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COMMENTARY

Model-Informed Approaches for Alternative Aripiprazole Dosing Regimens and Missed Dose Management: Towards Better Adherence to Antipsychotic Pharmacotherapy

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Systems pharmacology and pharmacometric modeling and simulation have become increasingly important in accelerating drug development and regulatory approval [1–4]; nevertheless, their use in precision pharmacotherapy and management of missed doses remain scarce [5]. Failure in the management of missed doses under various scenarios during treatment with antipsychotic medications might lead to a relapse of schizophrenia. In this issue, Hard and colleagues present a pharmacometric study of aripiprazole to characterize aripiprazole disposition following intramuscular (IM) administration of a nano-crystalline milled dispersion of aripiprazole lauroxil (AL_{NCD}) and AL and oral administration of aripiprazole, and to explore the feasibility of a 1-day initiation regimen using AL_{NCD} plus oral aripiprazole alternative to the 21-day initiation regimen of AL alone, and to inform strategies to manage missed doses of AL under different treatment scenarios [6]. The research might serve as a basis for alternative aripiprazole dosing regimens and missed dose management, aiming at better care for patients with schizophrenia and adherence to aripiprazole treatment.

The first requirement of model-based dosing optimization is a well-established therapeutic window or target exposures associated with approved dosing regimen tested in pivotal clinical studies, aiming to maximize the therapeutic benefit and minimize exposure-related toxicities. Although dissimilar therapeutic windows of aripiprazole were documented in different reports or clinical guidelines [7–9], Hard et al. [6] rationally adopted the plasma concentration range associated with therapeutic doses of AL using the 21-day initiation regimen as the reference aripiprazole plasma levels that should be matched following alternative initiation regimen of aripiprazole.

Before a pharmacometric model can be applied to assess the potential changes in exposure or response under complex clinical scenarios, the model should be adequately qualified, which should follow the "learn and confirm" paradigm. Ideally, the model should go through internal qualification to determine the adequacy of the model for current data and external qualification to evaluate performance using other data from a different population sample. Furthermore, the model may be refined in the "learn and confirm" cycles when new clinical data become available. In the study by Hard et al. [6], the model was built on the basis of data from three individual studies [Study 1 (ALK9072-B101), Study 3 (ALK9072-B103), and Study 2 (ALK9072-B102)] in a sequential manner, and then updated based on the pooled data from the three studies plus another Phase 1 study conducted earlier. The model performance was judged mainly by posterior prediction-corrected visual predictive checks and goodness-of-fit assessments. Surprisedly, the final population pharmacokinetic model overpredicted aripiprazole exposure following multiple oral dose administration of aripiprazole in Study 2. The final model was, therefore, re-updated to characterize the high variability in aripiprazole concentrations by accounting for a subgroup of patients with lower exposure among those receiving the 21-day initiation regimen in Study 2 via a mixture model. After then, the updated final model was used for simulations to evaluate the feasibility of 1-day initiation regimen involving AL_{NCD} and inform the strategies of manage missed doses using 1-day single injection of AL_{NCD}. In spite of lack of external qualification, the model development processes of aripiprazole generally followed the "learn and confirm" paradigm.

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Table 1 Model-informed strategies to manage missed doses of drugs acting on the central nervous system (CNS)

