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SAFER PRESCRIBING OF MOOD STABILIZER MEDICATION GUIDELINE

SCOPE: This Safer Prescribing of Mood Stabilizer Medications Guideline is intended to offer guidance for providers, clients and the interested general public to increase the effectiveness and safety of mood stabilizer use. It is not intended to be comprehensive in scope. These recommendations are not a substitute for clinical judgment. Decisions about care must carefully consider and incorporate the clinical characteristics and circumstances of each individual.

INTRODUCTION: Mood stabilizers are a heterogeneous group of medications. For the purpose of this document, mood stabilizers include lithium, various anticonvulsant medications, and antipsychotic medications. Antidepressants are commonly used as adjuncts to mood stabilizers. This is addressed later in the document.

Mood stabilizers are prescribed for multiple conditions in mental health. They are most often used for the treatment of bipolar disorder. Lithium has an anti-suicidality effect independent of its mood stabilizing effect. Thus it is sometimes prescribed for individuals with suicidal thinking, whether or not they have bipolar disorder. The anticonvulsant mood stabilizers are also used for the treatment of seizure disorders. Antipsychotic medications are frequently used for the treatment of schizophrenia and other types of psychosis. Antidepressant medications are most commonly used to treat depressive and anxiety disorders. Clinically, mood stabilizers are used for the treatment of impulsive aggression, although they are not FDA indicated for this purpose.

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 goal(s), client choice, past medication trials, family history, side effect profile and other factors. See Introduction and Treatment Guidelines in the References and Further Reading section at the end of this document for suggested treatment algorithms for the use of these medications.

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SPECIAL CONSIDERATIONS FOR CHILDREN AND ADOLESCENTS

Lithium and the second generation antipsychotics, aripiprazole, risperidone and quetiapine are the only medications with FDA approval for the treatment of bipolar disorder in children and adolescents. Lithium is approved for ages 12 years and older and the second generation antipsychotics for ages 10 years and older. In general, children and adolescents are more susceptible to adverse effects from medications and so dosing should start low and go as slow as is safe for the clinical presentation. Monitoring and follow up should also be more frequent and include education and collateral information from both the client and their caregivers. Care should be taken to deliver information about medications to children directly, in a developmentally appropriate manner. For additional information, see BHS Guideline for the Safer Use of Psychotropic Medications in Children and Adolescents.

SPECIAL CONSIDERATIONS FOR OLDER ADULTS

The use of mood stabilizers in older adults follow the same general guidelines established for younger adults. There should be 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 order to reduce the risks of accumulation and toxicity. Older adults tend to be more susceptible to experiencing medication-related adverse side effects. The American Geriatrics Society periodically releases updates to the Beers criteria for potentially inappropriate medication use in older adults; the most recent version was released in 2015.

LITHIUM

Background: A naturally occurring element, lithium is FDA approved for the treatment of bipolar 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 cleared 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 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. See Appendix 1 for a list of counseling points.

Dosing: Lithium dosing is generally based on the indication of usage and is guided by lithium serum levels. Usual doses range from 300mg-2400mg/day given once or in divided doses. Once daily dosing may 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 lithium level. See Table 1 below for lithium formulations.

Monitoring: Target serum lithium levels for acute mania are between 0.8-1.2mEq/L and for maintenance therapy in bipolar disorder between 0.6-1.0mEq/L. Lithium levels should be checked once steady-state concentrations are achieved, usually after 5 days of treatment initiation in healthy adults, or sooner if there is suspicion of toxicity, drug interactions or electrolyte/renal abnormalities. Levels should be drawn 12 hours post-dose. Maintenance levels should be checked at least once per year. Lithium toxicity can occur at levels ≥1.5mEq/L and can have severe consequences, thus levels should be monitored regularly as stated above. See Table 2 below for lithium monitoring parameters. For additional information about lithium monitoring, contact the pharmacy department.

Toxicity: Mild lithium toxicity occurs at lithium levels between 1.5-2.0 mEq/L with symptoms of nausea, vomiting, diarrhea, lethargy, coarse hand tremor and muscle weakness. Moderate lithium toxicity 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 ECG changes (flat or inverted T waves). Severe toxicity occurs at levels >2.5 mEq/L with the same symptoms as moderate toxicity in addition to grossly impaired consciousness, increased deep tendon reflexes, seizures, syncope and coma. Treatment of toxicity depends on the severity and can include lithium discontinuation, correction of fluid and electrolyte (salt) imbalances, supportive care and intermittent hemodialysis.

