to contact a healthcare provider immediately, if any of these signs or symptoms occur.

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Mood Stabilizer Prescribing Guidelines, Continued

VPA – Patient Counseling Points, continued	VPA may increase the risk of suicidal thoughts and behaviors. Patients, caregivers, and families should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Patients should be counseled to contact a healthcare provider immediately, if any of these concerning behaviors occur. VPA can cause Central Nervous System (CNS) depression, especially when combined with other CNS depressants (e.g., alcohol). Patients should be counseled to avoid consumption of alcohol while taking VPA, and advised not to engage in hazardous activities, such as driving a vehicle or operating dangerous machinery, until they know they are certain they are not experiencing significant CNS depression.
Carbamazepine - Background	Carbamazepine (CBZ) is FDA-approved for treatment of acute manic and mixed episodes of bipolar I disorder in adults. It may also be used off-label for maintenance therapy in bipolar disorder or in other bipolar spectrum disorders. CBZ, like other anticonvulsants, inhibits voltage sensitive sodium channels. It is generally considered second line treatment in psychiatry, due to significant drug-drug interactions, autoinduction of metabolism, and significant monitoring requirements.
CBZ - Dosing	Dosing for adults begins at 200mg twice daily and may be increased up to 200mg/day every 2-7 days. The FDA-maximum dose is 1600mg/day.
CBZ – Special Considerations for Geriatric Patients	Geriatric-specific problems are not expected to limit the usefulness of carbamazepine in the elderly. However, elderly patients are more likely to have confusion, hyponatremia, or agitation and age-related liver, kidney, or heart problems, which may require caution and an adjustment in the dose for patients receiving CBZ.
CBZ – Special Considerations for Children and Adolescents	It is important to note that while CBZ is FDA-approved for seizure disorders in children and adolescents, there are currently no FDA-approved indications for the use of CBZ for any psychiatric disorders in pediatric populations. However, off-label use may be considered in some circumstances.

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CBZ – Monitoring

Therapeutic serum CBZ levels are between 4-12 mcg/mL. Levels should be drawn before AM dose. CBZ autoinduces its own metabolism, therefore levels should be checked within 1-2 weeks of initiation and dosage changes to ensure levels are within the therapeutic range. Due to autoinduction, it may take >1 month of stable dosing to achieve a steady-state serum CBZ level.

See below for screening exams that are recommended before starting CBZ treatment and Table 10 for additional monitoring parameters.

The following screening exams are generally recommended before initiating CBZ treatment:

A. Liver Function Tests (LFT)
B. Complete Blood Count with diff. (CBC)
C. Complete Metabolic Panel (CMP)
D. Serum Iron
E. Blood Urea Nitrogen (BUN) and Creatinine
F. Renal Function Tests
G. Complete Urinalysis
H. Fasting Glucose
I. Fasting Lipid Profile
J. Body Mass Index (BMI)
K. Blood Pressure
L. Baseline and periodic eye examinations, including slit-lamp, funduscopy, and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes.

Table 7 - CBZ MONITORING PARAMETERS

Monitoring Parameter	Frequency
Serum level	1-2 weeks after initiation, change in dose, or change in overall medication regimen. Use trough levels (drawn prior to the first morning dose) 5 days after a dose change. Because of autoinduction, it may take >1 month to achieve steady-state with stable dosing.
Pregnancy test (in patients of childbearing age)	At baseline and if pregnancy is suspected
CBC with differential	At baseline and annually
Hepatic and renal function	At baseline and annually
Serum electrolytes	At baseline and annually
HLA-B*1502	At baseline in at-risk populations (e.g., persons of Asian origin; see full prescribing information for details)
HLA-A*3101	At baseline in at-risk populations (e.g., persons of Japanese, Native American, Southern Indian (for example, Tamil Nadu) and some Arabic ancestry; see full prescribing information for details)

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CBZ - Toxicity

CBZ toxicity occurs at levels higher than 40 mcg/mL (usual therapeutic levels are 4 to 12 mcg/mL). Adverse effects can occur at serum levels >12 mcg/mL, such as disorientation, ataxia, hallucinations, aggression, and seizures.

Symptoms of an acute overdose onset are usually delayed because of the delayed and erratic absorption of CBZ in the gastrointestinal (GI) tract. It causes dizziness, imbalance, drowsiness, coma, generalized seizures and abnormal cardiac conduction that can lead to arrhythmia. Treatment ranges from physiological clearance, use of activated charcoal, or extracorporeal therapy such as hemodialysis or plasmapheresis.

