

Therapeutic drug monitoring of antipsychotics

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Mr. Q, age 36, has a history of schizophrenia. He is brought to the hospital due to persistent auditory hallucinations and paranoid delusions. His history documents a trial and failure of risperidone, 4 mg twice daily, and aripiprazole, 20 mg/d. Based on this, the treatment team initiates haloperidol, 5 mg twice daily. Because he experiences persistent auditory hallucinations and paranoid delusions, Mr. Q is titrated to increasing doses of haloperidol over 2 weeks during the course of the hospitalization. Once Mr. Q is receiving a total haloperidol dose of 30 mg/d, the team decides to obtain a serum haloperidol level due to his persistent psychotic symptoms and the development of drug-induced parkinsonism. His serum haloperidol level is 24 ng/mL, which is within the expected range for his dose, but above the therapeutic window for efficacy. The team decides that the severity of Mr. Q's illness and documented treatment resistance (failing at least 2 adequate trials of antipsychotics) warrant a trial of clozapine.

Despite a long history of therapeutic drug monitoring (TDM) within psychiatry, routine monitoring of antipsychotic serum levels has not been unanimously adopted as standard practice. Clinical practice typically results in mostly a subjective assessment of the safety and efficacy of antipsychotics. This practice is in contrast to agents

such as valproic acid and lithium, which are routinely monitored for safety and efficacy using both subjective and laboratory measures. Clinicians may adhere to these monitoring practices for lithium and valproic acid because of these agents' narrow "therapeutic window" between toxicity and efficacy. However, antipsychotics can be viewed in a similar fashion.

To help conceptualize the therapeutic window for antipsychotics, it is important to understand that in most cases, the pharmacologic target for antipsychotics is dopamine (D2) receptor antagonism between 60% to 80%.¹ Total drug exposure would thus determine a patient's likelihood of minimizing positive symptoms, or exposure to adverse effects related to total dopamine antagonism. Serum drug concentrations are a better metric than total daily dose for determining drug exposure and achieving the pharmacologic target.² Evaluating serum antipsychotic levels also is a better method of determining true

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Practice Points

- **Exposure, and response, to antipsychotics** is better correlated with serum levels than with total daily dosage.
- Therapeutic drug monitoring (TDM) of antipsychotics may **help identify nonadherence, treatment resistance, and the likelihood of safety and efficacy.**
- Clinicians should **consult primary literature on TDM of antipsychotics**, and consider consensus guidelines to guide treatment decisions.

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Table

Antipsychotic therapeutic serum levels

Medication	Therapeutic range	Half-life
Aripiprazole	100 to 350 ng/mL	80 hours
Clozapine	350 to 600 ng/mL	16 hours
Fluphenazine	1 to 10 ng/mL	16 hours
Haloperidol	1 to 10 ng/mL	24 hours
Lurasidone	15 to 40 ng/mL	30 hours
Olanzapine	20 to 80 ng/mL	36 hours
Perphenazine	0.6 to 2.4 ng/mL	12 hours
Quetiapine	100 to 500 ng/mL	10 hours
Risperidone/9-OH risperidone	20 to 60 ng/mL	3 hours/20 hours
Ziprasidone	50 to 200 ng/mL	8 hours

Source: Reference 5

treatment failure than relying on the clinical judgment of the treating psychiatrist.³

Pros and cons of TDM

Benefits of using TDM for patients being treated with antipsychotics include⁴:

- ensuring adherence
- quantitatively adjusting dosages for medication interactions or genetic variations
- ensuring an adequate trial of a medication before considering it a treatment failure.

Potential drawbacks to TDM include:

- **Delayed results.** Access to expeditious testing may not be possible in certain laboratories, and this may require send-out testing, which could result in a delay in obtaining results. Continued advocacy and research on the value of TDM in antipsychotics may improve access to these resources in the future. Nonetheless, obtaining antipsychotic serum levels will still give clinicians insight into the antipsychotic exposure at a given dose. Further, obtaining antipsychotic serum levels may strengthen decisions about treatment resistance and the assessment of interactions, adherence, or the likelihood of adverse effects.

