



## Personalizing Antipsychotic Treatment of Schizophrenia

### Monitoring Plasma Levels for Improved Treatment Decisions

*Marcela Horvitz-Lennon, Zachary Predmore, and Soeren Mattke*

Despite the availability of efficacious antipsychotic drugs, the pharmacological management of schizophrenia remains a challenge, and it largely follows a trial-and-error paradigm. With notoriously high rates of poor antipsychotic drug adherence and limited means to detect it, prescribers are often uncertain whether a lack of treatment response is due to poor adherence or true lack of effect, which in turn may simply be a reflection of insufficient plasma concentration of the drug. Moreover, when encountering a patient with intolerable side effects, prescribers do not know whether to switch to another drug or merely reduce the dose. This uncertainty results in unnecessarily high rates of unwarranted treatment changes and antipsychotic polypharmacy, loss of adherence and disease control, and ultimately poor patient and societal outcomes. In this Perspective, we argue that point-of-care information on antipsychotic plasma levels—the amount of drug circulating in the patient’s blood—will result in better patient care, which should lead to better health

and better value for the health care system. While tests for antipsychotic plasma levels have long been available through specialized labs, they are not routinely used, in part because of delays in obtaining results. Access to information on antipsychotic plasma levels at the point of care would facilitate better use of currently available drugs and reduce the uncertainty associated with the management of complicated presentations by providing prescribers with a tool to “personalize” treatment to patients’ characteristics, including responsiveness to specific medications, metabolism, and adherence behavior.

### **The Dilemma of Antipsychotic Treatment Selection for Schizophrenia**

Powerful antipsychotic drugs have been available for well over 60 years, but optimizing their use remains a challenge because prescribers lack objective markers to guide treatment decisions. When selecting antibiotics or targeted cancer drugs, prescribers

can rely on biomarkers to make the right decisions, but no such markers exist to guide the selection of an antipsychotic among first-generation or more commonly used second-generation antipsychotic (SGA) drugs. When managing diabetes or hypertension, prescribers can monitor HbA1c levels and blood pressure to optimize medication management, but when managing schizophrenia, prescribers rely mainly on clinical observation and patient self-report, both subject to error. Thus, prescriber decisionmaking in the face of insufficient treatment effect or intolerable side effects is fraught with uncertainty.

Poor adherence<sup>a</sup> to antipsychotic drugs among patients with schizophrenia, worse than that seen in other chronic populations,<sup>1,2</sup> compounds the challenge.<sup>3,4</sup> In the United States, about four in ten patients with schizophrenia take little or none of their prescribed antipsychotic medication.<sup>4–6</sup>

The Centers for Medicare and Medicaid Services has selected antipsychotic adherence among beneficiaries with schizophrenia as a core quality measure<sup>7–10</sup> and reports, for example, that in 2013, only 58.5 percent of Medicaid patients were sufficiently adherent.<sup>11</sup> Again, prescribers largely rely on error-prone inputs (their own observations and patient self-report) to learn about problems with adherence, because gathering information with more-accurate approaches, such as electronic medication monitors, is resource intensive.<sup>12–14</sup>

Thus, when faced with a patient who is exhibiting uncontrolled psychotic symptoms despite ongoing treatment, prescribers are typically unable to discern the true cause. Is the current dose

subtherapeutic (i.e., pharmacokinetic or other factors leading to the rapid metabolism of the drug), and therefore a higher dose might be effective? Is the patient not taking the drug as prescribed? Or is it true treatment failure (i.e., the patient is adherent and the dose sufficient but the drug ineffective)?

A similar dilemma exists for patients with adequate treatment response but intolerable side effects. Are the side effects related to the patient metabolizing the drug slowly, thus leading to high plasma levels, which would point to dose reduction as the best course of action? Or does the patient simply not tolerate the drug at a dose necessary for clinical effect?

The prevailing paradigm of prescriber decisionmaking has been described as “trial and error”<sup>15</sup> because the best course of action is only clear for two subsets of patients: those in the upper left and those in the lower right segment of Figure 1. For the remaining patients—an estimated 40 percent—clinical presentation alone does not provide a solid basis for decisionmaking (see Figure 1).