For current information on the management of poisoning or overdosage, contact the National Poison Control Center at 1-800-222-1222 or www.poison.org

CBZ – Contraindications / Warnings

CBZ is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

CBZ is contraindicated in patients with a history of bone marrow suppression. CBZ should be used with caution in patients with blood dyscrasias caused by drug therapies or hematological disease because of the potential increased risk of hematologic toxicity. CBZ may cause life-threatening serious rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The estimated risk of developing these serious adverse effects is about 1 to 6 per 10,000 new users of CBZ in countries of mainly Caucasian populations, and an estimated risk which is 10 times higher in some Asian countries.

The increased risk of SJS and TEN in persons of Asian origin is believed to be linked to the presence of the HLA-B*1502 allele which is more common in this population. Therefore, it is recommended that patients at higher likelihood of having the HLA-B*1502 allele be tested for it. The test is considered positive if one or two HLA-B*1502 alleles are present. CBZ should be avoided in patients positive for the HLA-B*1502 allele, unless the benefits clearly outweigh the risks of serious dermatologic reactions.

Coadministration of CBZ with nefazodone is contraindicated, as it may result in insufficient plasma concentrations of nefazodone and its active metabolite to achieve a therapeutic effect.

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Mood Stabilizer Prescribing Guidelines, Continued

CBZ – Contraindications / Warnings, continued	Before administration of CBZ, MAO inhibitors should be discontinued for a minimum of 14 days, or longer if the clinical situation permits. Antiepileptic drugs (AEDs), including CBZ, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.
CBZ - Pregnancy	CBZ can cause fetal harm when administered to a pregnant patient. CBZ and its metabolites can be found in the fetus and may be associated with teratogenic effects, including spina bifida, craniofacial defects, cardiovascular malformations, and hypospadias. Developmental delays have also been observed following in-utero exposure to CBZ in some studies. If CBZ is used in pregnancy, or a patient becomes pregnant while taking CBZ, the patient should be counseled on the potential risks to the fetus. If used for the treatment of bipolar disorder, CBZ should be avoided during the first trimester of pregnancy. Respiratory depression, seizures, nausea, vomiting, diarrhea, and/or decreased feeding have been observed in neonates exposed to CBZ in-utero and may represent a neonatal withdrawal syndrome. CBZ may decrease plasma concentrations of hormonal contraceptives; breakthrough bleeding or unintended pregnancy may occur and alternate or back-up methods of contraception should be used.
CBZ - Lactation	CBZ and its active epoxide metabolite are found in breast milk. CBZ can also be detected in the serum of nursing infants. Transient hepatic dysfunction has been observed in some case reports. The decision to continue or discontinue breast-feeding during therapy should take into account the risk of exposure and adverse events to the infant and the benefits of treatment to the patient.

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CBZ – Adverse Effects

CBZ use is associated with low serum levels of folate and vitamin B12 and vitamin B2. This may lead to hyperhomocysteinemia. Hyperhomocysteinemia may contribute to cardiovascular disease, venous thromboembolic disease, dementia and neuropsychiatric symptoms. Consider supplementation with folic acid, riboflavin, pyridoxine, and cyanocobalamin in patients taking CBZ.

See **Table 11** for additional information about adverse effects from CBZ.

Continued on next page

CBZ – Adverse Effects, continued

Table 8 - CBZ SEVERE ADVERSE EFFECTS AND THEIR MANAGEMENT

System Affected	Adverse effect	Management
Hematologic	Blood dyscrasia, anemia, agranulocytosis	Monitor for early symptoms including: fever, sore throat, ulcers, easy bruising. Discontinue immediately if bone marrow suppression occurs.
Dermatologic	Toxic Epidermal Necrolysis and Stevens-Johnsons Syndrome. High risk for HLA-B*1502 allele which is more common in persons of Asian origin.	Provide extensive patient education. Perform a baseline skin examination including oral and ocular mucosa. Follow slow dosing titration and emphasize adherence. Examine for fever, blisters, red/purple rash, and sore throat. Discontinue immediately and seek emergency care if symptoms arise. Consider screening for HLA-B*1502 in at-risk populations or avoiding use in those populations.
Hepatic	Hepatotoxicity, slight to severe elevations in liver enzymes	Monitor liver function at baseline and throughout treatment.
Renal	Hyponatremia, SIADH, renal toxicity	Monitor sodium and renal function. Discontinue therapy if concerning changes from baseline.
Multiorgan	Hypersensitivity reactions increased in pts with the HLA-A* 3101 allele which occurs more frequently in African American, Asian, Indian, Latin American ancestry	Screen for history of hypersensitivity reactions in immediate family.
Psychiatric	Increased suicidal ideation, psychosis or agitation	Regular assessments of suicidal ideation and psychiatric symptoms.
Cardiovascular	Conduction abnormalities	Avoid use with underlying ECG abnormalities and preexisting cardiac history.
Cardiovascular	Conduction abnormalities	Avoid use with underlying ECG abnormalities and preexisting cardiac history.