- **Lack of guidance.** Unfortunately, there is no established guidance outlining what

to do once antipsychotic serum levels are obtained. The correlation of serum levels of commonly used second-generation antipsychotics with clinical efficacy needs to be more closely investigated; however, certain agents do have more data associated with appropriate ranges for efficacy/toxicity. While researchers should continue to study the precise relationship between antipsychotic serum levels and effect, clinicians still have resources available to help determine what the expected serum value for a given patient may be. Knowing an expected serum level may help clinicians determine whether there is an unknown interaction or genetic variation that is causing lower- or higher-than-expected levels. This may also help determine whether a patient is adhering to their medication regimen.

Growing evidence for TDM

In recent years, evidence supporting the use of TDM in patients receiving antipsychotics has been increasing, and recommendations from consensus groups have been strengthened. One of the most comprehensive assessments of these practices was published by the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP), a German-

Clinical Point

Obtaining antipsychotic serum levels may strengthen decisions about treatment resistance and adherence



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Haloperidol appears to lose benefit with dose increases beyond serum levels of approximately 10 ng/mL

Related Resources

- De Leon J. A critical commentary on the 2017 AGNP consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology. *Pharmacopsychiatry*. 2018; 51(1-02):63-68.
- Meyer JM. Is monitoring of plasma antipsychotic levels useful? *Current Psychiatry*. 2015;14(11):16,19-20.

Drug Brand Names

Aripiprazole • Abilify	Perphenazine • Trilafon
Clozapine • Clozaril	Quetiapine • Seroquel
Fluphenazine • Prolixin	Risperidone • Risperdal
Haloperidol • Haldol	Valproic acid • Depakene, Depakote
Lithium • Eskalith, Lithobid	Ziprasidone • Geodon
Lurasidone • Latuda	
Olanzapine • Zyprexa	

based psychopharmacology group consisting of researchers and clinicians. In 2018, the AGNP published consensus guidelines for TDM in various neuropsychiatric medication classes and recommendations for collecting, interpreting, and decision-making elements of the process.⁵ The *Table*⁵ (page 45) lists the AGNP-recommended therapeutic serum range for several commonly used second-generation antipsychotics.

Researchers should be encouraged to contribute to the body of knowledge on the correlation of clinical response to serum level. However, there is compelling evidence for the use of TDM across many first- and second-generation antipsychotics. Of the most common, haloperidol and clozapine have evidence of a therapeutic range that is better correlated with serum level than daily dose. Specifically, haloperidol appears to lose benefit with dose increases beyond serum levels of approximately 10 ng/mL.⁶

Clozapine levels may be reported by measuring the metabolite norclozapine, which is not correlated with efficacy, or as a total level (combination of clozapine and norclozapine). While norclozapine is not

associated with efficacy, the ratio of clozapine to norclozapine may indicate adherence to the medication, or any enzymatic modulation (genetic or drug–drug interaction) that may increase or decrease total exposure. A ratio of 1.5 to 2.0 (clozapine to norclozapine) is optimal; a ratio <0.5 may indicate non-adherence; and a ratio >2.0 may indicate inhibited drug clearance. A 12-hour serum clozapine level of ≥ 350 ng/mL is more likely to predict treatment response.⁷

CASE CONTINUED

Mr. Q is carefully tapered from haloperidol while initiating clozapine at 25 mg/d. As he is titrated on clozapine, Mr. Q's serum levels are periodically checked and compared with expected levels and levels associated with efficacy. Eventually, Mr. Q is titrated to a clozapine dose of 400 mg/d at bedtime.

While receiving clozapine for 4 weeks, Mr. Q's psychotic symptoms resolve, and he is scheduled for follow-up in the outpatient clozapine clinic.

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