

Use of the Clinical Laboratory in Psychiatric Practice



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KEYWORDS

- Clinical laboratory • Psychotropic prescribing practices
- Therapeutic drug monitoring • Urine drug testing • Substance abuse
- Blood drug levels • Urine drug levels

KEY POINTS

- The clinical laboratory is an invaluable tool for guiding prescribing practices of psychiatric medications. Laboratory results should always be correlated with a clinical examination and are rarely useful on their own.
- Care must be taken when testing patients for medication levels that the results of such testing can be useful and will affect treatment.
- There is much literature but still inconclusive evidence for the usefulness of medication levels in blood and other fluids for many psychotropic agents.
- For psychiatric care, medication levels may be best used when ordered with a specific clinical question as opposed to as a general screening battery for all patients.

INTRODUCTION

The clinical laboratory can be a useful tool in psychiatry, but is not always clinically indicated. Advances in laboratory testing technology can sometimes outpace clinical scientific advances of how to use this technology. When ordering a drug level or toxicology assessment in the discipline of psychiatry, one must think of the clinical setting, the potential significance of the results, the class of medication being tested, and most importantly whether the information will have an impact on treatment or expected treatment outcomes. Although the laboratory toxicology workup is used in pain, addiction, and other fields of medicine, psychiatric evaluation and assessment is unique in certain

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respects. Although the ability exists in our modern era to test for almost everything, the situations where one should test are far more limited. In this review, we address treatment considerations in different psychiatric settings and discuss how the clinical laboratory can be effectively used in each of these settings. We also review each of the major psychiatric medication classes and discuss how the clinical laboratory can be used to guide prescribing practices. Although substance use and addiction are closely intertwined with regular psychiatric care, therapeutic drug monitoring (TDM) and its role in psychiatric treatment are the primary focus of this review. Where applicable, we comment on the nonmedical use of psychiatric medication as well.

TREATMENT CONSIDERATIONS DEPENDING ON SETTING

The goals of treatment in psychiatry differ based on the clinical setting. The basic treatment settings are the emergency setting, inpatient setting (either psychiatrically or medically hospitalized), and the outpatient setting. Each setting will have slightly different considerations.

Emergency

In the emergency setting, the primary goal is stabilization of acute issues, some of which may be life threatening, and evaluation to determine if the patient can be treated as an outpatient or inpatient. In this setting, one can usually assume psychiatric treatment failure because many patients presenting to the psychiatric emergency room are in distress. Discharge planning is usually done in this setting to ensure continuity of care, but is not as involved as in the inpatient setting.

Contact between the clinician and patient is limited in this setting, with treatment often lasting less than 1 day. Patients sometimes present without records or collateral information, and their histories may be unknown, especially if a patient is unable to cooperate with a diagnostic interview. Safety is also always a concern in the emergency setting, and a thorough clinical interview and examination can be hindered by an aggressive or psychiatrically unstable patient.

In this setting, screening tests are invaluable sources of information, and clinicians will often order batteries of tests for every patient with minor adjustments when clinically indicated. Laboratory tests such as urine toxicology screens for drugs of abuse, thyroid-stimulating hormone levels, and computed tomography play an invaluable role in the evaluation of a patient in the emergency setting and play a large role in the decision-making process. In general, drug testing of urine may only be useful qualitatively, whereas drug testing in serum may be either qualitatively or quantitatively useful for therapeutic levels.

Checking for blood levels of therapeutic drugs with well-defined therapeutic windows, such as lithium or clozapine, can indicate whether treatment failure occurred when the patient was at a therapeutic level of a drug, or if low blood levels may have impacted a patient's psychiatric stability. It can also inform decision making when suspecting lithium toxicity, although this must also be correlated with a thorough clinical examination.¹ Specific medications where blood levels are more useful are discussed in the class-specific sections.

Although some studies have found routine drug screening to be helpful in the detection of substance use,^{2,3} others have found that they did not affect disposition or duration of inpatient stays,⁴ management,⁵ or diagnosis.⁶ There is little evidence for the usefulness of routine urine drug screening in the emergency setting for patients without clinical suspicion of substance use or intoxication.⁷ Testing for substances in an acute intoxication or overdose are discussed elsewhere.

We could not find any literature on how to use urine drug testing to assess the therapeutic effect of psychotropic medications in the emergency setting. However, the literature on urine drug screens for drugs of abuse suggests that routine screening for psychotropic medications, in particular, does not significantly affect the treatment outcomes of patients in the emergency setting, and that such tests should only be used to confirm a clinical suspicion when it would affect clinical decision making.

In summary, there is little evidence that routine drug screening of all psychiatric patients in the emergency setting guides clinical care, and a thorough history and clinical examination may sometimes be sufficient in this setting. However, with clinical suspicion and in certain situations where a medication presence and/or level would affect care, then we would recommend ordering a medication level or urine drug test.