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CBZ – Drug Interactions

CBZ is metabolized via enzyme CYP3A4 and induces CYP 3A4, CYP2C8, CYP2C9 and CYP2B6 which leads to significant risk for drug interactions. Table 12 indicates some interactions with common medications. However, drug interactions should be checked when considering starting CBZ or when patients already on CBZ have changes in their other prescribed medications.

Table 9 - CARBAMAZEPINE MAJOR DRUG INTERACTIONS

Interaction	Clinical Concern	Comments
CYP3A4 substrates (ex: aripiprazole, zolpidem)	CBZ may decrease serum concentrations of these medications	Avoid combination, if possible, may require increased doses of substrate for clinical effect.
CYP3A4 inducers (ex: atazanavir, St. John's wort)	May decrease serum concentrations of CBZ	Avoid combination
CYP3A4 inhibitors (ex: fluoxetine, grapefruit juice)	May increase serum concentrations of CBZ	Avoid combination or consider reduced dosing of CBZ
CYP2B6 substrates (ex: sertraline, bupropion, methadone)	CBZ may decrease serum concentrations	Monitor closely
CYP2C9 substrates (ex: NSAIDS, warfarin)	CBZ may decrease serum concentrations	Avoid co-administration
Myelosuppressive agents (ex: clozapine, dipyrone)	CBZ may enhance myelosuppressive effects	Avoid combination
Adenosine	CBZ may enhance the adverse effect, higher risk of heart block	Lower initial dose of adenosine if combination therapy cannot be avoided
Chemotherapy agents (ex: cyclophosphamide, vincristine)	CBZ may decrease the concentration of many agents used in therapy for metastatic cancer treatment	Avoid combination
Carbonic anhydrase inhibitors (ex: acetazolamide)	May increase serum concentration of CBZ	Consider lower doses of CBZ, avoid combination when possible
Hormonal contraceptives	CBZ can diminish therapeutic effect	Use alternative non-hormone contraceptive methods
Anticonvulsants (ex: lamotrigine, phenytoin)	May enhance adverse effects of carbamazepine, CBZ may increase metabolism	Avoid combination
Lithium	CBZ may enhance adverse effects of lithium	Monitor carefully

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CBZ – Drug Interactions, continued

Table 10 - CARBAMAZEPINE MAJOR DRUG INTERACTIONS (Continued)

Interaction	Clinical Concern	Comments
MAOI inhibitors (ex: phenelzine, isocarboxazid)	CBZ may enhance adverse effects	Combination contraindicated during or within 14 days of discontinuing MAOI
Quetiapine, olanzapine	May increase concentrations of CBZ, CBZ may decrease concentrations of SGA	Avoid co-administration, if unavoidable doses of antipsychotic may require increase

CBZ- Therapy Patient Counseling Points

CBZ is associated with many side effects, the most serious being early toxic signs, changes in blood counts, skin rash or psychiatric side effects. Patients, caregivers, and families should be counseled to contact a healthcare provider immediately if a new rash, fever, blisters, easy bruising, confusion, or increasing agitation occur.

CBZ has significant interactions with other prescription and over the counter medications. Patients, caregivers, and families should be counseled to contact a healthcare provider about any potential changes in their prescription medications, including over the counter products, while taking CBZ.

Patients, caregivers, and families should be counseled that CBZ can reduce the effectiveness of hormonal contraceptives and is also associated with fetal harm. Patients should be advised to use additional, non-hormonal forms of birth control while taking CBZ.

