Optimizing Antipsychotic Patient Management Using Population Pharmacokinetic Models and Point-of-Care Testing

B Green1*, J Korell1, B Remmerie2, A Savitz3 and A Vermeulen2

Schizophrenia is a common disease, characterized by progressive functional decline exacerbated by psychotic relapses that often result from a lack of full adherence to antipsychotic (APS) medication. Although atypical APS medications do not have clear therapeutic windows, as generally required for therapeutic drug monitoring (TDM), measuring APS plasma levels in the context of a population expected range at the point-of-care (POC) may provide valuable clinical insights for differentiating lack of efficacy from a lack of adherence to medication.

CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 573–575; doi:10.1002/psp4.12212; published online 2 June 2017.
plasma concentration range in 80% of subjects within a fully adherent population. We propose using the 80% prediction interval of the simulated plasma concentrations as reference ranges to capture most of the expected variability in the population without giving too much weight to the extrema. In contrast to a therapeutic range used in standard TDM, the proposed reference ranges herein do not explicitly link to efficacy and/or safety outcomes. Hence, comparing individual APS levels with these reference ranges will provide a more generalized approach to monitoring APS levels than standard TDM, mainly by offering both an indication of a patient's adherence to treatment, as well as a comparison of levels to the broader population, as opposed to explicit guidance on individual plasma levels to achieve a desired efficacy and/or safety level. Overall, clinicians often do not recognize non or partial adherence in their own patients and even partial adherence leads to increased risk of hospitalization.

Two interpretation examples are shown in Figures 1 and 2. In Figure 1, all individual APS observations are within the 80% reference range, allowing the clinician to conclude some form of consistent medication intake on multiple occasions, and

![Figure 1](image1.png)

**Figure 1** Interpretation example 1. The light green bars represent the antipsychotic medication reference range that captures 80% of subjects. The range has been averaged over the relevant time-since-last-dose bin. The dark green dots and numbers next to the dots represent individual concentrations collected from the patient, which are within the expected range given the dose and sampling time.

![Figure 2](image2.png)

**Figure 2** Interpretation example 2. The light green bars represent the antipsychotic medication reference range that captures 80% of subjects. The range has been averaged over the relevant time-since-last-dose bin. The dark green dots, orange triangles, and numbers next to these points represent individual concentrations collected from the patient. The orange triangles represent concentrations that are below the expected range.
allow them to confidently increase the dose (providing no adverse events were present) if the subject was not responding to therapy, or change the patient to an alternate drug. 

Figure 2 shows an individual with APS concentrations that are largely below the expected range under the assumption of 100% perfect adherence. This can have arisen under a range of conditions, although it indicates either systematic or erratic nonadherence on multiple occasions. This should lead to a conversation during the consultation to determine if the patient has been taking the medication as prescribed, or if the modalities of drug intake have changed (medication was taken with food, smoking habits changed, comedication was adapted, etc.).

A graphical tool, as suggested in Figures 1 and 2, would allow a clinician to visually compare an individual APS concentration to the predetermined reference ranges, and would allow information to be rapidly available to users as new reference ranges are determined. It could also be used by clinicians who obtain laboratory results from a centralized institution, as well as by clinicians who are using commercial POC testing devices if developed in the future. Such tools could easily be updated if models change, and could be further stratified in the future if pertinent factors become of interest to clinicians (e.g., reference ranges by genotype, smoking status, or concomitant medications). Furthermore, reference ranges for new drugs could be added, ensuring the most up-to-date information is always available for the end user.

The limitations

Although this reference range concept proposed to assess individual APS levels represents a significant advance over current APS monitoring approaches, it is not without limitations. Simulations from a single population PK model, even though internally and externally evaluated, do not encompass all information available in the literature. Whereas methods to combine information across multiple population PK models have recently become available,10 use of this approach remains more valuable when information between various publications is heterogeneous (i.e., one model exists for pediatric subjects, another for adults, and others exist describing nonlinear and time-dependent clearance mechanisms). Most importantly, drug plasma level monitoring is only complementary to a clinical evaluation, and treatment of a patient based upon laboratory results alone is not recommended. Artificially high concentrations could arise if patients took multiple or "make up" doses prior to a doctor's visit. In such situations, concentrations might appear within or above the expected range, respectively. Adjusting doses in these situations would be unwise and it is important for the clinician to engage in communication with the patient to learn why levels are higher or lower than previously observed. Conversely, artificially low concentrations are possible if the patient forgot to take their drug on the day they were monitored, or were truly not compliant. Given the nature of the disease, it might be difficult to determine what actually occurred, so if clinically responding to therapy, no dose adjustments are warranted. If not responding, more careful monitoring may be appropriate to help validate compliance. Further, some patients may respond to lower levels and it is expected that 10% of adherent patients will be below the 80% reference range anyway.

SUMMARY

Treatment of psychiatric disorders is complex as effective management plans need to consider the patient's presentation together with a myriad of other pertinent information. APS monitoring is only one aspect to consider, and the clinical status of the patient should be used together with the knowledge of the individual APS levels to determine if the patient is non-adherent or appears to be a nonresponder. Comparing APS levels with the proposed reference ranges would help clinicians to assess whether an individual's concentration is within the expected range. This objective data along with a full clinical assessment could facilitate communication between the clinician and patient and provide important insights to help a clinician differentiate a lack of efficacy from a lack of adherence and make appropriate treatment decisions.

Conflict of Interest/Disclosure. B.G. and J.K. are employees of Model Answers Pty Ltd, which received financial reimbursement from Janssen R&D. A.V., B.R., and A.S. are employees of Janssen R&D, which sponsored this research.

Author Contributions. B.G., J.K., A.V., B.R., and A.S. wrote the initial draft of the manuscript. All authors contributed toward development of the reference range concept, with B.G., J.K., and A.V. responsible for the PK model evaluations and simulations referred to in this leading article.