DSH PSYCHOTROPIC MEDICATION Operational Procedures

Lithium Protocol

I. **Indications (at least one of the following is documented in the chart):**

A. DSM bipolar mood disorder (especially type I).

B. DSM schizoaffective disorder.

C. Adjunctive augmentation treatment of DSM major depressive disorder.

D. Persistent or recurring suicidality, regardless of diagnosis.

E. Mild to moderate leukopenia.

F. Psychomotor agitation or assaultiveness demonstrated and documented to be unresponsive to behavior modification as part of a behavioral treatment program, especially in the contexts of mood disorder, personality disorder, traumatic brain injury, or neurocognitive disorder.

G. The individual cooperates with lithium monitoring.

II. **Contraindications:**

A. Demonstrated sensitivity to lithium or any components of the lithium preparation prescribed.

B. Acute renal failure. Individuals treated with stable renal transplant, peritoneal dialysis, or hemodialysis may be candidates for lithium treatment. In such cases, however, careful consultation and collaboration with a nephrologist is strongly recommended.

C. Psoriasis.

D. Sick Sinus Syndrome

E. Nephrogenic diabetes insipidus (renal arginine vasopressin insensitivity)

III. **Precautions (documented risk/benefit analysis supports use):**

A. Unstable renal function, e.g., as evidenced by abrupt declines in eGFR > 10 ml/min, fluctuations in eGFR > 20 ml/min, failure to return to prior eGFR baseline after lithium discontinuation or reduction to a lithium plasma concentration of < 1.0 mMol/L, or a progressive decline in eGFR from > 70 ml/min to < 60 ml/min importantly, longitudinal, as well as cross-sectional, renal function must be considered. These examples apply only if accurate e.g., verified through repeat eGFR, or the cause of eGFR changes are well understood.

In patients with existing lithium treatment, lithium may be discontinued or reduced until the patient's renal function stabilizes. If lithium is resumed or increased after an episode of acute renal failure or unstable functioning, renal function should be

closely monitored until it is clear that the patient's kidneys can tolerate lithium treatment without a substantial decline in renal function.

B. Hypothyroidism.

C. History of or current cystic acne.

D. Bradycardia or cardiomyopathy associated with bradycardia.

E. Pregnancy (increases Ebstein's anomaly from 1 per 20,000 live births to 1 per 2,000 live births when given during the first trimester prior to week five of gestation) or breast-feeding. Note, however, that lithium can be safely given during the second and third trimesters, i.e. following cardiac formation.

F. Concurrent use of thiazide diuretics, ACE inhibitors, or NSAIDs. **Combination with lisinopril especially should be avoided**, as this ACE inhibitor is 100% renally cleared and combination with lithium may lead to a decline in GFR and severe lithium toxicity, including permanent neural damage or death.

G. Recurring dehydration

H. Chronic (or recurring) hyponatremia, as renal efforts to reabsorb sodium also increase lithium reabsorption and may result in lithium toxicity.

I. Evidence of decreased renal concentrating capacity, as evidence by polyuria, polydipsia, and/or dilute early morning urine osmolality. In such cases, early treatment with amiloride to decrease lithium trapping inside distal nephron tubule principle cells leading to arginine vasopressin insensitivity and eventual nephropathy and loss of the number of functional renal nephrons. Also, early polyuria, polydipsia, and decreased urine concentrating capacity may portend development of frank nephrogenic diabetes insipidus as lithium concentrations are increased. [NOTE: The context of decreased urine concentrating capacity, as opposed to primary polydipsia, water intake must <u>not</u> be restricted, as such restriction will lead to plasma hyperosmolality and hyperkalemia that may result in death due to cardiac arrhythmia.]

IV. **Pretreatment workup:**

A. Informed consent or alternative legal authorization is present.

B. Pretreatment evaluation should include physical examination of the thyroid gland and taking of history regarding thyroid disease, renal disease, cardiac disease, and potential pregnancy.

C. Monitoring:

1. Baseline: (obtain if not done within the previous 30 days except for the ECG which is acceptable if performed within the prior 12 months)

a. Thyroid panel, including TSH.

b. CBC, BUN, creatinine, estimated glomerular filtration rate (eGFR), and electrolytes including calcium.

c. ECG. An ECG should be obtained as proximately as possible before beginning lithium treatment if relevant cardiopathology (e.g., sick sinus syndrome, recurring bradycardia, or cardiomyopathy with bradycardia) is suspected.

d. Pregnancy test in women who are of childbearing potential and are at risk of pregnancy.

e. Urinalysis and early morning urine osmolality. Note that decreased early morning urine osmolality is a marker for either excessive water intake and/or decreased renal concentrating capacity.

2. Weekly (for first month): Except for newly admitted or transferred Individuals on a stable dose of lithium. These Individuals may begin monitoring of lithium concentrations at a semi-annual frequency.

   a. Plasma lithium concentration. Steady-state plasma concentration is achieved 5 to 7 days after each dose adjustment.

3. Monthly:

   Lithium plasma concentration during months 2 and 3 of lithium treatment (except individuals admitted or transferred with stable lithium treatment). Additional labs during months two and three of lithium treatment should include eGFR and early morning urine osmolality. If eGFR and/or early morning urine osmolality show progressive declines, then monitoring should be continued at a monthly frequency until the values stabilize and/or lithium is discontinued.

4. Semi-annually:

   a. Lithium plasma concentration during the first year of lithium treatment.

   b. CBC, BUN, creatinine, eGFR, early morning urine osmolality, and electrolytes including calcium during the first year of lithium treatment.

   c. TSH during the first year of lithium treatment.