Faced with uncertainty or after erroneously inferring lack of effectiveness, prescribers may resort to antipsychotic prescribing that is not guideline-concordant, such as polypharmacy and high dosing.<sup>21,22</sup> Others may switch drugs prematurely—that is, without instituting such adherence interventions as long-acting injectable antipsychotics or dose changes that will optimize the treatment or make it more tolerable.<sup>23,24</sup> Or if a switch is warranted because of true treatment failure, prescribers rarely switch to clozapine, a highly effective but vastly underused second- or third-line drug.<sup>17,21</sup>

Although new antipsychotic drugs have expanded the armamentarium for the treatment of schizophrenia, there have been no breakthroughs that ensure treatment response and tolerability for all patients, or at least predictability of response and tolerability.

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<sup>a</sup> We use the term *adherence* broadly to refer both to the percentage of time a patient takes antipsychotic drugs (typically assessed with such measures as medication possession ratio) and to the duration of time from initiation to discontinuation of a specific antipsychotic, also referred to as *persistence*.

**Figure 1**  
**Percentage of Patients in Each Potential Response and Tolerability Category, with Most Adequate Course of Action**



SOURCE: Authors' estimates based on the Clinical Antipsychotic Trials of Intervention Effectiveness study's rates of discontinuation due to inefficacy (median of 25 percent across the study drugs) and side effects (median of 15 percent),<sup>16</sup> as well as studies on prevalence of treatment-resistant schizophrenia, with rates ranging between 20 and 48 percent and a median of approximately 33 percent.<sup>17-20</sup>

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## The Trial-and-Error Approach Leads to Poor Outcomes

As with many chronic diseases, the inadequate management of patients who are not responding well to treatment has substantial negative implications. Conversely, controlling psychotic symptoms quickly and decisively shortens acute psychotic episodes, avoiding immense patient and family suffering.<sup>25,26</sup>

In first-episode schizophrenia, longer duration of untreated psychosis can significantly impact short- and long-term prognosis.<sup>27-31</sup> In chronic schizophrenia, each relapse contributes additional illness-related disability and complicates ensuing treatment efforts.<sup>32,33</sup> Paraphrasing a slogan from cardiology, where prompt treatment of acute myocardial infarctions is summarized as “time is muscle,” the cumulative effects of delays in implementing optimal

treatment in the care of patients with schizophrenia may be summarized as “time is function.”

Patients with uncontrolled psychosis have a greater likelihood of poor treatment adherence, substance use, and suicidal behavior, as well as worse physical health outcomes (e.g., Novick, Haro, Suarez, et al. [2010]<sup>34</sup>). Poor social outcomes include decreased productivity for patients and their immediate caregivers, homelessness, victimization, and involvement in crime and the criminal justice system.<sup>42</sup> These poor outcomes exact a heavy economic toll on payers and society. For example, patients with acute psychotic exacerbations have health care costs between two and six times higher than well-controlled patients.<sup>35–37</sup>

Poor antipsychotic adherence is an important contributor to those excess health care costs: Nonadherent patients are nearly three times as likely as adherent patients to require a psychiatric hospitalization (34.9 percent versus 13.5 percent).<sup>5</sup> A 2008 study estimated that better adherence could save \$106 million (in 2005 U.S. dollars) by reducing psychiatric hospital admissions by 12.3 percent.<sup>38</sup> Additionally, most of the direct costs associated with social services and the criminal justice system are incurred by or on behalf of patients who are not doing well.<sup>39,40</sup> In the United States, where criminal justice system costs are typically borne by state governments, states would be able to save more than \$320

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per patient per year in direct non–health care costs if patients with schizophrenia had better symptom control.<sup>23</sup> (For more on the costs of schizophrenia, see Text Box 1.)

## **Better Decision Support Is Needed to Bridge the Gap**

To improve on the trial-and-error treatment paradigm, prescribers need actionable information to help them manage patients with poor response or tolerance to antipsychotic treatment. *Knowledge of these patients’ antipsychotic plasma levels would reduce uncertainty about the root cause of complicated treatment courses, providing prescribers with objective evidence on which to base their clinical decisionmaking.*

Plasma levels are routinely used to guide treatment in other areas of medicine, particularly for drugs that have a narrow therapeutic index or a therapeutic window (e.g., anticoagulants, immunosuppressants). Examples of psychiatric drugs falling into those categories in psychiatry are lithium, a mood stabilizer, and nortriptyline, a tricyclic antidepressant. Although assays are available for antipsychotics, plasma level monitoring (PLM) is rarely used to inform the management of patients with schizophrenia with a complicated treatment course,<sup>58,59</sup> despite published recommendations<sup>60,61</sup> and support from leading researchers (see Text Box 2).