Inpatient

In the inpatient psychiatric setting, immediate life-threatening problems are ideally already managed in the emergency room or inpatient medical unit, and a basic laboratory workup has already been completed. Patients are generally more stable at this time; however, the same acute issues that present initially in the emergency room may occasionally arise. Patient care still is time limited, and unless it is in a long-term psychiatric inpatient unit, management is still in the acute phase of the illness. The care of patients under long-term hospitalization (such as patients in state hospitals) has similar treatment implications as in the outpatient setting, except that these patients will have more supervision and closer access to medical and psychiatric care.

Inpatient psychiatric hospitalization often has the goal of stabilizing patients so that they can be managed appropriately in the outpatient setting. The evaluation of a patient is more in depth than in the emergency setting, with a greater emphasis on psychosocial factors as well as long-term considerations for treatment. Patients are often started and titrated on new medications on the inpatient units. There is often an emphasis on quick stabilization and discharge, with a decreasing duration of stay as reimbursement for longer hospitalizations declines.

TDM can be invaluable in medications that have well-established therapeutic windows. Medications such as mood stabilizers should be titrated to achieve a therapeutic blood level, and if symptoms persist despite a therapeutic level, adjunctive medications can be considered. In medications with less well-established therapeutic windows, drug monitoring can be used to check if a patient has been taking a medication, or to indicate if a patient is possibly an ultrafast or ultraslow metabolizer. Because there is a range of therapeutic levels even for the well-established therapeutic windows of mood stabilizers, clinical response should be considered when deciding if a patient has an acceptable medication dose. As always, blood levels must be correlated with clinical judgment and is of little value in the absence of a clinical examination.

Outpatient

Since the dehospitalization of psychiatry in the late 20th century, there has been a major shift of services for the mentally ill from the inpatient to the outpatient setting.⁸ The move brought with it many ethical and treatment implications that come with increased patient autonomy.

In contrast with the emergency and inpatient settings, decision making in the outpatient setting must take into account both immediate concerns as well as issues that may arise after years or decades of treatment. In addition, in the outpatient setting patients are volunteering themselves to be in treatment (except for cases of court-mandated treatment), and therefore have the right to adhere to or refuse treatment

recommendations. Successful treatment in this setting must be more collaborative than in the emergency or inpatient treatment settings and highlights the importance of therapeutic alliance. Time and time again, evidence has shown that the quality of the therapeutic alliance between the doctor and patient is a reliable predictor of positive clinical outcome, independent of the type of psychotherapy modality and outcome measure.⁹

Many present-day outpatient mental health services are composed of a multidisciplinary team that provide both psychotherapy and medication management, if indicated. Various modalities of psychotherapy are usually conducted by either a psychiatrist, clinical psychologist, or a licensed social worker, and the vast majority of medication management is provided by psychiatrists, primary care physicians, and nurse practitioners.

For a significant number of patients with mental illness, treatment includes taking psychiatric medication for the long term. Some of these medications have significant side effect profiles and well-defined therapeutic windows. For these medications, such as clozapine, lithium, and valproic acid, routine TDM is required for the entire duration of treatment to prevent side effects and toxicity. Patients taking medications like these, with well-established therapeutic ranges, should undergo blood level monitoring as standard of care.

Unless patients are in crisis and require a more restrictive treatment setting, patients' symptoms are generally less acute in the outpatient setting. As such, when medications are started, titrated, augmented, tapered, or discontinued, they are typically done so at a slower pace to prevent inducing avoidable side effects, dosing medications too high, inciting withdrawal symptoms, and to ensure treatment adherence. Accordingly, TDM for medications without clearly established therapeutic windows may be considered when there is treatment nonresponse or failure that is not better explained through a sound history and examination. In the outpatient setting, treatment failure is often owing to medication nonadherence. A systematic review showed that the mean rate of treatment adherence was 58% among patients with psychoses and 65% among patients with depression,¹⁰ leaving a significant percentage of patients nonadherent to medications. Another cause of treatment failure in the outpatient setting is medication diversion. TDM and urine drug testing may help the clinician to assess for possible treatment nonadherence when suspected.¹¹ Similar to the emergency and inpatient settings, drug testing of urine may only be useful qualitatively, to assess for the presence or absence of a medication.

In summary, psychiatric treatment in the outpatient setting is longitudinal, voluntary, and is often provided by various members of a multidisciplinary treatment team. These factors help to determine whether TDM should be a part of treatment. In the outpatient setting, for medications with a well-established therapeutic range, blood level monitoring should be the standard of care. For patients with treatment nonresponse or failure checking blood or other body fluids as appropriate may help to guide care.

HOW PSYCHIATRISTS PRESCRIBE

Many psychotropic medications are unique in their usage in that patients are often started on them at a relatively young age and continue to take them throughout their lifetime. Many psychiatric illnesses have their first presentation when patients are in their late teens to early 30s. Because of the lengthy duration of treatment, important consideration of side effects as well as efficacy are essential parts of the decision-making process. Because many side effects are dose related, the goal is always to maintain a patient on the lowest possible effective dose.

