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Is monitoring of plasma antipsychotic levels useful?

The literature on plasma levels of antipsychotics documents the difficulties faced in establishing therapeutic ranges with the predictive power of those established for mood stabilizers and tricyclic antidepressants.

Although there has been success in defining the minimum therapeutic response threshold for certain antipsychotics—for example, clozapine (350 to 450 ng/mL), haloperidol (3 to 5 ng/mL), and fluphenazine (0.8 ng/mL)—one aspect of antipsychotic plasma levels not widely discussed is their value as a marker of adherence.

Many schizophrenia patients achieve an optimal response to agents for which there is no depot formulation. For them, maintenance of symptom control depends wholly on oral medication adherence.¹ Regrettably, nonadherence with oral antipsychotic treatment is prevalent among patients with schizophrenia; yet, in routine clinical practice, the extent of nonadherence rarely is measured.

Studies have been able to quantify oral medication nonadherence using monitoring devices, such as the Medication Event Monitoring System (MEMS) that electronically records opening of the medication container and strongly correlates with pill count. Although patients knew they were participating in a trial

using MEMS technology, only 48% were able to take their medication at least 80% of the time in a 4-week study,² and only 43% met the 70% adherence threshold in a 6-month trial.³

Clinicians, patients: Unreliable indicators of adherence

Neither clinician rating nor patient self-reporting is a reliable predictor of adherence with an oral medication regimen. In the 6-month adherence trial,³ clinicians estimated that 95% of their patients met the 70% adherence threshold (the actual percentage was 43%); in a 12-week study, clinician ratings correlated weakly with adherence ($r = 0.32$; $P = .001$), but patient self-reporting showed no significant correlation ($r = 0.18$; $P = .08$) with pill count.⁴

Clinicians underestimate not only the extent of nonadherence but also the impact that even a brief period of modest nonadherence has on the risk of relapse. In an 18-month prospective study of patients who recently had been given a diagnosis of schizophrenia, and in whom clinician and patient reports were supplemented with a pill count every 1 to 2 weeks and plasma antipsychotic levels every 4 weeks, any period of at least mild nonadherence was significantly predictive of symptom exacerbation or relapse (hazard ratio [HR], 3.4; 95% CI, 1.4–8.4; $P < .002$).¹ Moreover, 50% to 75% adherence for ≥ 2 consecutive weeks increased the HR to 5.8, and

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moderate nonadherence (<50% for 2.0 to 3.9 weeks) to an HR of 28.5.

There might be a better method already available

Given the poor correlation between a clinician's judgment and a patient's actual pill-taking, it is clear that more accurate methods of tracking adherence must be devised. Because MEMS technology is not widely available, and because pill counts require a home visit or a cooperative patient who brings medications to office visits, plasma antipsychotic monitoring potentially is an appealing method of tracking adherence.

Correlation between the plasma antipsychotic level and relapse is not consistently seen in the literature,⁴ but plasma levels obtained during periods of clinical stability offer the opportunity to define, for the individual patient, a range of drug exposure that is associated with clinical response. The ideal plasma level baseline is obtained at steady state during a presumed period of observed adherence, such as during a hospital stay. Although patients can be nonadherent in the hospital, this setting offers the best proxy for an acute clinical response to a given plasma level. The alternative is to obtain several plasma levels during a period of outpatient clinical stability.

Clinicians must be mindful that changes in the plasma antipsychotic level after hospital discharge might not reflect poor adherence; environmental factors (eg, exposure to cytochrome P450 or P-glycoprotein inducers) can have a significant impact on results. Resumption of smoking is a classic example, and routinely is associated with a 50% reduction in plasma clozapine levels.⁵

There also is expected variability in plasma antipsychotic levels based on (1) the timing of prior doses with regard to trough levels, and (2) the effects of an occasional missed dose. Nevertheless, in a sample of adherent clozapine-treated

patients, investigators found that 98% of patients had a coefficient of variability (CV) of 30% for sequential plasma concentrations (mean CV, 14%).⁶

Clinicians should inform patients that the plasma antipsychotic level is a tool for helping track treatment engagement before relapse—the same way metabolic monitoring helps track abnormalities that can be associated with future cardiovascular events. (Clinicians also must be charitable with their patients when discussing a significant drop in the plasma antipsychotic level [eg, >30%], acknowledging that many patients often miss doses.)