Reasons for the low utilization of PLM include logistical constraints and questions about the strength of the evidence on its utility.

### **Low Utilization of PLM: Logistical Constraints**

Survey evidence from the United Kingdom suggests that poor access limits use of PLM. In one survey in which 181 psychiatrists with an average of 17.6 years of experience were asked about their views on therapeutic drug monitoring, a term that is oftentimes used

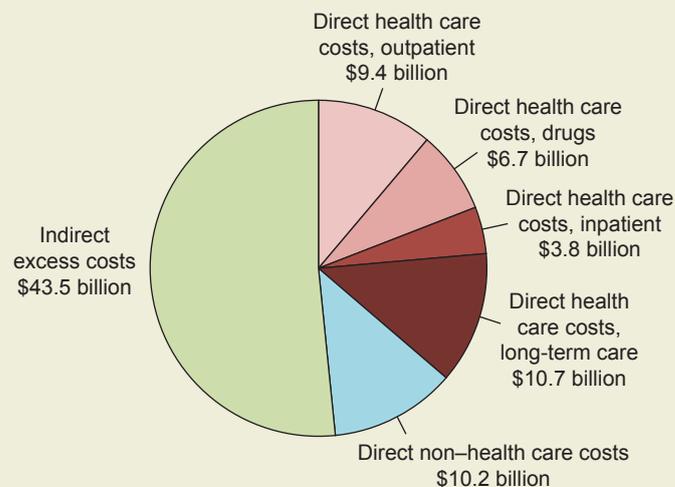
## Text Box 1: The Burden of Schizophrenia

Despite its relatively low prevalence (roughly seven cases per 1,000 persons<sup>41</sup>), schizophrenia is associated with a large burden of disease as a result of its early age at onset, chronic course, significant disability, and premature mortality.<sup>42–45</sup> It is a serious mental illness identified in all populations and cultures<sup>46</sup> and characterized by profound disturbances of thought and perception.<sup>47</sup> A U.S. study conducted in the early 2000s found that patients with schizophrenia die approximately 25 years earlier than age- and sex-adjusted peers.<sup>48</sup> While suicide and accidents play an important role, roughly 60 percent of the excess mortality is due to chronic medical conditions, with cardiovascular diseases accounting for more than half of this excess risk.<sup>49,50</sup>

The cost of schizophrenia, including direct costs of medical and social services and the indirect cost of economic burden,<sup>51,52</sup> is significant wherever it has been assessed.<sup>53–55</sup> In the United States, the overall annual cost of the illness was estimated to be close to \$85 billion in 2015 dollars (see Figure 2).<sup>56,57</sup>

While about half of that amount was accounted for by indirect costs, with mean per-patient costs estimated at \$29,589 in 2015, one-third was accounted for by direct health care costs, with mean per-patient costs estimated at \$20,768 in 2015; the remainder was accounted for by social services costs.<sup>56,57</sup> Direct health care costs include both insurance payments and out-of-

**Figure 2**  
Overall Annual Costs of Schizophrenia in the United States



SOURCE: Data from Wu, Birnbaum, and Shi (2006) and Halfhill (2015).<sup>56,57</sup>

NOTE: 2002 dollars were inflated to 2015 dollars using the Consumer Price Index.

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pocket spending by patients.<sup>56</sup> Direct non-health care costs include spending by “law enforcement, homeless shelters, and research and training related to schizophrenia.”<sup>56</sup> Indirect costs consist of losses in productivity in four categories: greater likelihood of unemployment, decreased productivity at work, early death from suicide, and additional time spent providing care by family members.<sup>56</sup>

interchangeably with PLM, 83 percent of the sample agreed that “if [PLM] for antipsychotics was readily available, I would use it.”<sup>68,69</sup> Another survey of 105 psychiatrists corroborates this finding, show-

ing 85-percent support for the same statement.<sup>69</sup> Samples commonly have to be sent to specialty labs, and the results are then typically available only days, if not weeks, later. This is a significant hin-

