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PERSPECTIVE

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

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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.
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MONITORING ANTIPSYCHOTIC TREATMENT

The challenges

The dose-concentration-effect relationship for antipsychotic (APS) medication varies greatly within and between individuals.[1] There are multiple contributors to this high level of variation, including CYP2D6 status for risperidone,[2] smoking status for olanzapine,[3] food intake patterns, and drug-drug interactions. Another significant cause of this variability is a lack of or inconsistent adherence to prescribed medication, leading to variable clinical responses, or a higher frequency of adverse events. With only 29–45% of APS concentrations within a consistent concentration range,[4] therapeutic drug monitoring (TDM) has been recommended for clozapine, olanzapine, amisulpride, aripiprazole, paliperidone, quetiapine, risperidone, sertindole, and ziprasidone.[5]

TDM aims to reduce variability in exposure, improve clinical response, minimize potentially toxic concentrations,[6] and provide information about a patient's adherence to therapy.[7] TDM is thought to be particularly useful when: nonadherence is suspected; side effects occur; clinical response is inadequate; known genetic differences exist that may result in unusually low or high concentrations; special populations are treated; and co-administered drugs alter concentrations.

All these situations are commonly encountered in clinical practice with APS treatment. However, therapeutic windows for APS are not clearly defined, as the relationship between concentration and clinical response is less clear, and interpretation of APS concentrations has been challenging for the clinician due to the variability in exposure between patients. For the clinician to best interpret individual APS levels, the results need to be placed in the context of the range of expected plasma concentrations, given the specific dose, blood sampling time, and other pertinent patient data. Specifically, the clinician wants to know if the APS level for the individual patient is similar to that of patients fully adherent to their medication. To date, no robust, comprehensive, and easy-to-use solution exists that allows the clinician to interpret individual APS concentrations in this context.

This article and its companion paper introduce a novel concept of "reference ranges" for APS concentrations derived from population pharmacokinetic (PK) models, which could help optimize patient management in conjunction with observed patient clinical response and other information collected during a visit with a prescribing clinician.

The solution

The range of expected APS plasma concentrations in a perfectly adherent population, given different doses and blood sampling times, can be determined using a pharmacometric approach. Once PK data from different studies have been combined to develop a population model, the expected concentration range across the population can be simulated under any number of differing clinical scenarios regarding dose/dose regimen, time after dose, patient population, etc. Practically, the concentration ranges do not need to be completed in real time; instead, predetermined ranges can be calculated ahead of time and populated into look-up tables or a cloud-based tool, which the clinician can then simply refer to, or be directly included in a point-of-care (POC) testing device.

Examples of proposed APS reference ranges for risperidone and paliperidone can be found in the companion article, together with a thorough description of the applied population PK models and their evaluation, as well as methods used to construct and evaluate the reference ranges. In brief, for each model, simulations were performed at steady-state to determine the expected range of concentrations over the dosing interval assuming perfect adherence in the population and given differences in random effects incorporated into the model. The reference ranges were determined using a database of demographics obtained from 50 clinical studies that included subjects treated with APS (for more information, refer to the companion article). Simulations were conducted for a range of dosing scenarios within currently approved drug labels, and the data extracted and summarized to determine reference ranges at various time points post-dose. Thus, the developed reference ranges captured the plausible