In general, psychotropic medications are started at a low therapeutic dose, and after a significant trial, titrated up for response. Sometimes medications are started at subtherapeutic doses when there are tolerability concerns. Medications should generally be titrated up to their maximum dose approved by the US Food and Drug Administration (FDA) if there is not a full remission of targeted symptoms. The length of time a clinician waits to increase the medication is determined by the pharmacodynamic and pharmacokinetic properties of the medication. Because of individual differences in these properties, the American Psychiatric Association practice guidelines recommends sometimes going above FDA-approved dosages for antidepressant medications to achieve adequate blood levels.¹² When checking blood levels, laboratory tests are usually drawn at the trough and care must be taken when ordering laboratory tests for a patient to have them drawn at the appropriate time to avoid misinterpretation of laboratory values.

For some medications, there are clearly defined therapeutic windows for blood levels. For these medications, too low of a blood level will not have therapeutic efficacy and too high of a level may either not be efficacious, or will unnecessarily increase the risk of side effects.

However, for a vast majority of psychiatric medications, there is not a clearly defined therapeutic window that is supported by scientific evidence. For these medications, we propose the following approach (Fig. 1). Proper medication administration must always be assessed, and a scrupulous assessment of how a patient is taking their medication must be performed whenever there is concern for improper medication usage. When a clinical assessment is either unrevealing or unreliable, then blood levels can help to guide treatment by grossly approximating whether or not the patient has too little or too much of a medication in their system.

For urine drug testing, there is no good evidence that urine medication levels can inform clinical efficacy of a medication. Urine drug testing for therapeutic medications (as opposed to medications being misused) may only be useful if the medication is not detected, which would indicate medication nonadherence. A positive value does not guarantee sufficient dosing or long-term and regular medication adherence, which are both important for medications to be effective. If the medication is absent from the

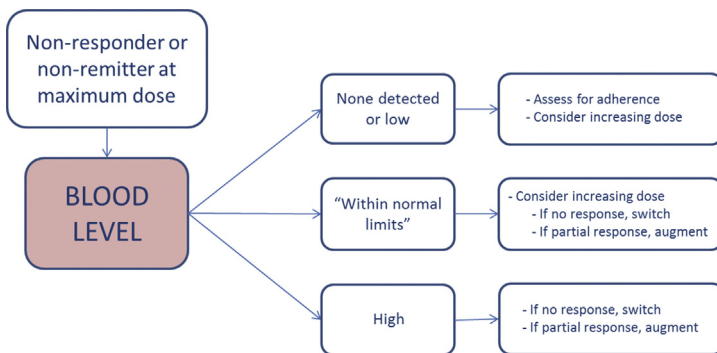


Fig. 1. General approach of using therapeutic drug monitoring for medications without well-established therapeutic windows. Blood levels are rarely useful alone and should always be correlated with a clinical assessment of variables such as medication adherence, drug-drug interactions, therapeutic response, and side effects. Considerations of individual medications should be taken into account when deciding dose adjustments, augmentation strategies, or switching between medications.

urine altogether, then the clinician can be reasonably certain that there is some degree of temporary medication nonadherence at the minimum, although this again does not inform long-term or regular nonadherence. Individual considerations of each medication by class are discussed in the sections herein.

ANTIDEPRESSANT MEDICATIONS

Antidepressant medications contain a heterogeneous group of medications that are used to treat not only depressive disorders, but also a variety of other psychiatric and pain disorders. Many psychiatric medications have a variety of FDA-approved indications, and antidepressant medications are perhaps the best exemplar of this. For example, fluoxetine, the oldest of the widely used selective serotonin reuptake inhibitors (SSRIs), is FDA approved for the treatment of major depressive disorder, obsessive-compulsive disorder, premenstrual dysphoric disorder, bulimia nervosa, panic disorder, and bipolar depression (when combined with olanzapine).¹³ Antidepressant medications are implemented regularly in the treatment of anxiety and obsessive compulsive disorder. Indeed, the term “antidepressant” is a misnomer now, because the scope of these medications extends far beyond depression.

Antidepressant medications are used as first-line treatments for depression and anxiety, with treatment often being chronic. Medication is usually continued for at least 1 year, and patients with more severe symptomatology often require lifelong pharmacotherapy for maintenance, even in the absence of symptoms. Antidepressant medications are only one of several treatment modalities for the treatment of depression, with psychotherapy, psychosocial interventions, and electroconvulsive therapy being other effective options. The nature of therapy indicated is determined in part by the severity of the depression, with more aggressive interventions recommended for a more severe illness.

Because many psychiatric medications are taken chronically, and the effects of missing doses or even discontinuing some medications are not felt acutely, medication adherence is an important issue to address in treatment. Some antidepressant medications can cause withdrawal symptoms if discontinued abruptly, with the medications with shorter half-lives being more likely to do so.

