Teachgression in a Treatment of Bipolar Disorder. Aside from understanding the therapeutic drug management of lithium and the factors that influence serum lithium concentrations, the student should understand the clinical usefulness of serum lithium concentrations, the reasons for obtaining them, and how to interpret them. Significant emphasis is placed on the student being able to apply the information to clinical scenarios and becoming an inquisitive problem solver. To that end, case studies are used to promote a deeper understanding of lecture material.

Keywords: Lithium, pharmacokinetics, therapeutic drug monitoring, bipolar disorder

INTRODUCTION
Therapeutic Drug Management is a 2-course sequence that emphasizes the application of pharmacokinetic principles to the individualization of drug regimens. The course philosophy is that students should learn to be problem solvers. They should be able to identify the problem, identify and retrieve missing information, apply appropriate principles, choose realistic solutions, and recommend appropriate follow up. The TDM of lithium therapy is taught via a traditional 80-minute lecture using PowerPoint slides. Students then complete case studies in an independent manner, followed by a 2-hour small-group work session in which students discuss their findings with peers and the instructor. After completing the course, students should be able to:

1. Describe the basic pharmacokinetic parameters of lithium;
2. Recognize factors that influence serum lithium concentrations;
3. List the important drug interactions of lithium;
4. State the usual therapeutic range for lithium in the acute and maintenance treatment of mania;
5. Recognize the various signs/symptoms of lithium toxicity;
6. Discuss reasons for obtaining a serum lithium concentration;
7. Interpret serum lithium concentrations that differ from expected values; and
8. Describe and apply lithium dosing methods.

INSTRUCTIONAL DESIGN
Clinical Use of Lithium
Despite the introduction of many other mood stabilizers, lithium continues to be considered first-line therapy for treatment of acute mania and long-term prophylaxis of bipolar disorder. It is also used in a variety of other conditions, such as schizoaffective disorder, major depressive disorder (adjunctive therapy), schizophrenia (adjunctive therapy), aggression, premenstrual dysphoria, and cluster headaches.

Basic Pharmacokinetics of Lithium
Lithium is available in regular-release tablets and capsules (as carbonate salt), extended-release tablets (as carbonate salt), and syrup (as citrate salt). The extended-release tablet has a slower absorption rate, a lower peak level, and lower bioavailability relative to the other dosage forms. Patients may prefer capsules if they cannot tolerate the taste of tablets. Extended-release tablets are more expensive and are usually reserved for patients who are experiencing peak-concentration related side effects such as tremor, nausea, or polyuria. The syrup is used primarily for patients who refuse to take medication or who have difficulty swallowing tablets or capsules.

Lithium is widely distributed into most body tissues and fluids. However, it is unevenly distributed among several tissue compartments, so for instance, the lithium concentration is higher in saliva and in the thyroid than in serum. Lithium initially distributes into an apparent volume that is about 25%-40% of body weight, and later into a volume that is about 50%-100% of body weight. The apparent volume of distribution at steady state ranges from 0.5 L/kg to 1.2 L/kg. Lithium has a smaller volume
Drug Interactions With Lithium

Some of the most clinically relevant drug interactions involving lithium are those that result in increased serum lithium concentrations. Some NSAIDs, such as indomethacin and ibuprofen, can increase serum lithium concentrations by approximately 40%, but aspirin and sulindac can increase serum lithium concentrations by approximately 25%. The purported mechanism of this interaction is the induction of natriuresis, which leads to a compensatory increase in the reabsorption of sodium (and thus lithium) in the proximal tubule. Angiotensin-converting enzyme (ACE) inhibitors, such as captopril, enalapril, and lisinopril, can increase serum lithium concentrations through volume depletion and reduction in glomerular filtration rate or a decrease in aldosterone levels that leads to sodium depletion and subsequent lithium retention. The onset of this interaction appears to be delayed (3-5 weeks), and elderly patients may be predisposed.

Drugs that have been reported to decrease serum lithium concentrations include carbonic anhydrase inhibitors (eg, acetazolamide), osmotic diuretics (eg, mannitol, urea), methylxanthines (eg, caffeine, theophylline), and sodium bicarbonate. Drugs that have minor, variable effects on serum lithium concentrations include loop diuretics (eg, furosemide) and potassium-sparing diuretics (eg, amiloride).

Usefulness of Serum Lithium Concentrations

Because lithium concentrations vary widely during a dosing interval, a representative single time point for serum lithium concentration monitoring was established for standardization. Although somewhat arbitrary, the 12-hour post-dose time point was selected for this purpose because it avoids the highly variable absorption and distribution phases. The usual practice is to obtain the sample in the morning before the first lithium dose and 12 hours after the previous evening dose.

Acute mania typically presents with a combination of mood (eg, euphoria, elation, lability, irritability), hyperactive (eg, decreased need for sleep, rapid speech, psychomotor agitation, racing thoughts), and behavioral (eg, intrusiveness, challenging, hypersexual) symptoms, and occasionally psychotic (eg, hallucinations, delusions) symptoms. Most clinicians advocate a serum concentration of 0.8-1.2 mEq/L during initial treatment of acute mania. On the other hand, during long-term maintenance treatment, serum concentrations of 0.6-1.0 mEq/L are usually adequate to prevent the recurrence of a manic episode. Some patients may require serum lithium concentrations outside the usual ranges. For instance, elderly patients may require lower levels.