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

Contraindications/warnings: 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.

Adverse Effects: Lithium is associated with a number of adverse effects; many of them can be easily managed. See Table 4 below for additional details.

Pregnancy: Lithium is classified as pregnancy category D. 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. Lithium levels should be monitored very closely throughout pregnancy and delivery.

Lactation: Lithium is highly excreted in breastmilk, and infant serum levels are 1/3 to 1/2 of the mother's serum levels. Signs of infant toxicity include cyanosis, hypotonia and hypothermia. Breastfeeding should be avoided in women 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.

TABLE 1: LITHIUM DOSAGE FORMS

Formulation	Dosage	Time to peak concentration
Immediate release capsule	150mg, 300mg, 600mg	30 minutes to 3 hours
Immediate release tablet	300mg	30 minutes to 3 hours
Extended release tablet	300mg, 450mg	4 to 12 hours
Solution	300mg/5mL	15 minutes to 1 hour

TABLE 2: LITHIUM MONITORING PARAMETERS

Monitoring parameter	Frequency
Serum level	After each change in dose then at least once per year or sooner if clinically indicated
Pregnancy test (in females of childbearing age)	Baseline and if suspicion for pregnancy
Electrocardiogram (ECG)	Baseline and annually, if over 40 years old or with cardiac concerns
Renal function	Baseline, every 3 months for 6 months, then annually
Serum electrolytes, TSH, CBC with differential	Baseline and yearly

TABLE 3: LITHIUM DRUG INTERACTIONS

Interaction	Clinical Concern	Comments
NSAIDs (ex: ibuprofen, naproxen)	Increase lithium levels by up to 60%	Magnitude of interaction depends on the agent; intermittent concomitant use not recommended. Aspirin and sulindac may not influence lithium levels
ACE inhibitors (ex: lisinopril)	Increase lithium levels by 30-40%	Interaction delayed by 3-5 weeks. Consider alternative antihypertensive that does not interact with lithium when possible
ARBs (ex: losartan)	Increase lithium levels up to 20%	Interaction delayed by 3-5 weeks. Consider alternative antihypertensive that does not interact with lithium when possible
Thiazide diuretics (ex: hydrochlorothiazide)	Increase lithium levels up to 40%	Avoid concomitant use when possible
Loop diuretics (ex: furosemide)	Over-diuresis can lead to lithium toxicity	Higher risk in older patients, medical co-morbidities and sodium restricted diets
Osmotic diuretics (ex: mannitol)	Decrease lithium levels by up to 40%	Enhances clearance of lithium; can increase risk of relapse
Potassium sparing diuretics (ex: amilioride)	Minimal effect on lithium levels	Can be used as an antidote for lithium induced nephrogenic diabetes insipidus
Methylxanthines (ex: caffeine, theophylline)	Decrease lithium levels by up to 60%	Abrupt changes in caffeine consumption can alter lithium levels

TABLE 4: 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
	Chronic kidney disease: 15-20% of patients develop slow decline in GFR	Monitor kidney function; $\leq$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

System Affected	Adverse Effect	Management
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

ANTICONVULSANTS

Many anticonvulsants have FDA indications for mood stabilization 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" (or "VPA") will be used to refer to all formulations, i.e., valproic acid and divalproex sodium.

Background: Valproic acid (VPA) is approved by the FDA for the treatment of acute manic or mixed episodes (with or without psychotic features) associated with bipolar disorder. Its exact mechanism of action in managing symptoms of bipolar disorder is not known but theories include the normalization of central GABA pathways and sodium/calcium channel activities, the reduction of intracellular inositol and protein kinase C levels, the presence of anti-kindling properties that are thought to decrease rapid cycling and mixed episodes, and the modulation of gene expression. See Appendix 1 for a list of counseling points.