Mechanism of Action

All antidepressant medications interact with the monoamine receptor system in the brain and have actions at the synapse. They all act to increase the amount of monoamines in the synapse.¹⁴ Antidepressant medications have antidepressant therapeutic effects that occur within a matter of weeks, much longer than it takes to increase the amount of monoamines in the synapse. The exact mechanism that makes these medications cause their clinical effects remains unknown.

Among the available classes of antidepressant medications are SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), norepinephrine reuptake inhibitors, serotonin receptor antagonists and agonists, norepinephrine-dopamine reuptake inhibitors, alpha-2-adrenergic receptor antagonists, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs).¹⁴ The different classes of antidepressant medications work on different parts of the synapse and on different variations of monoamines.

Antidepressant medications are almost all metabolized by the cytochrome P450 enzyme system and their blood levels are subsequently determined by both the dose of medication and level of enzyme activity. Pharmacogenomics can inform medication dosing, but known genotype differences that affect medication dosing often reflect differences in hepatic metabolism.¹⁵

Antidepressant medications almost all affect serotonin levels in the brain, with some antidepressant medications also affecting norepinephrine and/or dopamine. These medications likely do not have an immediate therapeutic effect through their known mechanisms of action¹⁶ and there is generally a lag time for response, usually taking 2 to 4 weeks.¹⁷ Consequently, patients do not feel an immediate improvement in their targeted symptoms as they would when taking an analgesic or a benzodiazepine. This lack of immediate efficacy can sometimes lead to cessation of medications, either because a patient may believe that they are not working, or that they no longer require the medication anymore because they are feeling better. Response monitoring is an important part of treatment, and can be monitored using scales or clinically assessing any improvement in symptoms or function.

The newer antidepressant medications (SSRIs, SNRIs, etc) all have more favorable side effect profiles over the older TCAs and MAOIs, and have consequently become the first-line treatment for depression. Because of the relatively safe side effect profiles of these newer medications, monitoring blood levels is no longer a necessary part of treatment like with the TCAs, which could cause cardiac toxicity and seizures at toxic levels.¹⁸ In the absence of significant toxicity from high blood levels, it is difficult to determine definitively what an optimal therapeutic window should be. Although there is some evidence for an optimal therapeutic blood level for some of the SSRIs and SNRIs,^{19,20} there are conflicting data on what that blood level should be and if blood levels are correlated with treatment response.²¹

Therapeutic Drug Monitoring

Although there has been evidence of a therapeutic window for some antidepressant medications, the literature remains inconclusive and following blood levels for most antidepressant medications is not a routine part of care when there is a good response to treatment.

Only plasma level monitoring of TCAs has been recommended specifically by the American Psychiatric Association.¹² Additionally, blood levels can be checked when using MAOIs to ensure that there are no drug interactions with other antidepressant medications that were being used before starting the MAOI, or after the MAOI has been discontinued. MAOIs used concomitantly with other antidepressant medications have a significant risk of serotonin syndrome, so greater care must be taken to ensure safety.

The literature on the usefulness of TDM for antidepressant medications has been inconclusive, with the exception of TCAs, for example, nortriptyline, amitriptyline, imipramine, and desipramine. Serum drug levels are useful for TCAs because there is a relatively well-established therapeutic window for these medications,²² but also, unlike the newer SSRIs and SNRIs, high levels can lead to serious toxicities, such as cardiac conduction abnormalities.²³

Several studies have demonstrated that for many antidepressant medications, there is a linear or curvilinear correlation between dose and plasma concentrations.²⁴ There is some evidence that using TDM early in treatment can help to lower medication dosages.²⁵

There are limited reasons to check serum drug levels, and it should not be a part of routine care when a patient is showing a good response to a medication and is without significant side effects. Wide recommended therapeutic ranges for most of the antidepressant medications and low toxicity for many make interpretation of serum drug levels difficult.²⁶ TDM may be considered in medication-sensitive populations such as patients with complicated medical issues, pediatric patients, older patients, or patients on extensive medication regimens. At this stage, owing to a lack of

well-established evidence of an optimal serum range for most antidepressant medications, TDM is of limited usefulness. The role of TDM for heterogenic antidepressant medications is further complicated by the fact that depression is a heterogenic illness, both in its symptomatology and neurobiology.²⁷

At this time, there is no literature on urine levels of antidepressant medications that can be used to guide drug therapy. If urine drug levels are to be used, we recommend checking random urine drug levels, similar to the use of random drug screens for substance abuse. Urine drug levels may be used to check medication adherence, although it does not inform long-term adherence or if the patient is on a significantly high dose. Although there is much literature on detection methods of various antidepressant medications in urine,²⁸ there is yet to be any evidence of what a therapeutic urine level would be. Thus, the usefulness of urine toxicology for antidepressant medications would be similar to that of when checking for drugs of abuse—to inform the clinician simply if a patient has taken the substance at all within a given amount of time that depends on the specific assay, half-life, and metabolites.

