NATIONAL PBM BULLETIN

JULY 25, 2016

DEPARTMENT OF VETERANS AFFAIRS
PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP),
VISN PHARMACIST EXECUTIVES (VPEs), AND THE CENTER FOR MEDICAL SAFETY (VA MedSAFE)

Alerts are based on the clinical evidence available at the time of publication. Recommendations are intended to assist practitioners in providing consistent, safe, high quality, and cost effective drug therapy. They are not intended to interfere with clinical judgment. When using dated material, the clinician should consider new clinical information, as available and applicable.

LITHIUM SAFETY

I. ISSUE

A local facility initiated a root cause analysis after a patient received treatment in the ICU for lithium toxicity where it was discovered that the patient's lithium level had not been checked for several years. Further review at that VA found that out of all Veterans prescribed lithium between June 2015-June 2016 (N=244), 59 (24%) had not had a lithium level drawn within the last 12 months. A review of national VA data found that of approximately 17,000 Veterans prescribed lithium, 19.5% had not had a lithium level checked in the past 9 months.

II. BACKGROUND

Vast clinical experience and well-controlled studies demonstrate the effectiveness of lithium in preventing both manic and depressive episodes associated with bipolar disorder. Lithium also has antidepressant effects and is sometimes used to augment other antidepressants in refractory patients. Lithium has a narrow therapeutic index that necessitates close monitoring of plasma concentrations.

III. DISCUSSION

Lithium toxicity is closely related to serum lithium levels and can occur at doses close to therapeutic levels, with tremor occurring at concentrations within the therapeutic range and more serious CNS effects (confusion, ataxia, seizures, and coma) occurring above the therapeutic range. Risk factors that predispose patients to elevated lithium concentrations and potential toxicity may include: decreased sodium intake or increased sodium excretion (i.e., low-sodium diet, diuretics, excessive exercise/sweating, diarrhea/vomiting, salt deficiency); decreased water intake or increased water excretion (i.e., dehydration, diuretics [thiazide, loop, potassium sparing], fever, physical illness [flu, surgery, diarrhea, vomiting], postpartum fluid changes, slimming diets); renal disease or decreased renal blood flow (i.e., renal dysfunction, nonsteroidal anti-inflammatory agents); and drug interactions (i.e., thiazide diuretics, furosemide, caffeine via diuresis, desmopressin, angiotensin converting enzyme inhibitors [ACEIs], angiotensin receptor blockers [ARBs], and nonsteroidal anti-inflammatory drugs [except sulindac]). Table 1 shows ranges of lithium concentration where signs and symptoms of toxicity can occur as well as guidance for the management of toxicity. Treatment of lithium toxicity depends on severity and should consist of supportive care with monitoring of vital signs, cardiac, pulmonary and neurologic status, electrolytes, and plasma lithium concentrations. During maintenance therapy with lithium, monitoring for several laboratory parameters can help to minimize potential adverse events. The recommended guidelines for laboratory tests and monitoring are listed in Table 2.

IV. PROVIDER CONSIDERATIONS/RECOMMENDATIONS

According to the VA/DoD Clinical Practice Guidelines:

- If lithium toxicity occurs, the primary goal of treatment should be to correct any fluid or electrolyte imbalance and to lower

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LITHIUM SAFETY *(continued from page 1)*

lithium concentrations. Signs and symptoms of lithium toxicity as well as management recommendations include:

Table 1. Signs and Symptoms and Management of Lithium Toxicity.

Lithium Concentration (12-hours post dose unless specified)	Interpretation Signs and Symptoms of Toxicity	Management
1.2 – 1.5 mEq/L	Warning of potential serious toxicity New onset or worsening of tremor, nausea vomiting, diarrhea, drowsiness, sluggishness	Hold lithium until concentration returns to therapeutic range. Identify causes of toxicity: drug-drug & drug-diet interactions, dosing errors. If a cause cannot be identified, then evaluate the patient's kidney function.
1.6 – 2.5 mEq/L	Serious, but not considered life-threatening Coarse, irregular tremor, apathy, sluggishness, drowsiness, sleepiness, speech difficulty, smaller myoclonic twitching, muscular weakness, ataxia, and small increase in serum creatinine	Hold lithium; determine when last dose taken; repeat lithium concentration $\leq$ 3 hours (if dose not taken in the past 12 hours); assess fluid status, electrolytes, and renal function. Assess for drug-drug & drug-diet interactions. Admission may be necessary to manage fluid and electrolytes.
>2.5 mEq/L	Severe toxicity; >3.5 mEq/L is a medical emergency. Nausea, vomiting, diarrhea, renal failure, hyperreflexia, myoclonic and choreoathetoid movements, ataxia, dysarthria, coarse tremor, confusion, delirium, hallucinations, seizures, stupor, and coma.	Admit patient for management and assessment.

- Recommendations for monitoring of lithium include:

Table 2. Recommended Pharmacotherapy Monitoring

	Starting Therapy		Follow-up during Ongoing Therapy (Stable Outpatient)
Medication	**Baseline**	**During Titration**	
Lithium 0.6 to 1.2 mEq/L	sCr, eCrCl, Electrolytes, Thyroid profile Pregnancy test	Lithium serum concentration every 4-14 days	- Every 6 months serum concentration - Annual sCr, eCrCl - Annual Thyroid profile - Annual CBC with diff

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LITHIUM SAFETY *(continued from page 2)*

- Providers should continue to report any adverse reactions with the use of lithium by entering the information into CPRS' Allergies/ Adverse Reactions field and/or via local reporting mechanisms. Adverse events should also be reported, as appropriate, to the VA ADERS program and FDA MedWatch (1-800-FDA-1088, fax 1-800-FDA-0178, online at https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm, or by mail).

V. REFERENCES

1. VA/DoD Clinical Practice Guideline for Management of Bipolar Disorder in Adults, Version 2.0; The Management of Bipolar Disorder Working Group, 2009. http://www.healthquality.va.gov/ . (Accessed 07/18/2016).
2. Fankhauser, MP and Benefield, WH. (1997). Bipolar Disorders. In DiPiro JT (Ed.), Pharmacotherapy: A Pathophysiologic Approach (pp. 1419-1441). Stamford, Connecticut: Appleton & Lange.

ACTIONS

- ***Facility Director*** *(or physician designee): Forward this document to the Facility Chief of Staff (COS).*
- ***Facility COS and Chief Nurse Executives:*** *Forward this document to all appropriate providers and health care staff (e.g., **primary care providers, mental health providers, including contract providers, etc.**). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.*
- ***ACOS for R&D:*** *Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).*