Dosing: Initiate 500 mg or 750 mg at bedtime with rapid titration (e.g., 500 mg daily) to target 20 mg/kg/day. The maximum recommended dose is 60 mg/kg/day. Initial doses of 20mg/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. See Table 5 below for divalproex dosage forms.

Hepatic disease: Decreases in hepatic clearance may warrant decreased doses. VPA should not be administered in 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.

Renal disease: No dosage adjustment appears to be necessary in individuals with renal failure as reductions in overall renal clearance are not substantial. Note that interpretations of total concentrations may be misleading as protein binding may be significantly reduced in individuals with renal failure.

Monitoring: Target steady-state VPA levels are 50-125 mcg/mL. Higher levels are associated with more adverse effects. VPA levels should be obtained once steady-state is achieved, usually 3-5 days after initiation or dose change. See Table 6 below for divalproex monitoring parameters. For additional information about VPA monitoring, contact the pharmacy department.

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.

Drug Interactions: There are several drug interactions with VPA that can have serious consequences. See Table 7 below for information about drug interactions with VPA.

Contraindications/warnings: VPA is contraindicated in individuals with hepatic disease or significant hepatic dysfunction, urea cycle disorders, mitochondrial disorders, and who have hypersensitivity to the drug. Epidemiological studies have suggested that children exposed to VPA in-utero have a greater risk of having lower IQ scores. Other warnings include pancreatitis, hepatic failure, hyperammonemic encephalopathy, and excessive bleeding.

Adverse Effects: VPA is associated with a number of adverse effects; some of them can be easily managed. See Table 8 below for additional details.

Pregnancy: VPA is classified in FDA Pregnancy Category D with a significant association with malformation risks, particularly neural tube defects (note that VPA in the treatment of migraines are designated as FDA Pregnancy Category X). It is not known whether folic acid supplementation is effective in reducing these risks. In general, VPA should be avoided in women of childbearing age unless there are contraindications to alternative agents or its use is essential for the management of the individual's illness.

Lactation: VPA is excreted in human milk. Caution should be exercised when VPA is administered to a nursing woman.

TABLE 5: VPA DOSAGE FORMS

Formulation	Dosage
Divalproex delayed-release tablet	125mg, 250mg, 500mg
Divalproex extended-release tablet	250mg, 500mg
Divalproex delayed release sprinkle capsule	125mg
Valproic acid capsule	250mg
Valproic acid solution	250mg/5mL
Valproate IV solution	100mg/mL

TABLE 6: VPA MONITORING PARAMETERS

Monitoring parameter	Frequency
Serum level	After initiation and each change in dose, then at least once per year or sooner if clinically indicated. Consider obtaining free serum concentration when altered protein binding might be expected (e.g., in elderly, malnourished, or medically ill individuals, or when clinically significant drug interactions are present).
CBC with differential,	At baseline, 2 weeks after initiation or dose change, then at semiannual to

Hepatic function	annual intervals
Monitoring parameter	**Frequency**
Renal function	At baseline
Pregnancy test (in women of childbearing age)	At baseline, and if pregnancy is suspected

TABLE 7: VPA MAJOR DRUG INTERACTIONS

Interaction	Clinical concern	Comments
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

TABLE 8: 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
Hematologic	Thombocytopenia	Reduction of dose or discontinuation of therapy

CARBAMAZEPINE

Background: Carbamazepine (CBZ) is FDA approved for treatment of acute mania, bipolar maintenance and has evidence for efficacy in mixed episodes and rapid cycling forms of the disorder. CBZ, like other anticonvulsants, inhibits voltage sensitive sodium channels. It is generally considered second line treatment due to significant drug interactions, autoinduction of metabolism and significant monitoring requirements. See Appendix 1 for a list of counseling points.

Dosing: Dosing for adults begins at 200mg twice daily with increases by no more than 200mg/day every 2-7 days, maximum dose 1600mg/day. CBZ is not approved for treatment of mood disorders in children. Children may be more susceptible to adverse effects. Use with caution as well in geriatric populations due to risk of SIADH or hyponatremia. Use reduced doses in both populations. Avoid use with significant renal or hepatic impairment. See Table 9 for CBZ available dosage forms.

Monitoring: Target serum CBZ levels are between 4-12mcg/mL. 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. See Table 10 for additional monitoring parameters.