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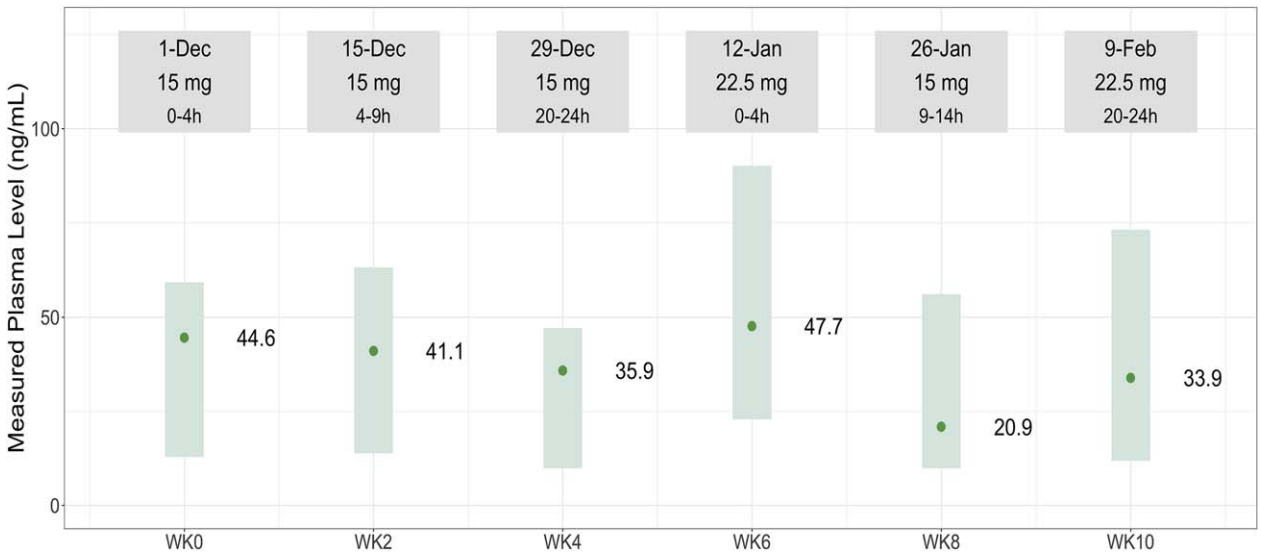

Figure 1 Interpretation example 1. The light green bars represent the antipsychotic medication reference range that captures 80% of subjects. The range has been averaged over the relevant time-since-last-dose bin. The dark green dots and numbers next to the dots represent individual concentrations collected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

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[8] and even partial adherence leads to increased risk of hospitalization.[9]

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

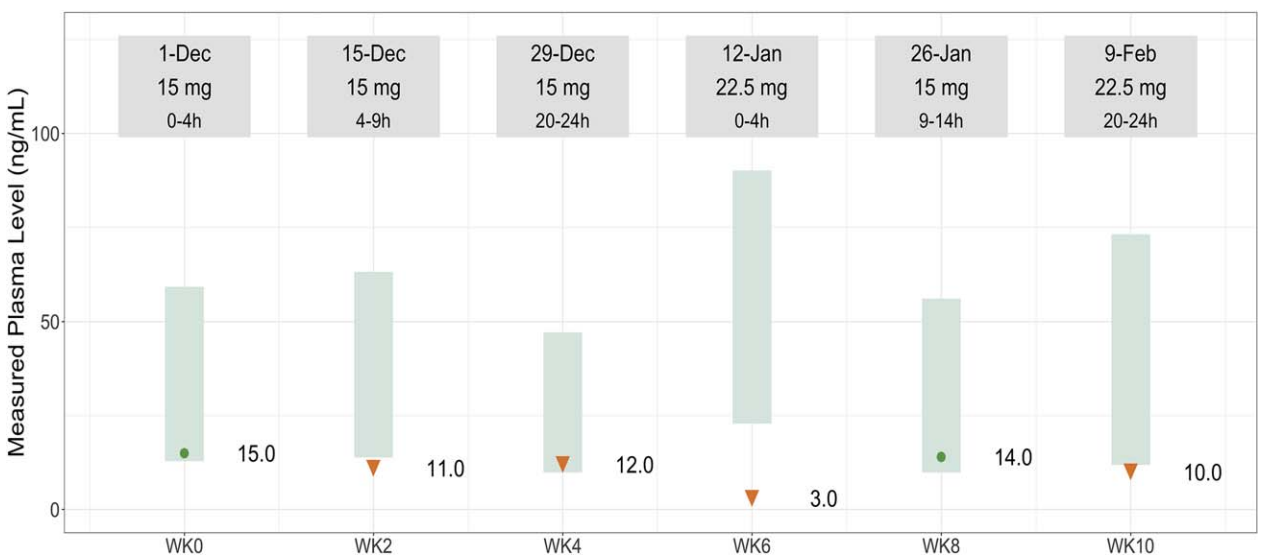

Figure 2 Interpretation example 2. The light green bars represent the antipsychotic medication reference range that captures 80% of subjects. The range has been averaged over the relevant time-since-last-dose bin. The dark green dots, orange triangles, and numbers next to these points represent individual 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 could 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 nonadherent 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.

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