CNS drug	Delayed or missed dose scenario	Model-informed strategy for missed dose management
Aripiprazole [6]	AL 1, 2, 3 weeks late under 441, 662, 882 mg q4wk scenarios; respectively, 4 weeks late under 882 mg q6wk scenario; or 6 weeks late under 1064 mg q8wk scenario	Original AL regimen + 7-day 15 mg oral aripiprazole, or original AL regimen + a single dose of AL_{NCD}
Paliperidone [10]	The third PP3M dose was missed	(1) Reinstate and continue the 3-monthly PP3M regimen if 3.5–4 months have elapsed (2) Reinitiate PP1M on day 1 and day 8 followed by PP3M after 4 weeks if 4–9 months have elapsed (3) Reinitiate PP3M if 9 months have elapsed
Benzodiazepine [11]	One daily dose missed under 7.5 mg tid or 22.5 mg qd scenarios	Replace the missed dose at next day
Carbamazepine/oxcarbazepine [12]	3, 6, 9, 12, 24 h late under 400 mg carbamazepine bid, 600 mg oxcarbazepine bid or 1200 mg oxcarbazepine bid scenarios	(1) Resume dosing when 3–12 h have elapsed (2) Take a double dose when more than 12 h have elapsed
Carbamazepine [13]	15, 21, 24 h late (one dose missed) or 27, 33, 36 h late (two doses missed) under 400 mg bid scenario	(1) When one dose is missed, take a single dose if the delay is less than 24 h, otherwise take a double dose (2) When two doses are missed, take a double dose as soon as possible
Eslicarbazepine [14]	12, 16, 18, 20, 24, 36, 40, 42, 44, 48 h late under 1600 mg qd scenarios	(1) If the missed dose is within 4 h of the next scheduled dose, take a 1.5-time dose (2) If the missed dose is 4–12 h to the next scheduled dose, take a dose immediately
Perampanel [15]	One dose missed at day 12 or 15 under 4 mg bid or 8 mg qd scenarios	Resume dosing
Topiramate [16]	8, 12, 24 h late under 100 mg IR q12 h or 200 mg XR qd scenarios	(1) With the delay of 8 h, resume dosing (2) With the delay of 12 h, resume dosing for XR while taking a double dose for IR (3) With the delay of 24 h, take a double dose for XR while taking a 1.5-time dose for IR
Valproic acid [17]	30, 36, 42, 48, 54 60, 66, 72 h late under 1000 mg or 2500 mg XR qd scenarios; 15, 18, 21, 24, 27, 30, 33, 36 h late under 500 mg or 1000 mg IR bid scenarios	(1) For 1000 mg XR qd, resume dosing when dose is delayed < 48 h, otherwise take a double dose (2) For 2500 mg XR qd, resume dosing when dose delayed < 54 h, otherwise take a 1.5 times dose (3) For 500 mg IR bid, resume dosing when dose is delayed < 24 h, otherwise, take a double dose (4) For 1000 mg IR bid, resume dosing regardless of dosing delay

AL aripiprazole lauroxil, AL_{NCD} nano-crystalline-milled dispersion of aripiprazole lauroxil, *bid* twice daily, *IR* immediate-release formulations, *PPxM* paliperidone palmitate x-month formulation, *qd* once daily, *qxwk* every *x* weeks, *tid* three times per day, *XR* extended-release formulations

Missed or delayed doses of antipsychotic medications are commonly encountered in clinical practice, leading to suboptimal therapeutic outcomes. For patients with schizophrenia or another central nervous system (CNS) disorders, subtherapeutic plasma levels under missed dose scenarios could result in a relapse or symptoms out of control. To prevent or minimize the risk of relapse, missed doses should be appropriately managed. Unfortunately, the impact of various missed dose scenarios on drug exposure and efficacy is not likely to be sufficiently investigated in pivotal clinical trials. Instead, system pharmacology and pharmacometric modeling and simulation offer great opportunities to better understand the in vivo behavior of medications in clinically challenging situations. Table 1 compiled some selected examples of model-informed strategies to manage missed doses of antipsychotic medicines or other CNS drugs, such as paliperidone, benzodiazepine, carbamazepine.

One of the limitations pointed out by Hard and colleagues [6] is that simulated data solely inform the alternative 1-day initiation regimen and the missed dose management. External clinical data should further reassure the clinical impact of the alternative initiation regimen and strategies to manage missed doses. In this regard, we believe, well-qualified pharmacometric models could serve as the basis for dosing optimization in the clinical setting. We are optimistic about clinical applications of their model since population pharmacokinetic models can be verified by routinely collected data through therapeutic drug monitoring.

Compliance with Ethical Standards

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Conflict of interest The authors have no conflicts of interest to declare.

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