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 11 indicates some interactions with common medications, however, drug interactions should be checked carefully any time considering starting CBZ or making changes to existing medication regimen.

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 12 for additional information about adverse effects from CBZ.

Pregnancy: CBZ is classified as pregnancy category D: **s**tudies in pregnant women have demonstrated a risk to the fetus. 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, however, socioeconomic and genetic factors as well as poly-therapy may contribute to these findings. When 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.

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. Nursing should be discontinued if adverse events are observed. The decision to continue or discontinue breast-feeding during therapy should take into account the risk of exposure to the infant and the benefits of treatment to the mother.

TABLE 9: CARBAMAZEPINE DOSAGE FORMS

Formulation	Dosage	Time to peak concentration
Immediate release tablet	200mg	4-5 hours
Immediate release chewable	100mg	4-5 hours
Extended release tablet	100, 200, 400mg	12-26 hours

TABLE 10: CARBAMAZEPINE MONITORING PARAMETERS

Monitoring parameter	Frequency
Serum level	1-2 weeks after initiation, change in dose or change in overall medication regimen
Pregnancy test (in women 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
HLA-A*3101	At baseline in at-risk populations

TABLE 11: 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
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

TABLE 12: CARBAMAZEPINE 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 Asian populations	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.

OXCARBAZEPINE

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

LAMOTRIGINE

Background: Lamotrigine is indicated to delay the onset of new mood episodes in the maintenance treatment of bipolar disorder. 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 has not received FDA indication for this purpose. Mechanisms of action for lamotrigine include inhibition of voltage sensitive sodium channels and reduction of release of the excitatory neurotransmitter glutamate. See Appendix 1 for a list of counseling points.

Dosing: Lamotrigine has a unique dose titration schedule due to rare but serious risk of dermatologic reactions. See Table 13 below for details on dosing and titration. Lamotrigine is available in immediate and extended release formulations and often can be ordered in a dosing kit with multiple strengths to simplify the titration process. See Table 14 below for available lamotrigine dosage forms. 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 lamotrigine has been withheld for more than 5 days, the medication should be restarted following the same protocol as an initial titration. Initial, escalation and maintenance doses should be reduced at least 25% in patients with moderate to severe liver impairment and 50% with ascites.

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 below for lamotrigine major drug interactions.

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 16 below for details. Routine measurement of lamotrigine levels are not recommended.

Pregnancy: Lamotrigine is classified in pregnancy category C (not enough research had been done to determine safety). Available review studies have found overall rates of congenital malformation in infants exposed to lamotrigine in-utero to be relatively low (1-4%) which is similar to the rate of malformation in the general population.

Lactation: Lamotrigine is expressed in breast milk at levels up to 50% of serum levels; as such breast feeding while on lamotrigine is not recommended, however risks and benefits to mother and child should be considered when deciding appropriate treatment course.

TABLE 13: 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

TABLE 14: LAMOTRIGINE DOSAGE FORMS

Formulation	Dosage	Time to peak concentration
Immediate release tablet	25, 100, 150, 200 mg	1-5 hours
Immediate release chewable	5, 25 mg	1-5 hours
Immediate release disintegrating	25, 50, 100, 200 mg	1-5 hours
Extended Release tablet	25, 50, 100, 200, 250, 300 mg	4-11 hours

*Lamotrigine is also available in dosing kits with multiple strengths to allow easier initial titration. Ask pharmacy for availability.

TABLE 15: LAMOTRIGINE MAJOR DRUG INTERACTIONS

Interaction	Clinical Concern	Comments
Valproic acid	May increase serum concentrations of lamotrigine	Avoid concomitant therapy if possible, see dosing schedules for dose adjustments
Inducers of glucuronidation (ex: carbamazepine, atazanavir/ritonavir)	May increase metabolism of lamotrigine	Avoid 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	Avoid 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

TABLE 16: 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.

ANTIPSYCHOTIC MEDICATIONS

Antipsychotic medications are effective for the treatment of acute mania and are frequently prescribed in the maintenance phase of bipolar disorder to prevent the recurrence of mania or hypomania. The antipsychotic medications quetiapine, lurasidone, olanzapine and the combination of olanzapine with the antidepressant fluoxetine have evidence as effective treatments for the depressed phase of bipolar disorder.