Unfortunately, lithium possesses a narrow therapeutic index. Toxic effects of lithium become more likely as serum concentrations rise, and most patients will experience some toxic effects with concentrations above 1.5 mEq/L. Symptoms of mild toxicity include such
things as nausea, diarrhea, tremors, muscle weakness, and fatigue. Symptoms of moderate toxicity include such things as sedation, confusion, lethargy, ataxia, coarse tremors, dysarthria, nystagmus, and increased deep tendon reflexes. Severe toxicity (>2.5 mEq/L) may result in permanent neurological impairment, seizures, coma, and death. The severity of lithium toxicity is related to both serum concentrations and the duration at which concentrations have remained high.\(^1\,^3\,^4\,^9\)

**Reasons for Monitoring Serum Lithium Concentrations**

There are many clinical reasons to obtain serum lithium concentration measurements. When lithium therapy is initiated, or anytime that the lithium dosage is changed, serum concentrations are helpful in determining optimal dosing.\(^4\) During maintenance therapy for prophylaxis of bipolar disorder, most clinicians obtain serum concentration measurements every 3-6 months.\(^4\) Signs/symptoms of either manic or depressive symptoms, or symptoms of possible lithium toxicity, necessitate serum lithium concentration determinations. When situations arise that may alter steady-state serum concentrations, such as development of medical disease (eg, diarrhea), significant increases in sweating, initiation/dosage alteration/discontinuation of drugs that may interact with lithium, and change in salt intake or diet, then the clinician is wise to obtain serum lithium concentration measurements.\(^1\,^4\) Finally, suspected noncompliance with prescribed lithium regimens frequently dictates the need for serum lithium concentration measurements.\(^1\)

**Interpreting Serum Lithium Concentrations**

There are various factors that can affect the accuracy and reliability of serum lithium concentration measurements. Certainly patient compliance with the lithium regimen, especially the doses immediately prior to the serum concentration determination, can affect the accuracy of the results.\(^7\) Because the standard concentration is considered a 12-hour post-dose determination, samples obtained before that timeframe result in falsely increased concentrations, while samples obtained after that timeframe result in falsely decreased concentrations. Due to the approximate 24-hour half-life in most patients, steady-state concentrations are obtained in about 4-5 days.\(^10\) Thus, samples obtained prior to that timeframe after increasing or decreasing the lithium dosage will result in falsely decreased or increased steady-state concentrations, respectively. The dosing interval can also affect the interpretation of lithium concentrations. Once-daily (ie, bedtime) dosing of lithium typically increases the 12-hour serum lithium concentration by about 0.2 mEq/L relative to twice-daily or thrice-daily dosing regimens.\(^2\,^7\) Recommendations for therapeutic concentrations (as noted above) are based on multiple daily dosing regimens. Finally, the accuracy and reliability of the laboratory can certainly impact the interpretability of serum lithium concentration determinations. Therefore, guidelines for ensuring the accuracy and reliability of standardized 12-hour serum lithium concentrations include: optimal compliance; sample obtained 12 ± 1/2 hours after the last evening dose; sample obtained after at least 4-5 days at a given dose; twice-daily or thrice-daily dosing schedule; and appropriate precision of laboratory analyses.\(^1\)

When interpreting unexpected serum lithium concentration values, the clinician must consider various explanations. Perhaps the serum concentration measurement reveals a “true” concentration, so the clinician should look for those factors that alter serum lithium concentrations, such as changes in water balance, sodium balance, and renal function. On the other hand, the clinician should consider whether the measurement is actually inaccurate or unreliable, and thus may be due to a missed or extra dose, improper timing, non–steady-state, dosing schedule, or laboratory error. Regardless, the clinician should not make hasty decisions based on aberrant values, rather he or she should consider obtaining another measurement for verification.

**Lithium Dosing Methods**

The lithium dosage must be individualized according to serum lithium concentrations, clinical response, and adverse effects. Various prospective dosing methods exist in order to minimize the number of serum lithium concentration determinations and decrease the amount of time required to achieve a therapeutic dose. However, there is no empirical evidence that these strategies actually result in a more rapid clinical response.\(^8\) In the Cooper method,\(^11\,^12\) a 600-mg test dose is given and the serum lithium concentration is determined 24 hours later. Depending upon that concentration, a chart reveals the predicted daily dose to yield a steady-state concentration of 0.6-1.2 mEq/L. Another example is the Perry method,\(^13\,^14\) which utilizes a 1200-mg test dose, with subsequent serum lithium measurement 24 hours later. The clinician then plots the 24-hour concentration against a desired steady-state concentration on a nomogram, revealing the approximate daily dose needed for that patient. Despite the availability of such prospective methods, the traditional (“retrospective”) method is almost always used by clinicians because of its ease and familiarity, as well as the fact that it minimizes initial adverse effects, which may increase the likelihood of long-term
CASE STUDIES

Case Study #1. CS is a 45-year-old woman who was brought to the state psychiatric facility by the police. She was causing a disturbance at a local television station by insisting on addressing the city during a news broadcast. She is euphoric and grandiose. She exhibits rapid speech and psychomotor agitation. She admits to racing thoughts and decreased need for sleep. CS denies that she has a mental illness and states that she does not need any medication. CS is diagnosed with bipolar disorder, manic episode. Her only medical illness is hepatitis C.