Patients of childbearing age/potential should be counseled that CBZ may cause fetal harm. Due to this risk, patients who are pregnant or are planning to become pregnant need to be counseled on the potential risks and benefits of treatment with CBZ. Patients should be counseled that if pregnancy occurs, they should contact their healthcare provider immediately.

Patients, caregivers, and families should be counseled that abrupt discontinuation of CBZ can cause seizures or an increase in seizure frequency. If there is a need to discontinue CBZ, the patient should be tapered off the medication gradually.

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CBZ- Therapy Patient Counseling Points, continued

If a patient uses alcohol while on CBZ therapy, this may contribute additive sedative effects. Since dizziness and drowsiness may occur, patients, caregivers, and families should be cautioned about the hazards of operating machinery or vehicles, or engaging in other potentially dangerous tasks, while on CBZ therapy, and to avoid use of alcohol while on CBZ therapy.

Patients, caregivers, and families should be counseled that AEDs, including CBZ, may increase the risk of suicidal thinking and behavior, so they need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Patients, caregivers and families should be instructed to report behaviors of concern immediately to a healthcare provider.

Grapefruit products may increase levels of CBZ. Patients, caregivers, and families should be counseled to read food/drink labels and avoid consuming grapefruit while taking CBZ

Oxcarbazepine

Oxcarbazepine is a structural derivative of carbamazepine with a ketone in place of the carbon-carbon double bond at the dibenzoazepine ring. This helps reduce the impact on the liver of drug metabolism, leading to some improvements in side effect profile and fewer drug-drug interactions than seen with carbamazepine. For this reason, oxcarbazepine has been used in clinical practice as a treatment for bipolar disorder, but it does not have FDA approval for this use. Oxcarbazepine is FDA-approved only for treatment of partial seizures. Monitoring parameters and risk of adverse effects are similar to that of carbamazepine.

Studies indicate some antimanic effects of oxcarbazepine, with absent or scarce data on its use in bipolar depression or as a 'maintenance' drug for bipolar disorder (i.e., to prevent future mood episodes). Oxcarbazepine may be considered as a treatment option in patients with bipolar disorder who responded well to carbamazepine but had to discontinue due to side effects or experienced significant drug-drug interactions.

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Mood Stabilizer Prescribing Guidelines, Continued

Lamotrigine - Background

Lamotrigine is FDA-approved for use in treating bipolar I disorder, to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy. It may be used as monotherapy for this purpose, or as an adjunct to other mood stabilizer medications. It also carries FDA-approved indications for several seizure disorders. It is also used commonly in clinical practice as a treatment for symptoms of bipolar depression, with lowered risk for inducing manic symptoms compared to some first line antidepressants, though it does not carry FDA approval for this indication.
Mechanisms of action for lamotrigine include: inhibition of voltage sensitive sodium channels and reduction of release of the excitatory neurotransmitter glutamate.

Lamotrigine - Dosing

Lamotrigine has a gradual dose titration schedule, due to rare, but serious risk of dermatologic reactions, including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). See Table 13 below for details on dosing and titration, as dosing varies based on whether or not a patient is on other mood-stabilizing medications (such as VPA or CBZ), as well as several other medications.

Lamotrigine is available in immediate and extended-release tablet formulations, as well as a chewable tablet. 'Starter kits' are available to simplify the initial dose titration process.
When discontinuing therapy, dosage should be gradually decreased by 50% per week over at least two weeks unless safety concerns indicate a more rapid withdrawal.

Additionally, if a patient has discontinued lamotrigine for more than 5 half-lives or lamotrigine has been withheld for more than 5 days, the medication should be restarted following the same protocol as an initial titration. While the prescribing information for lamotrigine indicates that the half-life of the medication is (on average) 25.4 hours after multiple doses are given in healthy volunteers taking no other medications, the half-life of lamotrigine can be affected by other medications a particular patient may be taking.

Lamotrigine – Special Considerations for Geriatric Patients

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

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Lamotrigine – Special Considerations for Children and Adolescents

It is important to note that while lamotrigine is FDA-approved for several seizure disorders in children and adolescents, there are currently no FDA-approved indications for the use of lamotrigine for any psychiatric disorders in pediatric populations. However, off-label use may be considered in some circumstances.

Notably, the prescribing information for lamotrigine indicates that while the safety and efficacy of the medication for bipolar disorder was studied for maintenance treatment of bipolar disorder in a pediatric population (ages 10-17 years old) with a current mood episode, safety and efficacy of the medication was not established.