## Text Box 2: Expert Views on Plasma Level Monitoring

We interviewed four leading experts in antipsychotic drug management about their views on PLM: Dr. Christoph Hiemke, a professor of neurochemistry and author of a 2011 German consensus clinical guideline on the use of PLM in psychiatry;<sup>60</sup> Dr. Oliver Howes, a psychiatrist based at the Institute of Psychiatry at King's College London, where he directs a service for refractory psychoses, and whose research focuses on the causes and treatment of psychosis;<sup>62</sup> Dr. John Kane, a psychiatrist researcher with considerable expertise in clinical schizophrenia research and co-author of a review of studies of nonclozapine SGA plasma levels published up to 2012;<sup>58</sup> and Dr. Paul Perry, a pharmacist researcher with expertise in clinical psychopharmacological research and author of several studies of antipsychotic plasma levels.<sup>63</sup> In the view of all four experts, plasma levels

should be widely used to assess adherence and toxicity, and also to assess likelihood of clinical effect in patients treated with the antipsychotics for which adequate evidence exists.<sup>64–67</sup> Dr. Howes regularly uses PLM to manage patients deemed treatment refractory, based on the view—shared by the other three experts—that plasma levels are very useful as a reliable means of assessing adherence.<sup>64–67</sup> He stated, “It’s surprising how there’s been relatively little research into this. People have used lots of other ways of dealing with adherence, mostly pill counts and questionnaires, which we know are quite unreliable, and yet we have a means that is actually telling you quite precisely what’s going on and there are still some issues that you need to consider, but it won’t lie, and yet we use it remarkably little. I’m fortunate in my service that we are set up to do these levels. I know in many clinical settings it’s not so easy, which is one of the reasons why people don’t do it as much.”<sup>66</sup>

drance, because a delay in adjusting an ineffective or poorly tolerated antipsychotic regimen can significantly impact adherence, treatment course, and prognosis. Moreover, for nonadherent patients, a delay in learning about an undetectable level may translate into an inability to prevent further deterioration and need for acute care. If PLM were available at the point of care, prescribers would be able to react immediately and reduce the likelihood of poor outcomes.

### Low Utilization of PLM: Doubts About Utility

Prescriber reluctance to use PLM may also stem from concerns about the utility of plasma levels to assess adherence, risk of toxic-

ity, and likelihood of therapeutic effect. We briefly summarize the evidence to speak to those concerns.

*Use of PLM to assess adherence.* There is substantial evidence that antipsychotic dose correlates with plasma levels, and the interpretation that an undetectable plasma level implies nonadherence, at least in the few days before the test, is incontestable. Recently published studies have augmented a body of research published up to 2012.<sup>58</sup> A systematic review published in 2013 that included ten studies published between 1997 and 2009 found that patients with higher daily oral doses of olanzapine, a commonly prescribed SGA, had higher plasma concentrations of the drug.<sup>70</sup> Similarly, a study

published in 2014 that used mass spectrometry to measure plasma levels of paliperidone, another SGA, found that a higher daily dose was associated with higher plasma concentration of the drug. Although plasma levels reflect only recent adherence behavior, they provide a more objective tool to assess adherence relative to the notoriously unreliable methods typically used in routine care (e.g., asking the patient, pill counts).<sup>14</sup>

*Use of PLM to assess risk of toxicity.* In two studies from the United Kingdom, eight out of ten psychiatrists surveyed stated that plasma monitoring would help “minimize the risk of toxicity.”<sup>68,69</sup> Plasma levels may be particularly useful for antipsychotics with dose-dependent risks—especially clozapine, given the drug’s risk for seizures above a certain plasma level.<sup>71,72</sup>