Antipsychotic medications tend to have a faster onset of action compared to other types of mood stabilizers and are useful in acute and crisis situations. Certain antipsychotics are available as long-acting injectable formulations which can be helpful for individuals who have difficulty taking oral medications daily.

Antipsychotic medications have numerous risks associated with their use including weight gain, metabolic syndrome, movement disorders which sometimes can be permanent, and other issues. See the related BHS Guideline, Safer Prescribing of Antipsychotic Medications, for additional information.

ANTIDEPRESSANT MEDICATIONS

Though switching between the depressed and manic/hypomanic phases of bipolar disorder can be a natural part of the condition, antidepressant medications given alone can induce these switches. Antidepressants do not treat or prevent mania/hypomania and should not be used for those mood dysregulations.

Antidepressant medications are often prescribed for the treatment of the depressed phase of bipolar disorder. They should only be used as adjunctive therapies in individuals taking a mood stabilizer that prevents mania/hypomania. There is published evidence for their effectiveness in the short term. Once depressive symptoms abate, attempts should be made to remove antidepressant medications to avoid the risk of switching to mania/hypomania. Should mania/hypomania develop while taking an antidepressant medication, the antidepressant agent should be stopped immediately.

There are numerous antidepressant medications available; each have different risks associated with their use. Common side effects for many of them include sedation or activation, sexual dysfunction and weight gain. More serious risks include the aforementioned mood switching, blood pressure changes, prolonged QT interval, and other effects. See the related BHS Guideline, Safer Prescribing of Antidepressant Medications, for more information.

ANTIPSYCHOTIC-ANTIDEPRESSANT COMBINATION

There is only one antipsychotic-antidepressant combination medication in a single capsule: olanzapine-fluoxetine. It has an FDA indication for the treatment of acute depression associated with bipolar disorder and for treatment-resistant depression. See Table 17 below for dosing information.

Side effects are those of both olanzapine and fluoxetine individually. Common side effects include somnolence, fatigue, edema, hyperglycemia, hyperlipidemia, weight gain (metabolic syndrome), increased appetite, dry mouth and others. See sections of this guideline on antipsychotic medications and antidepressant medications as well as the related BHS Guidelines, Safer Prescribing of Antipsychotic Medications, and Safer Prescribing of Antidepressant Medications, for more information.

TABLE 17: OLANZAPINE-FLUOXETINE COMBINATION DOSING

Combination product formulation	Equivalent olanzapine dose	Equivalent fluoxetine dose
Olanzapine 3mg/fluoxetine 25mg	2.5mg	20mg
Olanzapine 6mg/fluoxetine 25mg	5mg	20mg
Olanzapine 12mg/fluoxetine 25mg	12.5mg	20mg
Olanzapine 6mg/fluoxetine 50mg	5mg	50mg
Olanzapine 12mg/fluoxetine 50mg	12.5mg	50mg

* Usual dose range is olanzapine 6 to 18mg/fluoxetine 25 to 50mg. Lower starting doses should be used in children and adolescents, older adults, individuals predisposed to hypotension, hepatic impairment and those with combined risk factors for reduced metabolism (i.e. female, non-smoker)

ELECTROCONVULSIVE THERAPY

Electroconvulsive therapy (ECT) is a procedure in which an electrical charge is applied to stimulate a seizure in the brain. The mechanism of action is hypothesized to be seizure-induced changes in neurotransmitters, neuroplasticity and functional connectivity. It is efficacious for bipolar depression with response/remission rates of >50%. It can also be used for other phases of bipolar disorder including mania, mixed states and catatonia. Doses of antiepileptic mood stabilizers may need to be held during ECT treatment. Treatment guidelines often recommend ECT as third line treatment (or later) depending on specific bipolar phase.

ECT is contraindicated in those with recent myocardial infarction, active bleeding, or any cerebral lesions or hemorrhage. It is considered relatively safe during all trimesters of pregnancy. Side effects include confusion, impaired memory, headache and muscle aches; minimizing ECT dose and using unilateral electrode placement may minimize these side effects.