MOOD STABILIZERS

Mood stabilizers are another heterogeneous group of medications used to treat bipolar disorder. For treatment of bipolar disorder, clinicians must consider both the acute and maintenance phases for both depression and mania. Mood stabilizers should be used both in the treatment of acute mania, and also as long-term maintenance therapy for prophylaxis against further manic or depressive episodes. The mood stabilizers can be classified into 2 main groups: lithium and the anticonvulsants. Lithium was the first drug to demonstrate antimanic effects and was discovered when Cade²⁹ noticed its ability to pacify animals in 1949 and then tried it on manic patients with profound effect. Antipsychotic medications and benzodiazepines also have a major role in the treatment of bipolar disorder; their properties are discussed in their respective sections.

Mechanisms of Action and Therapeutic Drug Monitoring

Lithium is the most established medication for treatment of bipolar disorder, being the oldest medication and the most efficacious for treatment and prevention of mania. The exact mechanism of action responsible for lithium's therapeutic effect remains unclear, although there are several hypotheses. The most researched is the inositol depletion hypothesis, which hypothesizes that lithium acts to decrease the amount of inositol in neurons by inhibiting inositol monophosphatase to block inositol synthesis, dampening neurotransmission that depends on the phosphatidylinositol 4,5-biphosphate second messenger system.³⁰ Another hypothesis is that lithium inhibits glycogen synthase kinase 3 β activity, an enzyme that may play a role in signal transduction in the brain.³¹

Because lithium has a narrow therapeutic window, monitoring blood levels of lithium is an essential part of therapy. Additionally, its clinical efficacy has been correlated with blood levels and not the oral dose, with higher levels within the therapeutic window being more efficacious.³² Because of its potential toxicity (cardiac, renal, and neurologic, among others), clinicians must ensure that a patient's lithium dose is not in the toxic range. Additionally, side effects and toxicity from lithium increase as blood levels increase.¹ Because lithium is excreted almost entirely by the kidneys, a patient's lithium level must be closely monitored when changing any medications that may affect renal clearance.

The 3 main anticonvulsants with the most evidence for efficacy as mood stabilizers are valproic acid, carbamazepine, and lamotrigine.^{33–35} Valproic acid and

carbamazepine are more effective in treating and preventing manic episodes, whereas lamotrigine has shown better efficacy for the treatment and prevention of bipolar depression.

The mechanism of action of valproic acid for the treatment of bipolar disorder remains unknown, but it is known to increase synaptic levels of the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA). Although valproic acid has a variety of side effects and toxicities, and in an overdose severe neurologic symptoms such as sedation and ataxia may occur, death from an overdose is uncommon, unlike lithium.

Carbamazepine is thought to work by binding to the inactivated state of sodium channels to decrease repetitive action potentials and also block presynaptic sodium channels to inhibit depolarization of the presynaptic terminal. Like valproic acid, although this drug may have serious side effects, it is often not lethal in overdose, with the major concerns being atrioventricular block and excess sedation. Because carbamazepine induces its own metabolism through the cytochrome P450 system, periodic TDM is important to ensure that this medication is dosed sufficiently.

Lamotrigine is more effective for the treatment and prevention of bipolar depression than mania. Its mechanism of action for bipolar disorder remains unknown, but lamotrigine inhibits the release of glutamine, an excitatory amino acid, to decrease excitation in the central nervous system. It also blocks voltage-sensitive sodium channels. Therapeutic blood levels have not been clearly established for lamotrigine. An important side effect to be wary of is Stevens–Johnson syndrome, which may be fatal. This side effect is more likely to occur when dosages are increased rapidly, so a slow and gradual titration in lamotrigine is necessary.

Although there is evidence for therapeutic windows for valproic acid and carbamazepine, the ranges are wide and there is a poor correlation between blood levels and efficacy for mania. Blood levels of all of these medications are useful in assessing treatment adherence and for informing whether persistent symptoms are because of nonadherence or because of lack of efficacy of a medication. The presence of each of these mood stabilizers is testable in the urine, but there is no literature on what a therapeutic level would be. Thus, testing for these drugs in the urine will only inform the clinician if the patient has taken this medication at all within a given amount of time dependent on excretion rates.

In summary, mood stabilizers are a mainstay of treatment for patients with bipolar disorder. For many of the mood stabilizers there is evidence for maintaining blood levels within an established therapeutic window. Lithium has the most well-defined therapeutic window and, because of efficacy and toxicity concerns, it is imperative that the blood level be monitored and within the acceptable range. For other mood stabilizers, there is a wider range of therapeutic levels and less toxicity with overdose. TDM is important for correct dosing of these long-term medications to ensure that a patient is properly both treated and prophylaxed against any further mood episodes.