*Use of PLM to predict therapeutic effect.* The scientific evidence supporting the use of PLM to assess likelihood of therapeutic effect and as a guide for dose titration is not as well developed. There is good evidence for a relationship between plasma levels and clinical effect for haloperidol,<sup>73</sup> perphenazine,<sup>74</sup> and clozapine<sup>75</sup>—all three having empirical evidence supporting the existence of a therapeutic range.<sup>67,73–75</sup> However, with the possible exception of haloperidol, these drugs are infrequently used in the industrialized world,<sup>76,77</sup> and less evidence exists for the commonly used SGAs. A review of 11 studies of variable methodological quality published up to April 2012 that examined the association between nonclozapine SGA plasma levels and clinical response in acute psychosis concluded that the evidence was mixed for this association.<sup>58</sup> However, the authors noted that the study with the best methodological design suggested that a plasma level–response association exists for olanzapine.<sup>58</sup> Recent studies have augmented the evidence base. A 2013

review that included ten studies published between 1997 and 2009 reported agreement that a minimum plasma level of olanzapine of 20 nanograms per milliliter (ng/mL) was necessary for therapeutic effect. However, the studies differed in their findings for the maximum safe therapeutic level (between 40 and 80 ng/mL).<sup>70</sup> A 2014 study found that higher plasma levels of paliperidone were associated with improved symptom scores, as assessed with the Positive and Negative Syndrome Scale; however, the fact that scores worsened when plasma levels were too high is suggestive of the existence of a therapeutic window.<sup>78</sup>

The relative immaturity of this evidence has affected prescribers’ views about PLM. The survey studies already referenced found that 66 percent and 63 percent of psychiatrists considered the scientific evidence for the relationship between therapeutic effect and plasma levels of risperidone and olanzapine, respectively, to be weak.<sup>68</sup>

The four experts (see Text Box 2) agreed that clozapine was the SGA with the strongest evidence in support of using plasma levels to assess likelihood of therapeutic effect and that further research is needed to expand the depth and breadth of the evidence on the relationship between plasma levels and clinical effects.<sup>64–67</sup>

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## The Future of Antipsychotic Treatment

Our four experts agreed that a technology for the assessment and rapid reporting of plasma levels at the point of care would be a welcome development.<sup>64–67</sup> Such a tool would expand access to PLM to practices lacking laboratory services and increase the actionability of the results. As pointed out by Dr. Kane, launching a point-of-care PLM tool would need to be coupled with a robust effort aimed at educating prescribers on the uses and benefits of the tool to improve its reach and ultimate impact.<sup>64</sup>

With the availability of a point-of-care PLM tool, the schizophrenia treatment paradigm would shift from trial and error to personalized medicine for the approximately 40 percent of patients with complicated courses of treatment (see Figure 1).<sup>62,64</sup> The point-of-care tool would allow prescribers to make antipsychotic dosing and switching decisions for this large group of patients based on their responsiveness to specific medications, metabolism, adherence behaviors, and other individual characteristics.

Dr. Kane also expressed confidence that “the pharmaceutical industry and academia will respond by doing more studies and create more needed information” once prescribers have easier access to ascertaining their patients’ plasma levels.<sup>64</sup>

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## Insufficient Response but Tolerable Side Effects

Information on plasma levels would allow prescribers to determine whether the approximately 25 percent of patients in the category highlighted in the bottom left of Figure 3 have a poor response because of pharmacokinetic and other factors lowering plasma levels, nonadherence, or true treatment failure.<sup>62</sup> Although plasma levels cannot be used to differentiate between partially adherent patients and those whose levels are low as a result of pharmacokinetic factors, they are a valuable addition to other evidence that may be used to identify the correct causal mechanism.

The literature does not provide much guidance on the relative significance of each of these mechanisms, but prevalence estimates of treatment failure (with a minimum at approximately 10 percent<sup>17–20</sup>) and poor adherence (with a minimum at approximately 20 percent<sup>2</sup>) suggest that these are the largest contributors.<sup>b</sup>

