Serum Levels of Psychiatric Drugs

by John J. Miller, MD

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It was routine in the 1980s to obtain serum levels of several of our limited armamentarium of psychotropic medications. The standard was either a 12- or 24-hour postdose level, or in some cases, a trough level before the morning dose. Therapeutic ranges were established for lithium, many of the TCAs, valproic acid, and carbamazepine. After FDA approval of clozapine in 1989, its therapeutic serum range was established. However, with the exception of lithium, valproic acid, and carbamazepine, over the past 20 years serum psychiatric drug level use has been in decline. As we continue to unravel the numerous factors that can synergize to create a 10-fold variability in a drug’s serum level while using the same dosage in different individuals, the time has come to revisit the clinical utility of serum psychiatric drug levels.

Drug absorption issues

Pharmacokinetic and pharmacodynamic variables affect the ultimate steady-state serum level of psychiatric drugs. The same dosage of the same medication in 2 age- and morbidity-matched patients can result in dramatically different serum levels of that medication at steady state. How the drug is absorbed by the body can differ significantly. Reasons for this are varied and include the need for food to optimize absorption (ziprasidone, vilazodone, lurasidone), a period of time without food (levothyroxine), and the requirement for sublingual absorption (asenapine). In addition, there is variability in GI luminal wall contact, which is affected by the transit time through the intestines and hence the time available for drug absorption across the gut wall (eg, irritable bowel syndrome, bowel resection, gastric bypass, Crohn disease, ulcerative colitis, anticholinergic intestinal slowing) as well as altered absorption due to another medication or food supplement. Table 1 summarizes the factors that can affect the reliability and interpretation of a drug’s serum level.

Current serum drug levels

Lithium

Lithium is a simple salt and one of only 3 elements that existed immediately after the “Big Bang.” Given its structural similarity to sodium and potassium and the ubiquitous use of these two elements in many facets of neuronal physiology, it is not surprising that lithium found its way into medicine well before the 1800s. As one of our most studied drugs in psychiatry, a clear and predictable understanding of risks and benefits of varying serum lithium levels is well established.

For mania, mixed mania, and maintenance in bipolar disorder, the therapeutic range is 0.6 to 1.2 mEq/L. Levels below 0.6 render significantly less protection from a manic relapse. In acute mania, it is sometimes necessary to increase the level to 1.5 mEq/L, although at the cost of increased adverse effects. For maintenance treatment in a reasonably stable person with bipolar 1 disorder, a generally acceptable serum level is 0.6 to 0.75 mEq/L. Lithium

ACTIVITY GOAL

This article reviews the reasons for measuring serum levels of psychotropics and provides optimum serum levels for various psychotropic agents to optimize their effectiveness and safety.

LEARNING OBJECTIVES

At the end of this CE activity, participants should be able to:
1. Understand how serum levels of psychotropics guide treatment decisions.
2. Explain the various pharmacodynamic and pharmacokinetic factors that impact serum levels.
3. Gauge correct serum levels for various psychotropic agents.
4. Describe drug absorption issues that affect serum levels.

TARGET AUDIENCE

This continuing medical education activity is intended for psychiatrists, psychologists, primary care physicians, physician assistants, nurse practitioners, and other health care professionals who seek to improve their care for patients with mental health disorders.

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toxicity can occur in the therapeutic range but becomes more significant at levels of 2 mEq/L and higher. At higher serum levels, the risk of renal disease and the need for dialysis increase.1,3

Lithium is not effective as monotherapy in bipolar I depression. It is commonly used off-label as an augmentation strategy in refractory MDD. A good validation of this strategy is the use of lithium augmentation therapy in the NIH-sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, in which lithium was used as augmentation to an antidepressant. In this study, the lithium augmentation dosage was either 450 or 900 mg/d. The mean daily lithium dose at the end of Level 3 was 859.8 mg (SD = 373.1), and serum lithium levels were obtained in 56.5% of the participants in the lithium-augmented group, with a median serum lithium level of 0.6 mEq/L.4

The standard collection time for a lithium level is 12 hours postdose, after a person has been receiving the same dosage for at least a week. Several considerations exist when interpreting a 12-hour postdose lithium level, with no clear guidelines. Depending on a clinician’s preference, lithium may be dosed anywhere from 4 times a day to once at bedtime. These varying dosing schedules can result in a range of serum lithium levels with the same dosage in the same individual, and this must be taken into consideration. An additional complicating factor, with no clear guidance, is the delivery formulation of lithium on the 12-hour postdose level. Lithium carbonate and extended-release formulations will have a different time to maximum concentration (T_{max}), maximum concentration, and 12-hour postdose level.