ECT is available at ZSFG upon referral by sending a secure email to Melissa Nau (Melissa.nau@ucsf.edu) and Jo Ellen Brainin-Rodriguez (Jbrainin-rodriguez@ucsf.edu) or by leaving a message on the ECT referral voicemail at 415-206-2930 which is checked weekly.

POTENTIAL MOOD STABILIZING AGENTS UNDER INVESTIGATION

KETAMINE

Ketamine acts primarily as an antagonist of the NMDA receptor. It is currently used in medical practice as an anesthetic agent and for acute post-operative pain management. It has also been used as a recreational drug of abuse. At high doses ketamine produces a sensation of dissociation as well as visual and auditory hallucinations.

In recent years there have been a number of studies indicating promising efficacy of intravenous infusions of ketamine in addressing symptoms of treatment resistant bipolar depression. Phase 2 trials are currently underway involving an active metabolite of ketamine, GLYX-13, which is thought to possess the anti-depressant properties of ketamine with less risk for the dissociative side effects. At this time, ketamine is not routinely used for the treatment of psychiatric disorders, and is only available in select clinical or academic settings.

TRANSCRANIAL MAGNETIC STIMULATION (TMS)

TMS is a procedure during which a magnetic field generator delivers small electric currents to certain parts of the brain via a stimulator coil that is placed near the scalp. It is thought to modulate neuronal activity in dysfunctional areas of the brain. The effects of TMS depend on the frequency, intensity and duration of stimulation. TMS is FDA approved for the treatment of major depressive disorder in individuals who have failed at least one adequate antidepressant trial. Side effects include transient

headache, local pain, neck pain, toothache, paresthesia, transient hearing changes, seizure induction, transient hypomania induction and transient cognitive changes.

The use of TMS in bipolar disorder is not well established. It has not been studied in a systematic manner for bipolar depression, although several open-label studies showed a positive antidepressant effect. The possibility of TMS inducing hypomania or mania is a concern that should be taken into consideration. Discontinuation of TMS should be considered if TMS-induced mania or hypomania occurs. The use of TMS for acute mania or hypomania is controversial and requires further investigation.

Currently, TMS is not covered by Medi-Cal. Some Medicare plans may cover the cost of TMS.

TREATMENTS WITH INSUFFICIENT EVIDENCE TO RECOMMEND AS MOOD STABILIZERS

SEDATIVE-HYPNOTICS

Sedative hypnotics are not mood stabilizers. They do not have a direct role in mood regulation. However, frequently this class of medications is used to treat agitation in acute mania. They are sometimes used to treat insomnia related to mood disorders in the short term. There are numerous risks associated with chronic use of this class of medications including dependence, memory impairment and serious drug-drug interactions. Chronic use should be avoided. See the related BHS Guideline, Safer Prescribing of Sedative Hypnotics, for additional information.

GABAPENTIN

Published clinical trials have not found gabapentin to be efficacious as a mood stabilizing agent either as monotherapy or adjunctive therapy. Gabapentin is often used in other psychiatric and substance use disorders.

TOPIRAMATE

Topiramate was originally thought to have efficacy in treating mania based on open add-on trials. In subsequently conducted double-blind, placebo-controlled trials, topiramate did not separate from placebo and was found to be less effective than lithium as anti-manic therapy.

CANNABIS

At this time, there is insufficient evidence to recommend the use of cannabinoid products in the treatment of bipolar or mood disorder. Cannabinoids can worsen psychiatric symptoms in some individuals.

HERBALS

No herbal supplements have evidence to support their use in bipolar mania or mixed states. The omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have some limited evidence to support their adjunctive use in bipolar depression. The suggested dose is 1-1.5 grams/day of mixed EPA and DHA with a higher ratio of EPA. Adverse effects include gastrointestinal upset, diarrhea and constipation.

In contrast to prescription medications, companies that manufacture herbal supplements do not have to seek FDA approval before putting their products on the market. They can state that their products address nutrient deficiencies, support health or are linked to body functions, as long as they include a disclaimer that the FDA has not evaluated the claim. Once an herbal supplement is on the market, the FDA is responsible for monitoring its safety. If a product is found to be unsafe, the FDA can take action against the company and may require the product to be removed from the market.