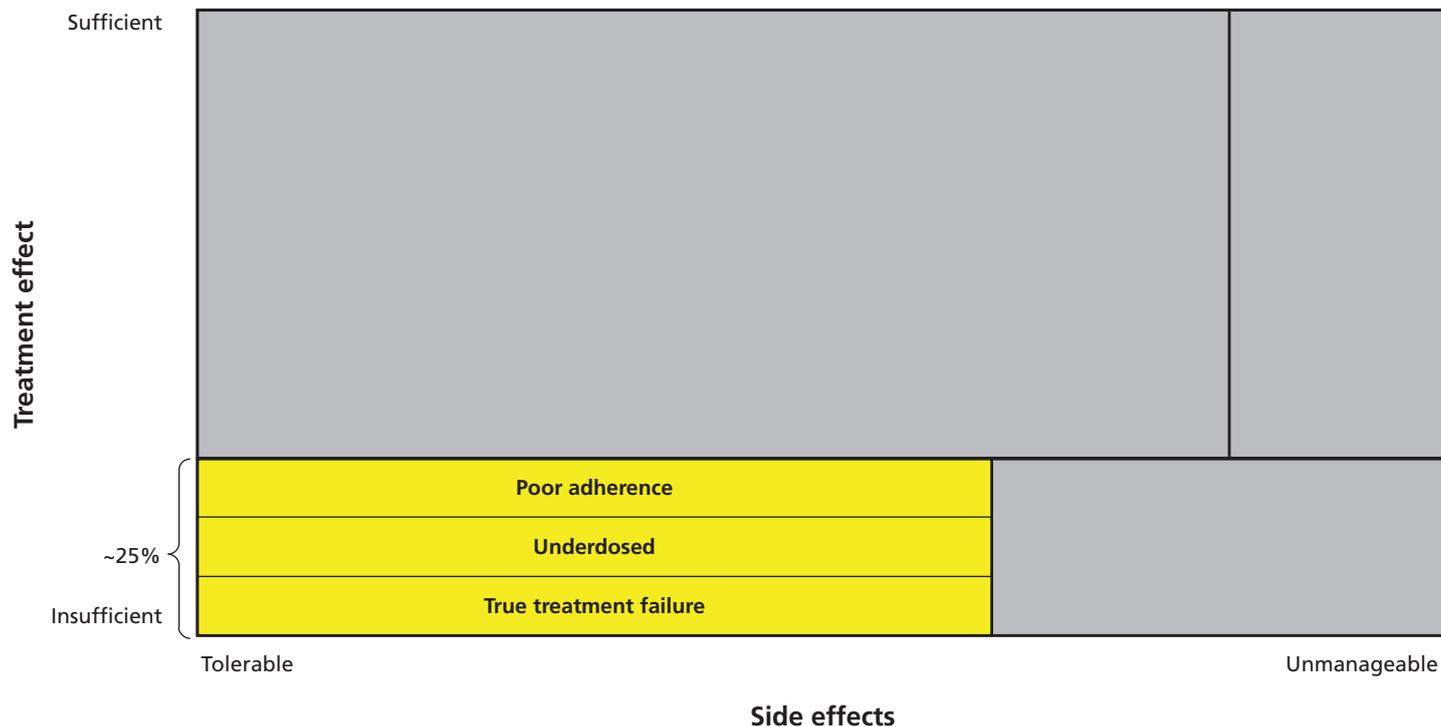
### Low Plasma Levels

In this scenario, pharmacokinetic factors (drug-drug interactions) or the patient’s rapid metabolism cause plasma levels to be low-normal or subtherapeutic even when the antipsychotic dose and the patient’s adherence are adequate.<sup>79,80</sup> As long as the patient is not exhibiting intolerable side effects, the prescriber would be well advised to gradually increase the dose to a range where treatment response is more likely.<sup>81</sup>

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<sup>b</sup> We note that, in the literature, the estimates of treatment failure on treatment-resistant schizophrenia apply to patients in both the tolerable and unmanageable bottom cells of Figure 3, while the estimates of poor adherence apply only to the tolerable bottom cell (highlighted in yellow).

**Figure 3**  
**Patients with Insufficient Treatment Effect and Tolerable Side Effects**



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### Poor Adherence

In this scenario, poor adherence causes plasma levels to be sub-therapeutic or undetectable (see Text Box 3 for a sample scenario). Once the prescriber is able to determine that this is not the result of pharmacokinetic or other factors, the priority for the prescriber would be to engage the patient in a discussion on reasons for poor adherence and its risks, followed by the implementation of basic pro-adherence interventions (e.g., consolidating doses, instituting reminders). The prescriber may also consider more-complex

evidence-based interventions, such as long-acting injectable antipsychotic drugs,<sup>82</sup> medication management programs that use technology to remind patients to take their medication,<sup>83</sup> and financial incentives.<sup>84</sup>

### True Treatment Failure

In this scenario, the patient has been on the antipsychotic drug for at least four to six weeks, the dose is adequate or even high, and plasma levels are high-normal or suprathreshold.<sup>18,85</sup> The