Carbamazepine
Carbamazepine has a generally accepted therapeutic level. For seizure disorders and bipolar mania, the commonly used target steady-state level is 4 to 12 µg/mL.5 The recommended dosing for immediate-release carbamazepine is 3 or 4 times daily; for extended-release formulations, dosing is twice daily, although in bipolar disorder, carbamazepine extended-release may be given at bedtime.

The dosing schedule should be taken into consideration when a serum level is obtained, because a morning trough level in a patient receiving oral carbamazepine 400 mg 4 times a day may differ significantly from that in a patient receiving oral carbamazepine extended-release 1600 mg at bedtime. As with lithium, there is no clear guidance in the literature on how to interpret the trough level from these different dosing schedules.

Carbamazepine levels require consideration of several additional pharmacokinetic and pharmacodynamic factors. Carbamazepine is a potent inducer of several hepatic cytochrome P-450 (CYP) metabolic enzymes, including CYP3A4, which is how carbamazepine is metabolized.5

A slow titration of carbamazepine is recommended because of the autoinduction of its metabolism—12-hour postdose levels 2 weeks after each dosage increase are needed. Once the dosage is stable, serum levels should be monitored every 2 to 3 months for the first year, then annually or as clinically indicated. Levels should also be obtained whenever a new medication that is either an inhibitor or an inducer of CYP3A4 is added. CYP3A4 inducers include phenytoin, phenobarbital, rifampin, and St John’s wort; inhibitors include macrolide antibiotics, antifungals, calcium channel blockers, and some antidepressants.

Carbamazepine is metabolized by CYP3A4 to its active metabolite carbamazepine-10,11-epoxide, which is further metabolized by epoxide hydrolase to an inactive metabolite. Valproate inhibits epoxide hydrolase, which can result in a significant increase in the active carbamazepine-10,11-epoxide metabolite. The level of the epoxide metabolite is not part of the serum carbamazepine level. Hence, an elevated combined carbamazepine/ carbamazepine-10,11-epoxide level may indicate severe toxicity, but the carbamazepine level may be low normal. Whenever the clinical picture suggests this toxicity as a possibility, a serum carbamazepine-10,11-epoxide level should be drawn.

Valproate
Valproate is available in a range of formulations, including valproic acid, sodium valproate, divalproex sodium, and divalprox sodium extended-release. Although the actual half-life for valproic acid is between 9 and 16 hours, the T_{max} can vary from 2 to 17 hours depending on the patient and formulation used. A unique property of valproate is that its plasma protein binding varies with its serum concentration. As the serum concentration increases from 40 to 130 μg/mL, the associated free fraction increases from 10% to 18.5%. It is the free fraction that is physiologically active and clinically relevant. Hence, comorbidities that impact plasma protein levels can significantly affect serum levels of free valproate.7

In general, the accepted therapeutic range for valproate levels in patients with bipolar disorder is between 50 and 125 g/mL. When plasma protein levels are uncertain, it is prudent to obtain a free valproate level, in which the corresponding range is 6 to 22 g/mL. The optimal level for maintenance treatment is considered to be between 75 and 100 mEq/L, which provides a reasonable balance of effectiveness and tolerability.6 However, interpretation of the valproate level needs to be viewed in the context of the time it was drawn after the last dose, the half-life variability among individuals (because of patient-specific and drug-drug interaction factors), plasma protein variability, and the formulation used. These uncertainties and complex variables highlight the limitations of serum levels for psychotropic drugs.

Lamotrigine
Lamotrigine is used in psychiatry to decrease the likelihood of a depressive relapse in patients with bipolar disorder; it also has various off-label uses. In neurology, it is a commonly used anticonvulsant for the treatment of seizure disorders. Although no absolute therapeutic range has been correlated with efficacy in either bipolar disorder or seizure disorders, the generally accepted reference range is 2.5 to 15 g/mL in patients receiving therapeutic doses. In one study of 811 patients with epilepsy, 3731 lamotrigine levels were obtained and correlated with significant adverse effects.6 Severe adverse effects were seen in 7% of patients with serum levels less than 5 μg/mL, 14% of patients with serum levels between 5 and 10 μg/mL, 24% of patients with serum levels between 10 and 15 μg/mL, 34% of patients with serum levels between 15 and 20 μg/mL, and 59% of patients with serum levels greater than 20 μg/mL.