5. Annually:

   a. Thyroid panel, including TSH.

   b. Calcium, electrolytes, BUN, creatinine, eGFR, and early morning urine osmolality.

6. Lithium plasma concentration should be measured 5 to 7 days after any dose increases.

V. **Dosing:**

A. Lithium (immediate release (IR) and extended release (ER)) is typically initiated at a dose of 600 – 900 mg at bedtime. NOTE: It should not be prescribed in divided doses as this increases the risk of long-term chronic renal disease. The ER formulation is less likely to result in post-dose nausea, a common adverse response to higher doses of the IR formulation. Switching from ER to an IR formulation or taking lithium with dinner helps resolve diarrhea

There is no difference in renal injury risk between the IR and ER lithium formulations.

Dosing is thereafter adjusted depending upon desired plasma concentration, e.g. 0.8 – 1.0 mMol/L in bipolar or schizoaffective illness or 0.6 – 0.8 mMol/L when used as an adjunctive augmenting agent for major depression or in elderly patients.

Long-term exposure to lithium plasma concentrations >1.0 mMol/L increases the risk of chronic renal disease.

In acute, severe mania, plasma concentrations of as much as 1.2 mMol/L may be required. Plasma concentrations > 1.0 mMol/L should be maintained for no more than two weeks. If needed, acute mania also can be stabilized using a second mood stabilizer, antipsychotic medications, or high-potency benzodiazepine (e.g., lorazepam or clonazepam). Because mania may be driven by antidepressants and/or sleep deprivation, antidepressants should be discontinued and effective sedation should be provided (e.g., via selective sedatives such as eszopiclone or orexan antagonists such as suvorexant).

In urgent cases, lithium may be loaded by giving 30 mg/kg of extended-release lithium (Lithobid®) in three divided doses on day one (e.g., at 1600, 1800, and 2000). The calculated lithium dose should be rounded to the nearest multiple of 300 mg, but should not exceed 3000 mg. If the lithium plasma concentration the next morning (day two) is <1.0 mMol/L, then prescribe immediate release lithium 1500 mg at bedtime. If the morning lithium plasma concentration is >1.0 mMol/L, then give immediate release 1200 mg at bedtime.

A follow-up lithium level should be obtained 5 to 7 days after beginning lithium treatment to permit further adjustment of the lithium dose.

Note that extended-release lithium is used only on the first day of loading. The reason for using the extended-release formulation on the first day (loading) is to decrease the risk of post-dose nausea.

Daily lithium doses >2100 mg for more than 15 days require Medication Review Committee (MRC) or Therapeutic Review Committee (TRC) consultation or review.

B. Use of once-per-day dosing will reduce impairment of renal concentrating capacity and the consequent induction of nephrogenic diabetes insipidus. This dosing strategy is usually limited by post-dose nausea and/or vomiting as peak plasma concentrations increase. Dosing at bedtime tends to decrease post-dose adverse effects.

C. Elderly patients have relatively lower total body water and, therefore, a lower volume of distribution for lithium. Additionally, decreasing glomerular filtration rates (GFR) in the elderly will reduce the dose required to achieve the same plasma concentrations. These factors also make elderly patients more vulnerable to lithium toxicity. The target plasma concentration range for most elderly is 0.6 to 0.8 mMol/L. **Lithium should be avoided in patient's whose eGFR is < 50 ml/min regardless of age.**

D. Lithium is not metabolized and is not protein-bound. All of its pharmacokinetic drug interactions are, therefore, renally based.

1. For example, NSAIDs may increase lithium plasma concentrations by up to 40%.

2. Thiazide diuretics may increase lithium concentrations several fold. These interactions are especially important because lithium has a narrow therapeutic index, with toxicity often observed at concentrations as low as 1.5 mMol/L.

3. At toxic concentrations, lithium traps itself within neurons by poisoning the sodium/potassium pump. Thus, concentrations above 2.0 mMol/L may cause permanent neurological injury despite hemodialysis to plasma concentrations of 0 mMol/L. Often repeated dialysis or prolonged forced diuresis is required to adequately remove intracellular lithium.

E. Pharmacodynamically, lithium interacts rarely with first generation antipsychotics to cause delirium, which may progress to a drug-induced dementia.

Lithium also may interact with calcium-channel antagonists (e.g., verapamil) to cause bradycardia or asystole.

Also, lithium may rarely interact with serotonergic medications (e.g., SSRI antidepressants) to cause serotonin syndrome.

VI. **Side-effects**

A. G.I. upset (post-dose)

B. Tremor

C. Diarrhea

D. Polyuria/polydipsia, up to and including nephrogenic diabetes insipidus

E. Hypothyroidism

F. Exacerbation of dermatitis, acne, psoriasis

G. Weight gain

VII. **Dose reduction /discontinuation is recommended when the following signs/symptoms are observed**.

WARNING SIGNS OF TOXICITY		
T-Wave Inversion	Ataxia	Lethargy
Vomiting	Vertigo	Hyperreflexia
Dysarthria	Confusion	Coarse Hand Tremor

VIII. **Factors Promoting Lithium Toxicity:**

FACTORS PROMOTING TOXICITY	
1	Too little sodium (e.g., due to chronic hyponatremia, low salt diet, fad diet, or salt substitute).
2	Dehydration, due to diuretics, excessive sweating, fever, or poor fluid intake (secondary to physical illness or mental illness).
3	Drug interactions (e.g., thiazide diuretics, ACE inhibitors, and NSAIDs).

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