

*The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. The patient described in this column is a composite with characteristics of several real patients.*

## Population pharmacokinetics and dosing of long-acting injectable antipsychotics

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A 29-year-old man with schizophrenia treated with aripiprazole 15 mg/d visited his psychiatrist accompanied by his mother, who mentioned that although her son is doing well, she must remind him to take his medication. The psychiatrist offered the patient injectable aripiprazole once monthly (AOM), and he agreed. The psychiatrist recently learned that Health Canada approved a new initiation regimen consisting of 2 separate intramuscular (IM) injections of 400 mg and a single 20 mg dose of oral aripiprazole.<sup>1,2</sup> However, the psychiatrist is uncomfortable with this initiation regimen because it was based on simulations, not traditional pharmacokinetics (PK).

Most clinicians are familiar with traditional PK studies, which are generally performed in Phase I of drug development. Conversely, many clinicians are not likely familiar with population PK (PopPK), a study of quantifying factors responsible for variability in drug concentrations among individuals who are the target population for the drug.<sup>3,4</sup> Unfortunately, PopPK is often viewed with skepticism by clinicians unfamiliar with its validity,<sup>4</sup> although government agencies approve its utility to inform drug use. Both traditional PK and PopPK have advantages and disadvantages (Table 1).<sup>3</sup>

There are 4 basic steps in PopPK. Step 1 is data collection. Some data may come from small, traditional PK studies but, by far, most data are obtained from Phase 2 and 3 efficacy/tolerability clinical trials using actual patients for whom the drug was intended. Step 2 is developing a model that best explains the data (e.g., 2-compartment model with first-order

absorption for IM injection). Step 3 is model validation. In simple terms, the model must be validated using various techniques including diagnostic plots or prediction-corrected visual predictive checks. Once the model has been validated, simulations (step 4) can be performed.

PopPK analyses have been approved by Health Canada for the initiation regimens of paliperidone palmitate (PP1M) and AOM. In the case of PP1M, the data for PopPK analyses come from 11 clinical trials ( $n = 1795$ ), resulting in 18 530 paliperidone plasma concentrations.<sup>5</sup> Several simulations were performed before choosing the approved initiation regimen of 150 mg (day 1) and 100 mg (day 8) given by IM administration via the deltoid muscle. PopPK analyses were also used to provide guidance regarding missed doses, CYP2D6 phenotype, race and smoking status.<sup>6</sup>

Similarly, PopPK was used to determine an alternative initiation regimen of AOM. The data for PopPK analyses come from 7 clinical trials ( $n = 817$ ), resulting in 8214 aripiprazole plasma concentrations.<sup>7</sup> Various simulations were performed, and a 2-injection initiation

regimen was approved by Health Canada as follows: 2 separate injections of 400 mg AOM at separate injection sites and a single 20 mg dose of oral aripiprazole. PopPK analyses also supplement the product monograph to guide dosing with regards to ethnic origin; smoking status; dosage adjustments for poor metabolizers of CYP2D6 and patients taking concomitant CYP2D6 and/or CYP3A4 inhibitors; and missed doses.<sup>2</sup> Following the 2-injection start, single monthly doses of AOM 400 mg are given.

Although the patient in our case was on 15 mg of oral aripiprazole, the product monograph (based on PopPK simulations) states that a single 20 mg dose of oral aripiprazole should be used with the 2-injection start, irrespective of the previous dose of oral aripiprazole or any other antipsychotic. The product monograph also states that the existing oral antipsychotic should be discontinued immediately following the 2-injection start. However, clinicians should use their judgment, as it may be better to gradually taper patients off the previous (nonaripiprazole) antipsychotic to prevent withdrawal reactions.

**Table 1: Advantages and disadvantages of traditional and population pharmacokinetics**

Advantages	Disadvantages
<b>Traditional PK</b>	
Small numbers of participants required (usually < 20)	Often done in “healthy” participants rather than the target patient population
Minimizes interindividual variability via fixed, restrictive sampling designs	Multiple blood samples required from each participant
Simple PK modelling and calculations	Cannot handle sparse sampling or identify covariates affecting variability in drug concentrations
<b>Population PK</b>	
Often done in patients for whom the drug was intended	Large clinical samples required
Accommodates flexible study designs, handles sparse sampling, and requires few blood samples from each patient	Entails handling large amounts of data
Quantifies covariates accounting for interindividual PK variability (e.g., age, weight, smoking, concomitant medications)	Complex statistical analyses (e.g., model building, diagnostics, missing data treatment)
PK = pharmacokinetic.	

Clinicians should be aware that approved dosing strategies for many drugs used in various therapeutic areas were based on PopPK analyses. However, it is also important to recognize that although PopPK explains variability in drug concentration among individuals, it does not help predict potential adverse events. Further education on PopPK will help to increase awareness of its role in drug development and dosing optimization.

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