ANTIPSYCHOTIC MEDICATIONS

Antipsychotic medications have been in clinical use since the 1950s and are used primarily to treat severe mental illnesses like schizophrenia, schizoaffective disorder, and other psychotic disorders. Since then, many antipsychotic medications have been developed and their use has expanded to treat other psychiatric disorders as well. Certain antipsychotic medications have since been FDA approved to treat mood disorders such as major depressive disorder and bipolar disorder, both as monotherapy and as adjunctive treatment. In clinical practice, antipsychotic medications are also used off-label, for example, to treat behavioral manifestations of neurocognitive

disorders and to treat symptoms of severe personality disorders, among others. Some commonly used first-generation antipsychotic medications are haloperidol, perphenazine, and fluphenazine. Commonly used second-generation antipsychotic medications are risperidone, quetiapine, clozapine, olanzapine, and aripiprazole, to name a few.

Mechanism of Action

Antipsychotic medications have complex binding properties, and accordingly it has been difficult to isolate the exact mechanism that confers antipsychotic properties. In general, antipsychotic medications are thought to treat psychosis primarily by blocking the dopamine D2 receptor in the mesolimbic and mesocortical dopamine tracts in the brain. However, they also block D2 receptors elsewhere, adding risk for causing extrapyramidal symptoms (EPS). As such, in general D2 receptor antagonism correlates both with efficacy and EPS, whereas serotonin 2A receptor blockade seems to diminish the risk of EPS.

The first antipsychotic medications developed have an increased risk for causing EPS and are thus called first-generation antipsychotic medications. They have been in use for more than one-half of a century. Additional antipsychotic medications were later developed in an effort to diminish the risk of EPS, and this was accomplished by developing medications with different receptor binding properties. For example, the newer antipsychotic medications antagonize the serotonin 2A receptor to a greater degree, thus lessening the risk of EPS. These antipsychotic medications that have a lower risk of EPS are called second-generation antipsychotic medications. First-generation antipsychotic medications in general tend to have a lesser affinity for antagonizing cholinergic, histaminic, and adrenergic receptors. This confers fewer metabolic side effects as compared with second-generation antipsychotic medications.³⁶ Both first- and second-generation antipsychotic medications have various options for routes of administration, including orally (as a pill or liquid), sublingually, intramuscularly, and intravenously. The intramuscular forms exist both in short-acting and long-acting forms for certain antipsychotic medications. Similar to antidepressant medications, full therapeutic effects take several weeks to accumulate, much slower than the time to dopamine blockade and steady state. This suggests that there potentially exists a secondary change in receptor blockade through receptor regulation.

Most antipsychotic medications are metabolized in the liver, where they are made more water soluble and thus more readily excreted. Liver metabolism is affected by several factors, including but not limited to age, intrinsic metabolic rates, and the presence of other hepatically metabolized medications, resulting in widely varying blood levels. Additionally, for certain antipsychotic medications, active metabolites exist following liver metabolism, which can confer additional antipsychotic properties.

Therapeutic Drug Monitoring

Because there are great individual differences in the metabolism of antipsychotic medications and nonadherence confers poor outcomes in patients with severe mental illness, it would be clinically useful to have an objective measure to assess for efficacy and adherence to these medications. Aside from clozapine, therapeutic drug level monitoring is not currently a routine part of care.

For clozapine, there is consistent evidence that there exists a therapeutic range that confers clinical efficacy. Studies have also shown that levels as low as 200 ng/mL can be therapeutic, whereas levels of greater than 600 ng/mL are associated with increased risk of side effects, most notably seizures.³⁷ As such, routine blood level

monitoring should be a mainstay, because there is strong evidence for its therapeutic window. Also, patients taking clozapine are already subject to routine blood draws owing to risk of agranulocytosis, making the task of blood level testing less cumbersome for the patient. TDM should be used when there are significant dose adjustments, when there is a worsening of symptoms, or if there is concern for toxicity.

For other antipsychotic medications, including both first generation and second generation, there is no clear consensus whether TDM has a role in clinical care, but there are differences among the classes. For both first- and second-generation antipsychotic medications, some studies indicate possible usefulness of drug level monitoring, whereas others show a clear inconsistency of drug levels between individuals and within the same individual on the same medication. Still, although there is an overall lack of consensus, there seems to be more consistent evidence for potential TDM for first-generation antipsychotic medications. For example, for haloperidol, perphenazine, and fluphenazine, there is evidence showing that blood levels can be indicative of clinical response,^{38,39} and others show a worsening in clinical response for haloperidol owing to EPS at levels of greater than 10 ng/mL.⁴⁰ This was similarly found for fluphenazine. For perphenazine, there is concern for EPS at blood level concentrations of greater than 5 ng/mL.⁴¹ There is less consistent evidence for the remainder of the first-generation antipsychotic medications. Still, testing serum drug levels for certain first-generation antipsychotic medications seems to be most clinically useful in protecting against EPS. Although this practice is currently not a routine part of psychiatric care because EPS is a clinical diagnosis and a thorough history, physical examination, and mental status examination are currently the mainstay of clinical practice, there may be a role for drug level monitoring in certain cases.