Significant individual heterogeneity exists in the metabolism of lamotrigine because of genetic polymorphisms of the UDP-glucuronosyltransferase (UGT) glucuronidation enzyme responsible for its metabolism. In addition, there are several important drug-drug interactions that can have a major effect on lamotrigine metabolism. Lamotrigine is not metabolized by any of the CYP enzymes, but rather it is primarily metabolized by UGT1A4. Valproate inhibits UGT1A4, which can significantly increase lamotrigine levels. Carbamazepine and estradiol induce UGT1A4, which lowers lamotrigine levels. These drug interactions can change the half-life of lamotrigine from 13 to 70 hours.6,7 Once at steady state, a serum lamotrigine level draw is recommended at 12 hours postdose, or as a predose trough.

In clinical practice, lamotrigine levels are rarely obtained. Given the heterogeneity of lamotrigine’s metabolism, as well as established drug-drug interactions, it may be prudent to more commonly use lamotrigine levels.

Clozapine
Clozapine was the first atypical antipsychotic in the United States; it was FDA-approved in 1989. A large literature exists on the utility of and recom-

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<table>
<thead>
<tr>
<th>Table 1 - Factors that can affect the reliability and interpretation of serum drug levels</th>
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<tr>
<td><strong>Nonadherence</strong></td>
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<td><strong>Variability in drug absorption</strong></td>
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<tr>
<td><strong>Genetic polymorphism of CYP or UGT metabolic enzymes</strong></td>
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<td><strong>Drug-drug interactions</strong></td>
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<td><strong>Requirement for specific caloric intake to maximize drug absorption</strong></td>
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<tr>
<td><strong>Time serum level is obtained postdose</strong></td>
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<tr>
<td><strong>Formulation of drug (immediate-release, slow-release, extended-release)</strong></td>
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<tr>
<td><strong>Half-life and time to maximum concentration of the drug</strong></td>
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<tr>
<td><strong>Medical comorbidities affecting drug metabolism</strong></td>
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<td><strong>Steady-state status of the drug</strong></td>
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CYP, cytochrome P-450; UGT, UDP-glucuronosyltransferase.
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medications on obtaining and interpreting serum clozapine levels. Although initially there was much interest in the possible role of clozapine's primary metabolite, N-desmethylclozapine (norclozapine), in clozapine's unique superiority in the treatment of schizophrenia, the current consistent conclusion in the psychiatric literature is that this metabolite plays little, if any, role in the efficacy of clozapine. Despite this, the common laboratory report for a serum clozapine level includes the levels of clozapine, N-desmethylclozapine, and the total combined level of these two molecules. The current recommendation is to make clinical decisions based solely on the serum clozapine level.11

Clozapine levels should be drawn 12 hours postdose, because its half-life is 12 hours. No extended-release formulations exist, which simplifies interpretation of the results. However, there are significant drug-drug interactions that can have a major impact on the metabolism of clozapine, and hence its steady-state level. Fluvoxamine and, to a lesser extent, caffeine are significant inhibitors of CYP1A2 and can raise serum clozapine levels. Cigarette smoke is a potent inducer of CYP1A2, which is the primary metabolic pathway for clozapine; thus, smoking can result in a 50% reduction in the serum clozapine level.13,14

These drug interactions can be of clinical significance when a patient with schizophrenia who smokes tobacco products and drinks caffeinated beverages is hospitalized for longer than 2 weeks and nicotine withdrawal is managed with a nicotine patch. During this 2-week period, the previous induction from the cigarette smoke will normalize because nicotine has no inducing effect on CYP1A2. Unless the caffeine intake equals that outside the hospital, inhibition of clozapine by caffeine can also vary. Once the patient is stabilized on clozapine and is discharged, there is a high likelihood that he or she will resume smoking tobacco and premedication caffeine consumption will resume. Reinduction of the CYP1A2 enzyme will occur over the next 2 weeks and can result in a 50% decrease in the serum clozapine level, putting the patient at risk for relapse. Changes in caffeine intake after discharge can further complicate the picture by inhibiting this same CYP enzyme. Obtaining a predischARGE 12-hour postdose serum level can provide a baseline level for reference.