Lamotrigine – Special Considerations for Patients with Renal Impairment

Initial doses of lamotrigine should be based on a patient's concomitant medications, while reduced maintenance doses may be effective for patients with significant renal impairment. Depending on the degree of renal impairment, reduction in dosing may be indicated.

Lamotrigine – Special Considerations for Patients with Hepatic Impairment

In general, no dosage adjustment is needed in patients with mild liver impairment. Initial, titration and maintenance doses should generally be reduced by approximately 25% in patients with moderate and severe liver impairment without ascites and 50% in patients with severe liver impairment with ascites. Escalation and maintenance doses may be adjusted according to clinical response.

Table 11 - LAMOTRIGINE TITRATION SCHEDULE

Week	Regimens without interacting medications	Regimens containing valproic acid	Regimens containing carbamazepine, phenytoin, phenobarbital, primidone, rifampin or ritonavir
Weeks 1 &2	25mg once daily	25mg every other day	50mg once daily
Weeks 3&4	50mg once daily	25mg once daily	100mg daily in divided doses
Week 5	100mg once daily	50mg once daily	200mg daily in divided doses
Week 6 and beyond	200mg-400mg/day	100mg-200mg/day	300mg-600mg/day in divided doses

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Lamotrigine - Monitoring

The value of monitoring plasma concentrations of lamotrigine in patients treated with lamotrigine has not been established. Many labs have established a therapeutic range of 3-15 mcg/mL, but this range is mostly applicable to the treatment of seizure disorders. Some studies suggest that the therapeutic range of serum lamotrigine levels to be lower than that used for seizure disorders (see Unholzer S, Haen E. Retrospective analysis of therapeutic drug monitoring data for treatment of bipolar disorder with lamotrigine. Pharmacopsychiatry. 2015 Sep;48(6):211-4. doi: 10.1055/s-0035-1559635. Epub 2015 Aug 7. Erratum in: Pharmacopsychiatry. 2015 Nov;48(7):296.)

Because of the possible pharmacokinetic interactions between lamotrigine and other drugs, including AEDs (see Table 13), monitoring of the plasma levels of lamotrigine and concomitant drugs may be indicated, particularly during dosage adjustments. In general, clinical judgment should be exercised regarding monitoring of plasma levels of lamotrigine and other drugs and whether or not dosage adjustments are necessary.

The following screening exams are generally recommended before initiating lamotrigine treatment:

A. Complete blood count (CBC)
B. Electrolytes
C. Blood urea nitrogen (BUN) and creatinine
D. Liver function tests (LFTs)
E. Fasting Glucose
F. Fasting Lipid Profile
G. Body Mass Index (BMI)
H. Blood Pressure
I. EKG (in patients >60 years old or <60 years old with cardiac disease or significant risk)

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Lamotrigine - Toxicity

Overdoses of lamotrigine involving quantities up to 15 g have been reported, some of which have been fatal. Overdose has resulted in ataxia, nystagmus, seizures (including tonic-clonic seizures), decreased level of consciousness, coma, and intraventricular conduction delay.

There are no specific antidotes for lamotrigine. Following a suspected overdose, hospitalization of the patient is advised. General supportive care is indicated, including frequent monitoring of vital signs and close observation of the patient. If indicated, emesis should be induced; usual precautions should be taken to protect the airway. It should be kept in mind that immediate-release lamotrigine is rapidly absorbed. It is uncertain whether hemodialysis is an effective means of removing lamotrigine from the blood.

For current information on the management of poisoning or overdosage, contact the National Poison Control Center at 1-800-222-1222 or www.poison.org.

Lamotrigine – Contraindications / Warnings

Lamotrigine is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

Lamotrigine use is contraindicated in patients who have demonstrated hypersensitivity to lamotrigine (e.g., rash, history of angioedema, acute urticaria, extensive pruritus, mucosal ulceration) or other life-threatening hypersensitivity or serious immune-related events.
There have been reports of blood dyscrasias with lamotrigine that may or may not be associated with multiorgan hypersensitivity (also known as DRESS Syndrome). These have included neutropenia, leukopenia, anemia, thrombocytopenia, pancytopenia, and, rarely, aplastic anemia and pure red cell aplasia. Patients should be monitored for signs of anemia, unexpected infection, or bleeding that may indicate a blood dyscrasia.