Aside from clozapine, as discussed, there is less evidence for the role of blood testing in second-generation antipsychotic medications. For example, a study showed that risperidone blood levels varied greatly between patients receiving the same dose, suggesting a variety of physiologic, genetic, and environmental factors effecting blood levels. However, these variations in blood levels do not correlate with efficacy of the medication.^{42,43} There is similarly inconclusive evidence for many other second generation antipsychotic medications.

For both first- and second-generation antipsychotic medications, there is no clear evidence for the role of urine drug testing in patients taking these medications.

In summary, TDM should be a part of treatment for patients taking clozapine, and can be considered in certain cases for patients taking first-generation antipsychotic medications. There is an overall lack of consistent evidence for the remainder of second-generation antipsychotic medications. There seems to be no well-defined role for urine drug testing for all antipsychotic medications in the assessment of therapeutic efficacy.

BENZODIAZEPINES

Benzodiazepines are a class of medications used for a variety of psychiatric disorders and symptoms, including anxiety disorders, alcohol withdrawal, insomnia, agitation, and catatonia, to name a few. While benzodiazepines have anticonvulsant, muscle relaxant, and amnesic properties, it is their sedative, hypnotic, and anxiolytic actions that are used to treat patients with psychiatric illness.⁴⁴

Mechanism of Action

Benzodiazepines act on the central nervous system by binding to specific sites on the GABA_A receptor, a ligand-gated channel that binds GABA, the major inhibitory

neurotransmitter in the brain. When a benzodiazepine binds to the GABA_A receptor, it alters the conformation of the receptor, increasing its affinity for GABA. This results in an influx of anions, leading to hyperpolarization, and thus inhibition of neuronal firing and subsequent central nervous system depression. The half-life for commonly used benzodiazepines range from 6 to 100 hours, and are divided into rapid, intermediate, and slow onset of action.

The most commonly used benzodiazepines are metabolized through the liver by the cytochrome P450 enzyme system. Aside from a few notable exceptions, benzodiazepines are metabolized initially by hepatic microsomal enzymes through various processes, including oxidation, hydroxylation, and demethylation. These products are then conjugated with glucuronic acid, which are readily excreted in the urine. Some benzodiazepines have active metabolites that produce clinically significant effects, whereas others do not. Notable exceptions to these metabolic steps are oxazepam, temazepam, and lorazepam, which are metabolized only by glucuronidation. As such, they have no active metabolites and are less sensitive to changes seen in liver disease and aging.

The clinical efficacy depends on the presence of at least a minimum effective concentration in the blood; however, there is great variability between benzodiazepines and between patients. For example, diazepam has a great volume of distribution, so a single dose will be active for only a short period. However, after repeated administration and saturation, owing to its long elimination half-life, it becomes bioavailable for a much longer time period. The opposite is true for many other benzodiazepines, which have low volumes of distribution and long elimination half-lives. At the furthest extreme are the rapid onset, high-potency, short half-life benzodiazepines. These properties make this subset of benzodiazepines very effective in producing sedative, anxiolytic, and hypnotic effects; however, they also are known to have a high abuse potential, cause tolerance, and pose a risk for withdrawal. As such, although a minimum concentration is at least needed to produce pharmacologic effects, a particular blood level in one individual may show efficacy, whereas the same level in another patient may not produce any effect at all, or worse, may cause intoxication or toxicity.⁴⁵

Therapeutic Drug Monitoring

There is evidence showing a clear inconsistency between benzodiazepine blood level and clinical response. As such, TDM using blood levels does not play a role in guiding treatment with benzodiazepines. This is primarily owing to issues of tolerance and the variability of clinical response between patients.^{46,47} Additionally, because the effects of benzodiazepines are rapid, treatment should instead be guided by immediate clinical impression rather than drug monitoring.

Although TDM using blood levels is not a routine part of care, urine drug screens can be used when there is concern for nonadherence or diversion. This should not be used indiscriminately, and should be guided by clinical judgment. For example, if a patient shows a lack of therapeutic effects under usual doses, a urine drug screen may help to inform the clinician about adherence. However, this is not a universal rule. There are many benzodiazepines that are not identified reliably on routine urine drug screens, so caution and sound clinical knowledge should be used when ordering urine drug screens.⁴⁸

STIMULANTS

Attention deficit hyperactivity disorder (ADHD) is a childhood-onset disorder that affects a behavior, attention, and impulse control and is estimated to affect 3% to 8%

of children.⁴⁹ One of the mainstays of treatment for children with ADHD is a stimulant medication, which has been shown to be superior to intensive behavioral treatment and community care.⁵⁰ Although stimulants only have indications for ADHD and narcolepsy, they are also used off-label for the treatment of apathy and withdrawal in geriatric patients, antidepressant augmentation, and for SSRI-induced apathy and sexual dysfunction. Still, as compared with other psychiatric medications, stimulants have a narrow list of uses.

