The Role of Antipsychotic Plasma Levels in the Treatment of Schizophrenia

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Case 1: Recent Exacerbation in a Previously Stable Patient With Schizophrenia

A 50-year-old woman with chronic schizophrenia is brought to the emergency department with an acute psychotic exacerbation. The record indicates that she is being treated at an affiliated clinic where she had been noted to be increasingly psychotic over the previous 3 months after stepdown from supervised housing to independent living. The record notes an increase in her dosage of olanzapine, to 20 mg/day, 2 months prior to the emergency department visit and the addition of perphenazine, at 16 mg twice daily, 2 weeks prior; the record also notes that she reported adherence to both medications. The patient is admitted, and plasma levels drawn on admission, less than 4 hours after she reported taking her morning doses, register undetectable levels of both drugs. Taken with the other clinical information, in particular the patient's previous good treatment response and the onset of the exacerbation on moving from supervised housing, the plasma level information provides objective evidence that poor adherence has contributed to the exacerbation. When the results are discussed with the patient, she admits to having struggled to take her medications as prescribed but had not wanted to bring this up for fear of losing her independent housing. With her consent, the patient is started on a long-acting injectable antipsychotic to simplify the treatment regimen and support adherence. In this case, availability of plasma level information identified poor adherence rather than treatment resistance as the focus for clinical intervention. Moreover, had plasma levels been available when the patient began decompensating, a pro-adherence intervention could have been implemented in lieu of adding a second antipsychotic, and the psychiatric admission may have been avoided.

Case 2: A Patient With True Treatment Resistance

A 20-year-old man first diagnosed with schizophrenia about 1 year ago continues to experience distressing auditory hallucinations and delusions, including the delusion that a microchip embedded in his brain spreads his thoughts around the world. He was initially started on aripiprazole, titrated up to 15 mg daily. He took this dosage for 3 months with little response despite supervised medication administration and plasma levels in the expected range. He was eventually switched to olanzapine, at 20 mg once daily, which he has been taking for 3 months, but his symptoms have persisted. He reports good adherence, and plasma levels have been within the expected range for the dosage. We refer to the expected range rather than therapeutic range because, as discussed below, the therapeutic range is not well established for a number of antipsychotics. However, in this case, it is not necessary to have an established therapeutic plasma range to presume treatment resistance—this is the likeliest cause of poor response because plasma levels have provided evidence of adherence and they were also used to rule out rapid metabolism. Since the patient has a favorable risk-benefit profile for the use of clozapine and is accepting of the drug, his psychiatrist registers him in the clozapine registry and starts him on a trial the next day.

Case 3: Effectiveness and Safety Monitoring of Clozapine in Treatment-Resistant Illness

A woman in her 40s who has long been stable on clozapine treatment has a seizure roughly 2 months after she decided to halve her smoking habit to one pack per day. The admission workup reveals a clozapine level that is well over the recommended range. She is eventually restarted on clozapine at a lower dosage but because her smoking habit has been variable since her discharge, the treatment is being closely monitored with clozapine plasma levels.

Case 4: Recent Onset of Intolerable Side Effects in Treatment-Responsive Illness

A 28-year-old man makes an appointment to see his psychiatrist earlier than scheduled. He had responded well to risperidone up to 4 mg once daily started 6 months earlier,

continued

See related feature: **Clinical Guidance** *(Table of Contents)*

but he is bothered by an excruciatingly uncomfortable feeling of restlessness. Because the symptom started soon after initiating bupropion for smoking cessation, his psychiatrist suspects risperidone-induced akathisia due to a pharmacokinetic interaction with bupropion. A plasma level drawn the next day registers a high risperidone level. The psychiatrist reduces the dosage and monitors plasma levels to ensure that levels drop without imperiling the patient's response.

Antipsychotic drugs are highly efficacious in the treatment of positive psychotic symptoms of schizophrenia (1). However, a large fraction of patients either fail to respond to the prescribed antipsychotic drug or, while treatment responsive, are unable to tolerate the drug because of side effects. An approximation to the prevalence of these complicated courses of antipsychotic treatment may be gleaned from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study (2), which found median rates of treatment discontinuation due to inefficacy and side effects of 25% and 15%, respectively.

The challenge for prescribers is that the root cause of these complicated courses of antipsychotic treatment cannot be readily determined. Poor response may be caused by poor antipsychotic adherence, rapid elimination of the drug, or treatment resistance. Similarly, poor tolerance may be caused by slow elimination of the drug or high drug sensitivity. Because patient self-report and clinical intuition are unreliable sources of information to identify the cause of either presentation, treatment decisions are made under uncertainty.