1. The psychiatrist is considering lithium or valproate to treat CS’s mania. Why might lithium be the best choice for CS?

2. Lithium is available in several different dosage forms. What would be your advice to the psychiatrist concerning choice(s) of dosage forms and why?

3. Describe the various dosing techniques that could be utilized to treat CS’s manic episode. Which would you prefer and why?

4. What is the most appropriate serum lithium concentration range to treat CS’s condition?

5. CS is started on 300 mg of lithium 3 times daily and has a steady-state lithium concentration of 0.6 mEq/L. If the desired lithium concentration is 1.0 mEq/L, what should the dosage be adjusted to?

6. Describe the maintenance treatment of CS with lithium, including desired steady-state serum concentrations and frequency of serum concentration monitoring.

Comments: The student should recognize that lithium would be preferred over valproate in a patient with active liver disease, as lithium is not metabolized and is renally excreted. The syrup formulation should be used, at least initially, owing to the patient’s lack of insight into the need for medication and consequent likelihood of non-compliance. Although prospective dosing methods would yield quicker therapeutic serum concentrations, and thus possibly a quicker response, the increased likelihood of adverse effects, with resultant effects on compliance, is a major drawback. The retrospective dosing method is slower, but conventional and easy and allows for improved tolerability of therapy. Since CS is acutely manic, the most appropriate serum lithium concentration range is 0.8-1.2 mEq/L. First-order linear kinetics mean that the patient’s dosage should be increased to 1500 mg/day. Assuming no other reasons for more frequent monitoring, serum lithium concentration measurements should be made every 3-6 months, with a desired concentration of 0.6-1.0 mEq/L.

Case Study #2. The outpatient psychiatrist in the mood disorders clinic has called you for consultation concerning one of his patients, LS, a 46-year-old black male patient with a long history of bipolar disorder. He is rather well-known for being compliant with therapy overall, yet very absent-minded; for instance, he always shows up for his clinic appointments but is frequently very early or very late because he cannot remember when the appointment is. You have known LS for quite some time, and recall that he was receiving lithium, 600 mg twice daily, and nifedipine, 30 mg three times daily, the last time you checked his profile several months ago.

The reason the psychiatrist has called you is because of LS’s serum lithium concentration. LS generally has a serum lithium concentration of approximately 0.9 mEq/L. A routine level was drawn this morning and was just reported as 1.6 mEq/L. The psychiatrist states that although he has made some recent adjustments to LS’s lithium therapy, he has not altered the daily dose for many years. He also states that LS appears as usual, except that he complains of “not feeling good lately,” which LS attributes to either a “stomach virus caught from my nephew” or “side effects from that new pill they gave me in hypertension clinic.”

Based upon the information above:

1. What are the possible factors, which may, individually or collectively, explain why LS’s serum lithium concentration is so much higher than usual?

2. What information would you need to gather from various sources (eg, patient, psychiatrist, laboratory studies, medication profile) in order to either rule out or further substantiate each of the aforementioned factors as the etiology for the high level?

Comments: The student should consider that the serum lithium concentration may or may not be accurate and reliable. The patient may, in fact, be lithium toxic, as he describes gastrointestinal distress. It is important to note that symptoms such as diarrhea and vomiting may be the cause or effect of lithium toxicity. So perhaps he really does have a stomach virus that has indirectly caused the serum lithium concentration to increase. It is also important to rule out a drug interaction as the cause of an elevated lithium concentration, which may be the case.
if the new medication prescribed in the hypertension clinic is hydrochlorothiazide or an ACE inhibitor. On the other hand, the concentration may be falsely elevated due to the forgetfulness of the patient (eg, may have taken a dose in the morning), a change to bedtime dosing by the psychiatrist, or simply laboratory error. Regardless, the psychiatrist should confirm this particular serum lithium concentration measurement by obtaining another measurement.

**SUMMARY**

Major principles of the therapeutic drug management of lithium are consistently highlighted through the learning objectives, lecture content, case studies, and test questions. Aside from understanding information specific to lithium, students must use their information retrieval skills to obtain information regarding other drug therapy. The students must then apply their understanding of pharmacology to determine whether the drugs’ mechanisms of actions may impact lithium therapy. Students must understand the usual drug therapy for certain medical diagnoses and predict when potentially prescribed drugs might impact lithium therapy. Students must evaluate the many possible explanations for the patient’s symptoms and determine the probability of those that are important. Significant emphasis is placed on students being able to apply the information to clinical scenarios and becoming inquisitive problem solvers.

**REFERENCES**