### **Text Box 3: Acutely Psychotic Patient Presents to the Emergency Department**

The patient is a 50-year-old man with chronic schizophrenia brought to the emergency department (ED) with an acute psychotic exacerbation, a presentation that is by now familiar to the ED staff because this is his third visit in the past year. The electronic health record indicates that he is an active patient at an affiliated outpatient clinic, where he had been noted to be increasingly psychotic for the previous month. The record

notes a recent dose increase of risperidone, followed two weeks later by the addition of aripiprazole; the record also notes that he reports to be adherent to both. At the ED, the point-of-care tool registers an undetectable plasma level for both drugs. The patient is admitted and responds well to oral risperidone and is started on the long-acting injectable version of the drug prior to discharge. He is discharged after it has been determined that he tolerates the long-acting injectable well.

appropriate course of action is to switch the patient to another antipsychotic drug. According to the guidelines, if the patient has failed two or more drugs, the prescriber should consider a switch to clozapine (unless contra-indicated).

### **Treatment Response but Intolerable Side Effects**

Information on plasma levels would allow prescribers to determine whether the approximately 15 percent of patients in the category highlighted in the top right of Figure 4 have side effects because of pharmacokinetic and other factors increasing plasma levels or because of absolute intolerance to the drug. There is insufficient guidance in the literature to provide approximate estimates of the relative contributions of these mechanisms.

### **High Plasma Levels**

In this scenario, drug-drug interactions or the patient's poor metabolism cause plasma levels to be too high even when the dose is adequate.<sup>86–88</sup> In this setting, the prescriber would have a clear

rationale to gradually decrease the dose of the antipsychotic while evaluating the patient's mental status and side effects, a strategy that might improve tolerability and enable a trial of adequate duration. (See Text Box 4 for a sample scenario.)