Although there is no clear relationship between serum clozapine levels and efficacy or toxicity in schizophrenia, the literature is consistent regarding general interpretations.12-13 First of all, the N-desmethylclozapine and total clozapine levels should be ignored. Secondly, the clozapine dosage should be titrated upward using clinical efficacy or poor tolerability as the primary guide. Clozapine levels in the range of 100 to 250 ng/mL tend to be less effective than higher levels, but they may be adequate in some patients. Clozapine levels in the range of 250 to 350 ng/mL are commonly associated with good clinical response.

If a patient has not responded after an adequate period with a documented level between 250 and 350 ng/mL, it is reasonable to increase the clozapine dosage to achieve a 12-hour postdose serum clozapine level between 350 and 500 ng/mL. Clozapine levels greater than 1000 ng/mL should be avoided because there is a significant increase in adverse effects, including seizures.

Tricyclic antidepressants

When TCAs were initially FDA-approved in the 1960s to treat MDD, they were perceived as much safer than the MAOIs, which were the only other class of antidepressants at the time. However, it soon became apparent that there was a low benefit to risk ratio for this medication class. An overdose on 1 to 2 weeks of a TCA could lead to death by cardiac toxicity. In addition, there is considerable variability in the CYP enzyme polymorphisms that can result in dramatically different serum levels in a similar population of patients.

Nortriptiline and desipramine in particular are primarily dependent on CYP2D6 for clearance.15 One patient may have a therapeutic serum level of nortriptiline with 10 mg/d, while another similar patient may require 100 mg/d to achieve the same serum level. As shown in Table 2, TCAs have differing optimal therapeutic ranges.20 Commonly co-prescribed medications can contribute to significant serum level changes that can be lethal.

Serum TCA levels should be drawn at least 1 week after a stable dosage has been achieved, to ensure a steady-state level. An exception would be when a second medication is added that is a potent inhibitor of the TCA's primary CYP metabolic pathway—a general principle after adding any potent inhibitor to an associated enzyme substrate.21 Inhibition will occur immediately, so a next-day serum level may be obtained. Check with the laboratory that is performing the serum level assay regarding the postdose time that their reference range is based on (usually 12 or 24 hours postdose). If the TCA is tertiary (amitriptiline, imipramine, clomipramine, doxepin), the report should also include that drug's active secondary metabolite level, and both levels should be added together for the clinically relevant total level.

CASE VIGNETTE

BJ is a 28-year-old man with no medical problems who presents with MDD with only partial response to 100 mg/d of desipramine; the 12-hour postdose serum level is 104 ng/mL. Desipramine is augmented with 20 mg/d of fluoxetine. Over the next 72 hours, BJ becomes increasingly confused and agitated and has a seizure; the desipramine serum level is 832 ng/mL.

Fluoxetine and its active metabolite norfluoxetine are potent inhibitors of CYP2D6, the primary metabolic pathway for desipramine. The 20 mg/d of fluoxetine converts BJ to a poor metabolizer at CYP2D6, and his desipramine level is elevated over 400%, into the toxic range.21 Because of the prolonged half-life of fluoxetine (72 hours) and its active metabolite norfluoxetine (14 days), once discontinued it can take a month or longer for the fluoxetine level to drop to where it will not significantly elevate the desipramine level. In BJ's case, the desipramine should be discontinued and serial desipramine levels obtained until the level drops back into the therapeutic range. The desipramine should then be restarted at a much lower dosage, and levels should be monitored regularly.

The lack of solid evidence

Most psychotropic medications lack solid evidence for a therapeutic range, although there are many circumstances in which a serum level can still be quite informative clinically. Table 3 lists clinical situations in which a 12-hour postdose or trough serum level can shed considerable light on why a patient is either not responding to or is intolerant of a medication. Serum levels can be ordered for virtually all psychotropic medications. It is judicious to research the collection criteria of the laboratory that the serum will be sent to so maximal benefit and information may be obtained.

Genetic polymorphism of CYP hepatic enzymes

Since the completion of the sequencing of the human genome in 2001, there

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Table 2 - Generally accepted serum levels of psychotropic medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reference rangea</th>
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<tbody>
<tr>
<td>Lithium</td>
<td>0.6 - 1.2 mEq/L</td>
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<tr>
<td>Carbamazepine</td>
<td>4 - 12 µg/mL</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>50 - 125 µg/mL</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>2.5 - 15 µg/mL</td>
</tr>
<tr>
<td>Clozapine</td>
<td>200 - 700 ng/mL</td>
</tr>
<tr>
<td>Amitriptyline + nortriptyline</td>
<td>95 - 250 ng/mL</td>
</tr>
<tr>
<td>Imipramine + desipramine</td>
<td>150 - 300 ng/mL</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>50 - 150 ng/mL</td>
</tr>
<tr>
<td>Desipramine</td>
<td>150 - 300 ng/mL</td>
</tr>
</tbody>
</table>

a Serum level does not necessarily correlate with clinical efficacy.
Adapted from Jacobson SA. Laboratory Medicine in Psychiatry and Behavioral Science. 2012.20
Table 3 – Reasons to obtain a serum drug level