The regulations surrounding herbal supplements do not guarantee that they are effective or safe for anyone to use. Supplements should be reviewed for possible adverse effects and drug interactions before being cleared for patient use. Most insurance plans do not cover herbal supplements, so individuals may have to pay out-of-pocket if they wish to try them.

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APPENDIX 1: MOOD STABILIZER COUNSELING POINTS

***The National Alliance on Mental Illness (NAMI) has information sheets for many mental health medications that are aimed at consumers. They are available at:**

https://www.nami.org/Learn-More/Treatment/Mental-Health-Medications

LITHIUM

1. Lithium should be taken at the same time every day. Lithium may be taken with food if it causes an upset stomach. Adequate hydration should be maintained and dehydration avoided. Excessive thirst and/or significant urination should be reported.

2. Blood levels will be measured to check that the lithium is in the right range to achieve the most benefit with minimal risk of developing side effects.

3. Significant changes in sodium intake, excessive caffeine intake, or abrupt changes in caffeine intake can alter lithium levels.

4. Over-the-counter (OTC) anti-inflammatory medications such as ibuprofen or naproxen can interact with lithium. All providers should be aware when a patient is on lithium so they can watch out for drug interactions.

5. 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. Periodic blood tests will be done to monitor for certain side effects.

6. Lithium may increase the risk of birth defects or complications if taken during pregnancy. Healthcare providers should be contacted immediately if a patient on lithium becomes pregnant. Lithium has some associated risks when used while breastfeeding; health care provider should be consulted if you plan on breastfeeding.

VALPROIC ACID

1. VPA can be taken with or without food. Medication may be taken with food if it causes an upset stomach.

2. DR and ER tablets should be swallowed whole. They should not be crushed, chewed, or split (except for sprinkle capsules which can be opened up and mixed in food).

3. Blood levels should be measured to check that the VPA is in the right range to achieve the most benefit with a minimal risk of developing side effects.

4. Side effects of VPA may include: feeling sleepy, 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 symptoms occur.

5. VPA may cause birth defects if taken during pregnancy. A reliable form of birth control is recommended while taking this medication. If pregnancy occurs, healthcare providers should be contacted immediately. VPA has some associated risks when used while breastfeeding; healthcare providers should be consulted if a patient on VPA plans to breastfeed.
6. VPA can potentially cause liver problems with serious side effects, even resulting in death. Signs of liver failure include yellowing of the skin or eyes, dark urine, extreme fatigue, decreased appetite, nausea, or vomiting. Healthcare providers should be contacted immediately if any of these symptoms occur. Blood tests should be taken periodically to monitor for the development of liver problems.
7. VPA can potentially cause pancreatitis. Signs of pancreatitis include severe nausea and vomiting, abdominal pain, or decreased appetite. Healthcare providers should be contacted immediately if any of these symptoms occur.

CARBAMAZEPINE

1. Carbamazepine has significant interactions with other prescription and over the counter medications. Healthcare providers should be told about any changes in prescription medications or over the counter products while patients are taking carbamazepine.
2. Carbamazepine is associated with many side effects, the most serious being changes in blood counts, skin rash or psychiatric side effects. Healthcare providers should be contacted immediately if a new rash, fever, blisters, easy bruising, confusion, agitation or increase in suicidal thinking occur.
3. Grapefruit products may increase levels of carbamazepine. Patients should read food/drink labels and avoid consuming grapefruit while taking carbamazepine.
4. Carbamazepine can reduce the effectiveness of hormonal contraceptives and is also associated with birth defects when taken during the first trimester. Patients should not use carbamazepine if they are pregnant or planning to get pregnant. Additional non-hormonal forms of birth control should be used while taking carbamazepine.

LAMOTRIGINE

1. Lamotrigine can cause a rash rarely. Healthcare providers should be contacted immediately if a rash, fever or swelling occur.
2. Lamotrigine can cause an increase in suicidal thinking. Healthcare providers should be notified if this occurs.
3. Lamotrigine may cause dizziness, tiredness and fatigue. Patients should not operate potentially dangerous machinery until they know how lamotrigine will affect them.
4. Healthcare providers should be notified if patients are using contraceptives, plan to start or stop contraceptives or become pregnant or are breastfeeding while taking lamotrigine.