Although they are currently primarily used for ADHD, in the 1930s amphetamine was used medically for various pulmonary pathologies because they cause bronchodilation and respiratory stimulation, and then later for the treatment of depression. In 1954, methylphenidates were developed. In 1970, owing to their abuse potential, the FDA moved stimulant medications to schedule II, thus greatly limiting their use. Still, studies have consistently showed the child and adolescent patients with ADHD taking stimulants show a reduced risk of substance use disorders later in life.⁵¹

Mechanism of Action

Both amphetamines and methylphenidates, the two main classes of stimulants used in psychiatry, generally are well absorbed orally, and have a short half-life. Peak blood levels are seen within a few hours after taking, and thus they need to be dosed several times per day. Blood level concentrations of sustained-release formulations peak an hour or two longer after their immediate release counterparts, and have a longer half-life, allowing for once a day dosing. Both the amphetamines and methylphenidates act by causing the release of norepinephrine, dopamine, and serotonin in monoamine neurons; however, they do so in slightly different ways. Amphetamines primarily cause the exocytosis of vesicles carrying monoamine neurotransmitters, whereas methylphenidates act by regulating both presynaptic and postsynaptic dopamine neurotransmitters in the prefrontal cortex and striatum.

Therapeutic Drug Monitoring

Although overdose, abuse, and central nervous system side effects are potential issues in patients taking stimulant medications, there is currently no role for TDM for several reasons. These medications are rapid onset and have short half-lives. As such, the medications' therapeutic effect and duration before metabolism and excretion is short lived. Symptoms instead should be monitored clinically, and dose adjustments should be made thoughtfully to target cognitive and behavioral symptoms while minding potential side effects such as headache, insomnia, and hypertension.

Many standard urine drug screens can detect amphetamine-derived stimulant medications. Similar to previous classes of medication, this may potentially be used to help the clinician when there is a question of adherence or diversion. However, given the rapid on-off of these medications, it should only be used in settings where the test can be administered within a few days after a dosing, and the clinician must still take into account the false-positive and false-negative results for these medications.

NONMEDICAL USE OF PSYCHIATRIC MEDICATIONS

In psychiatry, medication management plays an important role in treating many psychopathologies. Although most medications improve outcomes in patients with mental illness, certain classes of medications have the potential for nonmedical use, diversion, and addiction. Addressing the potential for addiction remains a core part of routine psychiatric care. There are psychiatric medications that have the potential to be misused. The classes of medications used in psychiatry that are most at risk

for misuse are benzodiazepines, stimulants, and sleep aids. Before prescribing these medications, it is important for the psychiatrist to take a thorough substance use history, social history, and family history; and to remain open and nonjudgmental. If patients are at risk for nonmedical use but the benefit of treatment outweighs this risk, the medication may still be prescribed. In these cases, informed consent, consistent prescribing practices, and setting a treatment framework are of utmost importance. In certain cases, part of the treatment framework may include drug testing. If the psychiatrist and patient agree to urine drug testing, there are a few concepts that must be kept in mind. The frequency and randomness of the collection, the pharmacokinetics of the medication, and the limitations of the laboratory assay being used are just a few examples that may affect the usefulness of drug testing.⁵²

In addition to these medications, there is limited but emerging evidence that other psychiatric medications have potential for nonmedical use as well. There are several case reports of quetiapine, particularly when combined with other known drugs of abuse.⁵³ Certain antidepressant medications have similar evidence. Case reports of bupropion abuse are emerging, via intranasal and intravenous administration.^{54,55} There is also some evidence for abuse of TCAs, likely owing to their anticholinergic and antihistaminic properties.⁵⁶ More research is needed before TDM is a routine part of treatment in patients being prescribed these medications.

SUMMARY

Laboratory assessment is an invaluable tool for psychiatrists and has great potential to increase efficacy and decrease unwanted effects of psychiatric medications. However, the clinical laboratory should in no way be a substitute for a psychiatric examination. Because there is an incredible amount of variability in response to medications even at the same blood levels, laboratory values are meaningless without a clinical correlate, and are sometimes even meaningless with one. There is much research but mostly inconclusive evidence for the usefulness of blood levels improving outcomes, aside from the medications with well-established therapeutic windows, as discussed. These inconsistencies may reflect the heterogeneity of illnesses that we group under a single diagnosis, such as “major depressive disorder.” For urine drug levels, in contradistinction to other fields of medicine (pain, addiction, emergency medicine, etc), we could not identify significant literature on how differences in levels affect clinical outcomes for those unique to psychiatry. When ordering laboratory tests, clinicians should already have in mind how any of the possible results would affect their patient’s treatment. Laboratory assessment should be used to augment clinical judgment and should be used incisively. Psychiatry is a field that emphasizes longitudinal care and a therapeutic alliance with the patient. With the growing technological and scientific advances, psychiatrists would be best served by combining the good practices of clinical expertise with educated laboratory orders.

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