- Established standard of care for a drug
- Drug with nonlinear pharmacokinetics that is an inhibitor or inducer of the metabolic enzyme for which it is also a substrate
- Patient nonresponse in context of what is considered a high dose
- Patient with severe adverse effects in context of what is considered a low dose
- Monitor adherence
- Acute mental status change: rule out drug toxicity or withdrawal
- Adding a drug that is a known inhibitor or inducer of the CYP or UGT metabolic enzyme that is responsible for metabolizing the drug in question
- Starting, stopping, or considerably changing the amount of tobacco product smoking while using a drug with known metabolism by CYP1A2
- PredischARGE once psychiatrically stable to compare with postdischarge if clinical picture changes
- Pre-GI surgery to obtain an effective baseline while stable, to assist in drug dosage changes post surgery

CYP, cytochrome P-450; UGT, UDP-glucuronosyltransferase.

has been a rapid advancement in our understanding of the genetic polymorphisms of the many enzymes responsible for drug metabolism. Not all CYP enzymes have significant polymorphisms, but several have a wide range of activity that can be clinically significant. Specifically for psychiatric medications, CYP2D6, CYP2C9, CYP2C19, and CYP1A2 can have wide-ranging drug metabolizing effects depending on the alleles of the genes that code for these enzymes. The phenotypes that result can be ultra-rapid metabolizers (1 or 2 highly active genes), extensive metabolizers (2 active genes), intermediate metabolizers (1 active and 1 slow gene), and poor metabolizers (2 slow genes).13

CASE VIGNETTE

TS is a 41-year-old man with depression who has significant residual symptoms while taking 450 mg/d of bupropion XL. Treatment is augmented with 10 mg/d of paroxetine. Over the next week, TS experiences increasing agitation, irritability, insomnia, and akathisia. Pharmacogenetic testing reveals that he is an intermediate metabolizer at the CYP2D6 gene; a 12-hour postdose paroxetine level is unusually elevated. The paroxetine is stopped, and over the next week, the adverse effects improve.

Both bupropion and paroxetine are potent inhibitors of CYP2D6. The bupropion converted TS from an intermediate metabolizer to a phenotypic poor metabolizer by inhibiting the CYP2D6 enzyme before the paroxetine was started. Bupropion is metabolized by CYP2B6, so its serum level was not altered. Paroxetine both inhibits and is metabolized by CYP2D6, hence its serum levels rapidly became toxic with virtually no CYP2D6 activity.

CASE VIGNETTE

AC is a 32-year-old woman who is discharged from a 1-month psychiatric hospitalization after being stabilized on 20 mg/d of olanzapine for an acute exacerbation of schizophrenia. She is a 2-packs-per-day cigarette smoker, but while hospitalized she received a nicotine patch to minimize withdrawal. On discharge, she resumes smoking, and 2 weeks later she presents to the psychiatric emergency department acutely psychotic. Despite a subtherapeutic olanzapine level compared with her 12-hour postdose serum olanzapine level before discharge, she insists that she had been treatment-adherent. This is corroborated by her family. Pharmacogenetic testing reveals that she has the "F" allele on one of her CYP1A2 genes.

CYP1A2 has significant genetic polymorphism, and the "F" allele is associated with significant induction of this enzyme by the smoke from ciga- rettes (not the nicotine). During her initial hospitalization, she was smoke-free for 1 month, and the CYP1A2 induction due to her heavy smoking habit remained. After discharge, she immediately resumed cigarette smoking, and over the next 2 weeks her CYP1A2 enzyme was again induced, which lowered the olanzapine to a subtherapeutic dose—hence the relapse.

Conclusion

Serum levels of psychotropic medications provide a useful tool, when interpreted correctly, to monitor our patients' response to medications and adjust dosing appropriately. For some medications, monitoring serum levels is the established standard of care. For others, serum drug levels can shine light on why a patient is nonresponsive or overly sensitive to a particular medication.

References