All currently licensed antipsychotics are $D_{2/3}$ receptor antagonists, but they vary in their degree of binding to other neuroreceptors. Although molecular imaging has shown that $D_{2/3}$ neuroreceptor blockade is necessary for efficacy in the control of positive psychotic symptoms (3) and is linked to side effects related to dopamine blockade (e.g., 4), this technology is not readily available in routine care (5). Antipsychotic plasma levels are related to $D_{2/3}$ neuroreceptor occupancy in most circumstances, thus providing a useful alternative to measuring neuroreceptor blockade (e.g., 6). Moreover, they provide a ready means of objectively assessing adherence. Thus, access to antipsychotic plasma levels can improve prescribers' ability to discern the underlying cause of a complicated treatment course and to select the correct intervention. However, antipsychotic plasma levels are rarely used in clinical practice.

In this article, we review the clinical circumstances in which antipsychotic plasma levels may be used to guide the management of patients with schizophrenia who exhibit poor response or poor tolerance—patients who are currently managed largely on a trial-and-error basis. We first review the potential causes of these complicated treatment courses and the role of antipsychotic plasma levels in discerning among them. We then provide recommendations for the evidence-based use of antipsychotic plasma levels, and we end with a discussion of practical considerations.

CAUSES OF COMPLICATED COURSES OF ANTIPSYCHOTIC TREATMENT

Poor Response

For patients with an adequate dosage and duration of an antipsychotic treatment, the potential causes of persistent psychotic symptoms fall into three main categories: poor adherence, rapid elimination of the drug, and treatment resistance.

Poor adherence. As former U.S. surgeon general C. Everett Koop famously quipped, "Drugs don't work in patients who don't take them." Poor adherence to prescribed medications is common across all disorders, particularly chronic conditions requiring long-term treatment (7). The likelihood of poor adherence is particularly high for people with schizophrenia because of their cognitive deficits and poor insight, as well as the medical and substance use disorder comorbidities and social precariousness often associated with the illness (e.g., 8).

Rapid elimination of the drug. If the drug is rapidly metabolized, poor response may be observed even when the dosage and duration are adequate and adherence is optimal. For all practical purposes, these patients behave similarly to those with suboptimal dosages. Rapid antipsychotic metabolism can be due to genetic variation, for example, in cytochrome P450 (CYP) metabolic enzymes, or induction of metabolic enzymes by other drugs or dietary factors. Rapid and ultrarapid metabolism due to genetic variation is largely a concern for drugs whose elimination is significantly mediated by CYP2D6 (9, 10), namely, aripiprazole, haloperidol, perphenazine, and risperidone, which are prescribed for more than one-third of people taking antipsychotics in the United States (11), as well as brexpiprazole and zuclopenthixol. Genetic polymorphisms of CYP2D6 associated with rapid metabolism are seen in about 5% of Caucasians and a higher proportion, potentially up to 29%, of black people with African ancestry (10). CYP2D6 polymorphisms are an important driver of variations in the pharmacokinetics of drugs for which the 2D6 system is a major metabolic pathway. (For a thorough review of this topic, see reference 12.)

Smoking by-products and caffeine are potent inducers of metabolic enzymes, particularly CYP1A2 (13). Several enzymes are involved in the elimination of clozapine and olanzapine, with olanzapine also metabolized by glucuronidation, but CYP1A2 is a major metabolic pathway for both. As a result, drug levels of clozapine and olanzapine are, respectively, about 50% and 30% lower in cigarette smokers

(14). Since over half of patients with schizophrenia smoke tobacco and caffeine consumption is also common (15), these substances' metabolic effects can have a significant impact on clozapine and olanzapine treatments. Inductive pharmacokinetic interactions may also affect antipsychotics whose metabolism is influenced by the activity of the drug transport protein P-glycoprotein (PGP) and/or the CYP3A4 (e.g., haloperidol, olanzapine, clozapine, quetiapine, and ziprasidone) if patients are also treated with PGP and/or 3A4 inducers, including selected anticonvulsants (e.g., phenytoin) and the herbal product St. John's Wort.

Treatment resistance. Poor response may be observed despite adequate plasma levels and optimal neuroreceptor blockade (4)—in other words, in patients in whom the drug is inherently inefficacious. Treatment resistance in schizophrenia has received significant research attention, including a call to standardize its measurement (16). A recent finding that antipsychotic plasma levels may be inadequate in up to half of patients with schizophrenia previously identified as treatment resistant (17) raises the possibility that treatment resistance may be overestimated in routine practice.

Poor Tolerance

Intolerable side effects to antipsychotics may be due to slow elimination of the drug or high drug sensitivity.