Lamotrigine therapy increases the risk of developing aseptic meningitis. Patients should be monitor for signs of meningitis during treatment. Because of the potential for serious outcomes of untreated meningitis due to other causes, patients should be evaluated for other causes of meningitis and treated as appropriate.

Patients, caregivers, and families should be counseled that AEDs, including lamotrigine, may increase the risk of suicidal thinking and behavior, so they need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Patients, caregivers and families should be instructed to report behaviors of concern immediately to a healthcare provider.

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Lamotrigine - Pregnancy

Lamotrigine use during pregnancy may be associated with risks to the fetus, including congenital malformations (such as oral cleft and palate). However, there has not been enough research conducted to definitively determine safety of use in pregnancy. Data from several prospective pregnancy exposure registries and epidemiological studies of pregnant patients have not detected an increased frequency of major congenital malformations or a consistent pattern of malformations among patients exposed to lamotrigine compared with the general population. The overall risk of congenital malformations may be significantly lower for lamotrigine, when compared to other AEDs used in bipolar illness. Patients of childbearing age/potential should be counseled on the possible fetal and congenital risks of lamotrigine.

Maintenance of adequate dosage of lamotrigine during pregnancy should be considered, as there may be changes to serum levels due to changes in fluid volumes and increased hepatic metabolism. In addition, as estrogen levels rise during pregnancy, lamotrigine serum levels may decrease by up to 50%. Healthcare providers utilizing lamotrigine in a patient who is pregnant or is planning to become pregnant may wish to review the algorithm published in the following journal article for further guidance on lamotrigine dosing and monitoring: Sabers A. Algorithm for lamotrigine dose adjustment before, during, and after pregnancy. Acta Neurol Scand. 2012 Jul;126(1):e1-4. doi: 10.1111/j.1600-0404.2011.01627.x. Epub 2011 Dec 9.

A summary of the algorithm can also be found at: https://womensmentalhealth.org/posts/lamotrigine-lamictal-dosing-during-pregnancy/

Lamotrigine - Lactation

Lamotrigine is expressed in breast milk at levels up to 50% of serum levels. Infants have immature glucuronidation capacity, and glucuronidation is needed for lamotrigine clearance. As such, infants being breastfed by patients taking lamotrigine may experience adverse events, including: rash, apnea, drowsiness, poor sucking, and poor weight gain.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for lamotrigine and any potential adverse effects on the breastfed infant from lamotrigine or from the underlying maternal condition.

Lamotrigine – Adverse Effects

Common adverse effects of lamotrigine include fatigue, dizziness, nausea/vomiting, constipation, cough/rhinitis and dysmenorrhea. There are several rare, but serious side effects associated with lamotrigine use- see **Table 14** for details. Routine measurement of lamotrigine levels is not recommended.

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Lamotrigine – Adverse Effects, continued

Table 12 - LAMOTRIGINE SEVERE ADVERSE EFFECTS AND THEIR MANAGEMENT

System Affected	Adverse Effect	Management
Dermatologic	Stevens-Johnson Syndrome, Toxic epidermal necrolysis (higher risk in children)	Provide extensive patient education. Perform a baseline skin examination including oral and ocular mucosa and document. Follow slow dosing titration and emphasize adherence. Examine for fever, blisters, red/purple rash, and sore throat. Discontinue immediately and seek emergency care if symptoms arise.
CNS	Suicidal ideation or emotional lability	Frequent patient contact during initial 6-week titration phase with screening for suicidal ideation or behavioral change
	Aseptic meningitis	Screen for symptoms of fever, vomiting, rash, photophobia, nuchal rigidity or severe headache
Hematologic	Blood dyscrasias (neutropenia, leukopenia, anemia, thrombocytopenia)	Rare, consider baseline CBC but otherwise monitor symptoms
Ophthalmologic	Melanin binding	Lamotrigine binds to melanin and may accumulate in melanin containing tissues over time, particularly the eye. Downstream effects of this are unknown. Providers should be aware of the potential for ophthalmologic effects and encourage regular vision health maintenance.

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Lamotrigine – Drug Interactions

Lamotrigine is metabolized predominantly by glucuronic acid conjugation. Drugs that are known to induce or inhibit glucuronidation may affect the apparent clearance of lamotrigine.

See **Table 15** for lamotrigine major drug interactions.