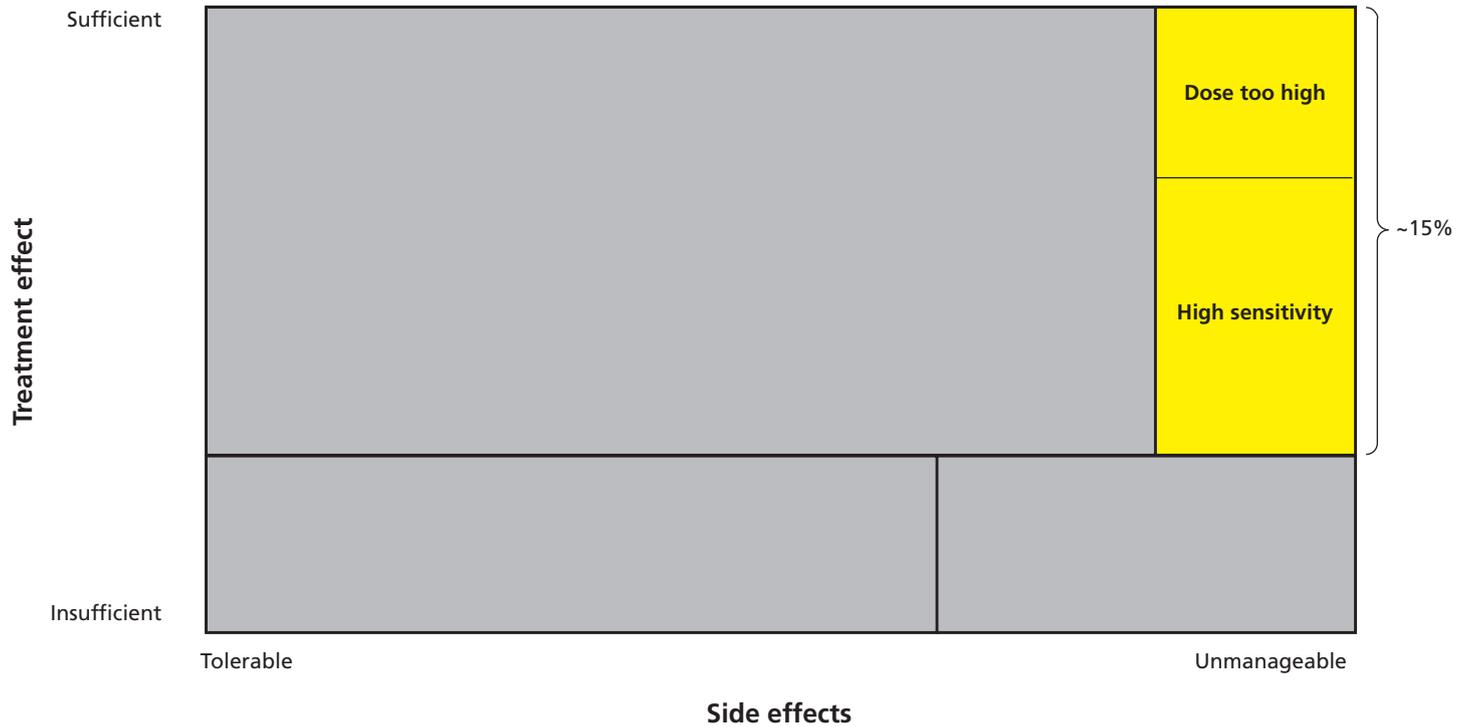
### **High Sensitivity to the Drug**

In this scenario, patients exhibit intolerable side effects as a result of sensitivity to the antipsychotic drug even when their plasma levels are within or below range.<sup>58</sup> In this setting, the appropriate clinical decision is to switch the patient to a different antipsychotic drug.

### **Summary: Personalized Antipsychotic Treatment**

In sum, based on the well-supported application of PLM for assessing adherence and toxicity, and its narrower yet valuable application for assessing likelihood of therapeutic effect, point-of-care access to plasma level information has the potential to significantly improve disease management decisions and quality of care delivered to patients with schizophrenia. Although the patients who would

**Figure 4**  
**Patients with Sufficient Treatment Effect but Unmanageable Side Effects**



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**Text Box 4: Well-Controlled Patient Presents to the Office with Disturbing Side Effects**

The patient is a 25-year-old male with recent onset schizophrenia who has done very well since he started antipsychotic medication. However, he presents to the office complaining of akathisia. The prescriber wants to confirm that akathisia is in fact a side effect of the prescribed antipsychotic and that there is

room for dropping the dose without compromising the patient’s response. After the point-of-care tool registers a high plasma level of the drug, the prescriber reassures the patient that the symptoms are likely related to his liver removing the medication too slowly, which leads to an accumulation of the medication in his body. The prescriber reduces the dose and monitors closely the side effect and the patient’s mental status.

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be most evidently helped by this resource are those exhibiting poor symptom control or intolerable side effects, such a tool might also be helpful for other scenarios. For example, it would allow prescribers to make downward dose adjustments for treatment responders whose high plasma levels are not yet causing intolerable side effects.

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In light of the serious consequences of unsuccessful treatment, the value of having rapid access to information that may be used to reorient the treatment cannot be overstated. Timely knowledge of antipsychotic plasma levels of patients with complicated courses of treatment would allow prescribers to make highly consequential decisions based on data rather than guesswork. Although more research is needed to expand the scientific evidence on the relationship between antipsychotic plasma levels and clinical effect, such research will be undoubtedly spurred by the broader use of plasma levels in routine care. Research is also needed to determine if a point-of-care PLM tool might, as expected, improve patient outcomes and value of health care for this population.

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## About This Perspective

This Perspective describes the rationale and opportunity for using a point-of-care diagnostic technology to improve the management of schizophrenia patients. We argue that point-of-care information on antipsychotic plasma levels—the amount of drug circulating in the patient’s blood—will result in better patient care, which should lead to better health and better value for the health care system.

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## About the Authors

**Marcela Horvitz-Lennon** is a physician scientist at the RAND Corporation and a professor at the Pardee RAND Graduate School. She is also a member of the medical staff at Cambridge Health Alliance. She has conducted mental health services and policy research on utilization and quality of care for adults with mental illnesses.

**Zachary Predmore** is a research assistant at the RAND Corporation, with training in chemistry, global health, and health policy. He has conducted research on costs and quality of care for people with schizophrenia.

**Soeren Mattke** is a senior scientist at the RAND Corporation, a professor at the Pardee RAND Graduate School, and the managing director of RAND Health Advisory Services. Mattke is an expert in evaluating new technologies and products, as well as innovative approaches to organizing and delivering health care services, especially for chronic care.

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