Slow elimination of the drug. For drugs with dose-dependent side effects, poor tolerance may occur even when the dosage is appropriate if the patient eliminates the drug slowly because of pharmacokinetic interactions or poor metabolism (18). Examples include high-potency first-generation antipsychotics and selected second-generation antipsychotics whose risk for extrapyramidal symptoms and prolactin elevation is dose dependent (4, 19). Inhibitory pharmacokinetic interactions and poor metabolism mainly affect antipsychotics eliminated through CYP2D6 metabolism due to 2D6 polymorphisms. Although their prevalence is not well established, 2D6 polymorphisms associated with poor metabolism affect approximately one in every 15 Americans, with higher rates among whites and lower rates among Asians (20). The possibility of pharmacokinetic interactions should be suspected in patients who are also taking potent 2D6 inhibitors, including selected antidepressants (e.g., fluoxetine).

High drug sensitivity. Although all drugs may be associated with idiosyncratic sensitivity, the risk may be smaller than previously thought (21). With the notable exception of clozapine, which is associated with agranulocytosis and myocarditis (22), there is little evidence of idiosyncratic sensitivity to antipsychotics.

THE ROLE OF ANTIPSYCHOTIC PLASMA LEVELS IN THE MANAGEMENT OF SCHIZOPHRENIA

Distinguishing between the possible causes of poor response and poor tolerance requires objective information. Since assays are available for most antipsychotics, plasma levels could be used to provide objective information on the underlying cause of an untoward antipsychotic treatment outcome.

Poor Response

The management of poor response depends on whether the cause is poor adherence, rapid elimination of the drug, or treatment resistance: instituting pro-adherence interventions, increasing the dosage, or switching to a different first-line antipsychotic or clozapine, respectively (e.g., 1). Hence, correctly identifying the cause is of paramount importance. However, prescribers largely rely on patient self-report and clinical intuition to manage these patients. This is troubling because self-report significantly overestimates adherence relative to objective methods, including pill counts and use of a medication event monitoring system, the current gold-standard method (23). Moreover, prescribers tend to overestimate antipsychotic adherence among their patients with schizophrenia (24). Antipsychotic plasma levels provide an efficient approach to improving the reliability of the assessment of adherence (25), with the caveat that they only reflect recent adherence behavior, as well as rapid elimination of the drug and treatment resistance.

Poor Tolerance

The management of poor tolerance due to slow elimination of the drug (dosage reduction) is very different from that of high drug sensitivity (drug discontinuation). Although prescribers' accuracy in distinguishing between these phenomena has not been studied, evidence of high rates of antipsychotic switching in routine practice (26) suggests that prescribers overestimate the relative importance of high sensitivity. Since high sensitivity is not related to dosage or plasma levels, high plasma levels suggest that slow elimination of the drug is the likeliest cause of poor tolerance. Hence, plasma levels may be used to discern the correct cause of poor tolerance.

The potential value of using antipsychotic plasma levels as an aid in the management of patients with schizophrenia with complicated treatment courses has long been recognized (e.g., 27), and more recently, it has been recommended by clinical guidelines (1, 28, 29) and published reviews of the evidence (e.g., 30). However, antipsychotic plasma levels are used infrequently, even in industrialized countries (17), in stark contrast with the routine use of plasma levels to guide treatment in other areas of psychiatry (31). Although the reasons for their low utilization are not well understood, potential drivers include logistics (e.g., access to laboratory services) and prescribers' concerns with the strength of the scientific evidence (32).

STRENGTH OF THE SCIENTIFIC EVIDENCE

In this section, we summarize the empirical evidence supporting the use of antipsychotic plasma levels to assess adherence and intolerable side effects and to predict therapeutic effect.

Assessing Adherence

The use of plasma levels to detect nonadherence was endorsed by the 2011 Consensus Guidelines for Therapeutic Drug Monitoring in Psychiatry published by the Working Group for Neuropsychopharmacology and Pharmacopsychiatry (Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie [AGNP]) (28). Although an undetectable plasma level is highly suggestive of nonadherence, prescribers should bear in mind that ultrarapid metabolizers may have undetectable levels of antipsychotics even when adherent. Genetic testing may be necessary to distinguish between the two potential causes, but for risperidone, measurement of its active metabolite, 9-hydroxyrisperidone, suffices, as the metabolite's levels would be high in ultrarapid metabolizers with adequate adherence. Plasma levels may also be used to assess partial adherence based on evidence of a linear correlation between dosage and plasma concentration (33–38). It should be recognized, however, that for some drugs the evidence is not conclusive. In the case of quetiapine, the strength of the relationship between dosage and plasma concentration varies considerably between studies, potentially because of differences in study designs (39, 40) or the drug's short half-life (40). However, it is often not necessary to have a detailed understanding of the relationship between dosage and plasma concentration for plasma levels to be useful in clinical practice, because often the key question is whether the patient is taking the medication at all.