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Lamotrigine – Drug Interactions, continued

Table 13 - LAMOTRIGINE MAJOR DRUG INTERACTIONS

Interaction	Clinical Concern	Comments
Valproic acid	May increase serum concentrations of lamotrigine	Consider avoiding concomitant therapy if possible, see dosing schedules for dose adjustments
Inducers of glucuronidation (ex: carbamazepine, atazanavir/ ritonavir)	May increase metabolism of lamotrigine	Consider avoiding concomitant therapy if possible, see dosing schedules for dose adjustments
Oral contraceptives (OCP) containing estrogen	May increase metabolism of lamotrigine	If already taking OCP, target lamotrigine dose may need to be increased up to two fold, but continue standard initiation schedule; If starting OCP, consider dose increase at the same time no more rapidly than 50mg/wk based on symptom response; If stopping OCP, decrease dose not more than 25% of daily dose per week based on clinical response
CNS depressants (ex: alcohol, opioids)	Additive effect of CNS depressants	Consider avoiding concomitant use if possible, but if other therapies not efficacious or available consider lower starting dosage and dose titration
Acetaminophen, orlistat	May decrease serum concentration of lamotrigine	Use with caution; advise patients and monitor
Mefloquine	May decrease therapeutic levels of lamotrigine	May be contraindicated for malaria prophylaxis in persons who would experience severe symptoms from lower levels of lamotrigine
Metformin	Lamotrigine may increase serum concentration of metformin	Monitor for metformin toxicity

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Lamotrigine – Therapy Patient Counseling Points

Patients, caregivers, and families should be counseled that lamotrigine may cause serious skin rashes that could require hospitalization or result in death, and that benign rashes may also be caused by lamotrigine. However, it is not possible to predict which rashes will prove to be serious or life threatening. Patients, caregivers, and families should be advised to discontinue lamotrigine at the first sign of a rash (unless the rash is clearly non-drug related) and to a call a healthcare provider or seek immediate medical attention, if they experience any of the following: skin rash, blistering or peeling of the skin, hives and/or painful sores in the mouth or around the eyes.

Patients, caregivers, and families should be counseled that lamotrigine may cause hemophagocytic lymphohistiocytosis (HLH), a life-threatening syndrome marked by signs and symptoms extreme systemic inflammation. Symptoms of HLH have been reported to occur within 8 to 24 days after the first dose of lamotrigine is taken. Patients, caregivers, and families should be advised to seek immediate medical attention while taking lamotrigine, if the experience any of the following:

A. Fever, usually >101°F;
B. Enlarged liver; symptoms may include pain, tenderness, or unusual swelling over the liver area in the upper right belly;
C. Swollen lymph nodes;
D. Skin rashes;
E. Yellow skin or eyes;
F. Unusual bleeding.

Patients, caregivers, and families should be counseled to notify their medical provider if they stop taking lamotrigine for any reason, as well as if they have stopped lamotrigine, they should not resume lamotrigine without consulting their medical provider.

Lamotrigine may cause dizziness, tiredness and fatigue. Patients, caregivers, and families should be counseled to not operate potentially dangerous machinery until they know how lamotrigine will affect them.

Patients, caregivers, and families should be counseled that AEDs, including lamotrigine, may increase the risk of suicidal thinking and behavior, so they need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Patients, caregivers and families should be instructed to report behaviors of concern immediately to a healthcare provider.

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Lamotrigine – Therapy Patient Counseling Points, continued	Patients, caregivers, and families should be counseled to discuss plans to start or stop use of oral contraceptives or other female hormonal preparations with the healthcare provider, as this can significantly affect lamotrigine serum levels. Starting estrogen-containing oral contraceptives may significantly decrease lamotrigine plasma levels and stopping estrogen-containing oral contraceptives may significantly increase lamotrigine plasma levels. Patients, caregivers, and families should be counseled to notify their healthcare provider if they become pregnant or intend to become pregnant during lamotrigine therapy, and if they intend to breastfeed or are breastfeeding an infant.
Related Policy or Procedure	DBH Standard Practice Manual: • Antidepressant Prescribing Guidelines (MDS2035) • Sedative Hypnotics Prescribing Guidelines (MDS2037) • Antipsychotic Treatment Practice Guidelines (MDS2039)
Reference(s)	• Retrospective Analysis of Therapeutic Drug Monitoring Data for Treatment of Bipolar Disorder with Lamotrigine • A Pilot Study of Prophylactic Management of Lamotrigine in Pregnant Women