Using the patient's input about specific difficulties with a medication regimen, clinicians should strive to find ways to improve oral medication adherence. In many cases, the clinician can assist through medication simplification, consolidation of multiple daily doses, provision of pill boxes, and discussions about long-acting injectable (LAI) antipsychotics.

In short, plasma antipsychotic levels offer an opportunity to have a richer, evidence-based discussion about adherence, beyond the trite, ineffective question "Did you take your medication?" Use of an objective measure can (1) serve as a benchmark for the patient (eg, "You seemed to do better when your clozapine level was above 400 ng/mL"), and (2) remind clinicians of the variable adherence inherent with oral medication regimens.

A note about long-acting injectable antipsychotics

Because nonadherence is seen throughout the course of schizophrenia, discussion of LAI therapy should not be limited to patients with chronic illness. Results of recent naturalistic⁷ and randomized studies⁸ show significant reduction in the rate of psychotic relapse and improved symptom control⁸ among

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The plasma antipsychotic level is an opportunity for an evidence-based discussion about adherence, beyond the ineffective question, 'Did you take your medication?'

first-episode patients who are taking an LAI. Moreover, compelling data show that most first-episode patients who are taking an oral antipsychotic will accept a recommendation for treatment with an LAI.⁹

Summing up: 2 Tools for achieving therapeutic success

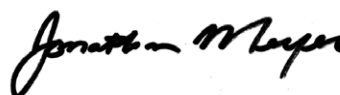
Monitoring plasma levels of antipsychotics offers a method for quantifying the problem of nonadherence. For many patients, an LAI antipsychotic provides a solution to nonadherence, and the increasing variety of LAI preparations means more options with which to match individual patients.

References

1. Subotnik KL, Nuechterlein KH, Ventura J, et al. Risperidone nonadherence and return of positive symptoms in the early course of schizophrenia. *Am J Psychiatry*. 2011;168(3):286-292.
2. Remington G, Teo C, Mann S, et al. Examining levels of antipsychotic adherence to better understand nonadherence. *J Clin Psychopharmacol*. 2013;33(2):261-263.
3. Byerly MJ, Thompson A, Carmody T, et al. Validity of electronically monitored medication adherence and conventional adherence measures in schizophrenia. *Psychiatr Serv*. 2007;58(6):844-847.
4. Velligan DI, Wang M, Diamond P, et al. Relationships among subjective and objective measures of adherence to oral antipsychotic medications. *Psychiatr Serv*. 2007;58(9):1187-1192.
5. Meyer JM. Individual changes in clozapine levels after smoking cessation: results and a predictive model. *J Clin Psychopharmacol*. 2001;21(6):569-574.
6. Dugan DJ, Ereshefsky L, Toney GB, et al. Dose and interval adherence among stabilized clozapine-treated patients measured by medication event monitoring. Presented at: Meeting of the New Clinical Drug Evaluation Unit; May 30-June 2, 2000; Boca Raton, FL.
7. Tiihonen J, Haukka J, Taylor M, et al. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. [Erratum in *Am J Psychiatry*. 2012;169(2):223]. *Am J Psychiatry*. 2011;168(6):603-609.
8. Subotnik KL, Casaus LR, Ventura J, et al. Long-acting injectable risperidone for relapse prevention and control of breakthrough symptoms after a recent first episode of schizophrenia: a randomized clinical trial. *JAMA Psychiatry*. 2015;72(8):822-829.
9. Weiden PJ, Schooler NR, Weedon JC, et al. A randomized controlled trial of long-acting injectable risperidone vs continuation on oral atypical antipsychotics for first-episode schizophrenia patients: initial adherence outcome. *J Clin Psychiatry*. 2009;70(10):1397-1406.

Clinicians have a limited amount of time to spend with patients in the office, but time spent discussing LAIs is an investment in the patient's stability and functional outcome. Minutes once spent managing nonadherence can be devoted to understanding the patient's aspirations and to developing strategies to achieve those goals.

In the end, isn't that what we'd rather be talking about with our patients?



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