Assessing Intolerable Side Effects

Plasma levels may be used to assess dose-dependent side effects. The evidence for this application is strong for clozapine, whose risk for seizures is dose dependent (41), while it is growing for quetiapine (42), risperidone (38, 43), and olanzapine (43, 44).

Predicting Therapeutic Effect

The evidence for the use of plasma levels to predict therapeutic effect is not as well developed. While there is strong evidence for haloperidol (e.g., 45), perphenazine (e.g., 46), and clozapine (e.g., 1), the evidence is limited or mixed for the more commonly used second-generation antipsychotics (30, 44), although it is promising for olanzapine, risperidone, and aripiprazole (34, 35, 47). Because many studies have used inadequate methodologies (e.g., flexible dosing, small sample sizes, short durations), methodologically sounder research may yield more definitive evidence and further expand the role of plasma levels in the management of complicated schizophrenia (30).

RECOMMENDATIONS

First and foremost, antipsychotic plasma levels should be used as part of a thorough clinical evaluation and not used in isolation. Consistent with the evidence reviewed above, prescribers should strongly consider ordering antipsychotic plasma levels in the following clinical scenarios:

1. To rule out poor adherence or rapid elimination of the drug in patients who fail to respond or decompensate despite adequate dosage and duration of the treatment (as in cases 1–3 presented at the start of this article). Plasma levels should be drawn after directly observing drug administration or when patients are most likely to be adherent (e.g., while hospitalized). Other sources of information may be brought to bear to differentiate between nonadherence and ultrarapid metabolism, or between partial adherence and rapid drug elimination. Genetic testing may be used to determine whether CYP2D6 polymorphisms are affecting metabolism. If this distinction cannot be made, a trial of a long-acting injectable form of the drug or an alternative drug may be implemented to avoid 2D6 metabolism. Measuring peak levels may help in the further assessment of partial adherence (see references 39, 40 for a further discussion of this issue as it pertains to quetiapine). If the antipsychotic is haloperidol, perphenazine, or clozapine, plasma levels may also be used to improve the likelihood of therapeutic effect.
2. To rule out slow drug elimination in patients who are treatment responsive but exhibit intolerable side effects (as in case 4 presented at the start of this article). Plasma levels should be routinely used when safety concerns arise in clozapine-treated patients.

Conversely, routine antipsychotic plasma levels are not currently indicated in the following scenarios:

1. In patients who have been stabilized on an antipsychotic and are at most exhibiting tolerable side effects. However, a one-time plasma level obtained to determine the level associated with adequate treatment response and tolerance may serve as a valuable baseline for future reference if the clinical presentation were to change.
2. In patients who despite failing to respond to an antipsychotic, a plasma level would not assist with the management because 1) the dosage or duration are inadequate, 2) there is already clear evidence of poor adherence, or 3) dose-dependent side effects are an indication that the plasma level is not low but rather the opposite.
3. In patients who are starting a new drug that is not haloperidol, perphenazine, or clozapine, and the intended use of plasma levels is to guide dosing for therapeutic efficacy.

PRACTICAL CONSIDERATIONS

Important considerations to ensure valid and reliable results when ordering antipsychotic plasma levels include 1) availability of clinically validated assays for immediate-release formulations and, if available, for extended-release formulations as well; 2) ordering the test after the drug has achieved steady state, usually at least 5 drug half-lives; 3) testing at

the recommended sampling time; although a random level is adequate when nonadherence is suspected, a trough level is preferable, particularly for drugs with short half-lives or to rule out rapid metabolism; and 4) informing the laboratory of the possibility of inadequate adherence and whether the drug is immediate release or extended release.

The expected range of plasma levels for a given dosage are available from drug companies and are summarized for many drugs in easy-to-use formats (e.g., 48).

CONCLUSIONS

Antipsychotic plasma levels are a valuable yet underutilized tool in common clinical situations in which patients with schizophrenia are currently managed largely on the basis of error-prone information. Lacking objective information, prescribers are less likely to identify the correct cause of complicated courses of antipsychotic treatment and make the correct treatment decision. Prescribers may prematurely discontinue an otherwise promising drug instead of instituting pro-adherence interventions or dosage changes aimed at optimizing the treatment or making it more tolerable (49). When patients exhibit poor response, prescribers may add another antipsychotic or blindly increase the dosage above the recommended range. These guideline-discordant practices not only lack evidence of effectiveness but also increase the risk of side effects and iatrogenic lapses in adherence (50). Inaction or delays in implementing changes to a regimen perceived by the patient to be a treatment failure is problematic, as adherent patients may stop taking their medication and some may become negatively predisposed to all antipsychotics as a result of this experience.

Improving decision making through greater access to antipsychotic plasma level information has the potential to have a significant impact on quality of care and outcomes of patients with schizophrenia. Efforts are needed to expand the use of antipsychotic plasma levels.

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