LETTER TO THE EDITOR

Comment on "An Integrated Pharmacokinetic–Pharmacodynamic–Pharmacoeconomic Modeling Method to Evaluate Treatments for Adults with Schizophrenia"

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Dear Editor,

A recent article by Piena et al. [1] used integrated pharmacokinetic (PK)–pharmacodynamic (PD)–pharmacoeconomic modeling to compare costs and effects (relapses) of long-acting injectable (LAI) aripiprazole monohydrate (AM) and aripiprazole lauroxil (AL) dosing regimens in patients with schizophrenia. Because risk of relapse remains high in patients treated with antipsychotic drugs [2, 3], this important area of research can inform treatment decisions. However, clinically meaningful results from this pharmacoeconomic model depend on valid input from PK–PD modeling and simulations, and some of the assumptions underlying the PK–PD model appear to be incorrect. We therefore question the article's pharmacoeconomic conclusions.

Input for the pharmacoeconomic analysis included simulated relapse rates from the PK–PD model for several AM and AL regimens. That model was established based on minimum plasma aripiprazole concentrations (C_{min}) from simulated steady-state exposures using a dichotomous hazard function with a cutoff of 95 ng/mL. The probability of relapse for each simulated patient during each dosing interval was based on whether C_{min} for that cycle fell below 95 ng/mL.

The use of a binary framework based on a threshold of $C_{min} = 95$ ng/mL to estimate the probability of relapse for AL regimens is problematic for several reasons. First, Piena et al. cite no clinical evidence for the use of 95 ng/mL or

for an association between that threshold and the probability of relapse for AL. Results reported in a subsequently published article suggest that the 95 ng/mL value may have been selected based on an exposure-response analysis using clinical trial data from patients with schizophrenia treated with AM 300 or 400 mg monthly [4]. No AL data were included in that analysis, and PK profiles for AL and AM are known to differ. Compared with AM, AL is associated with extended exposure to aripiprazole [5] and lower peak-to-trough variability for comparable dosing regimens [6–8]. Importantly, no exposure-response relationship has been observed for oral aripiprazole or for AL [9, 10], and, consistent with those findings, Piena et al. failed to observe the reported PK–PD relationship when C_{min} was used as a continuous variable. For these reasons, applying the unvalidated 95 ng/mL threshold in an analysis of AL data introduces bias and results in potentially inaccurate conclusions.

Second, Piena et al. described the 95 ng/mL threshold as "consistent with the lower boundary of the established therapeutic window for aripiprazole" [1] based on the median C_{min} at steady state for the lowest effective dose of oral aripiprazole (10 mg/day) [11, 12]. They then assumed that aripiprazole exposures with a C_{min} below that median value fall outside of the therapeutic window and therefore are associated with an increased risk of relapse. However, as previously noted [13], this assumption is not true. The boundary of the therapeutic window has been established based on a *median* value; therefore, half of all C_{min} values for the effective oral aripiprazole 10 mg/day dose, by definition, fall below that threshold. Median C_{min} at steady state describes one aspect of aripiprazole PK at the population level, not an absolute limit for therapeutic exposure in individual patients. Indeed, although the model-simulated aripiprazole C_{min} is more likely to fall below 95 ng/mL after administration of AL 441 mg monthly or 1064 mg every 2 months compared with higher doses, both regimens have established efficacy in patients with schizophrenia [14, 15] and no clinically

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meaningful efficacy differences were observed between the 441 mg and 882 mg monthly doses in a 12-week pivotal trial [14]. All AL dosing regimens provide plasma aripiprazole concentrations within the range associated with AL efficacy [6, 16, 17].

Third, the use of dichotomous hazard function for C_{min} (regardless of the threshold value) is also of concern. It is well known that dichotomization contributes to loss of information. In addition, it assumes that, within a dosing cycle, the likelihood of relapse is the same whether plasma aripiprazole concentrations cross the threshold at a single timepoint or remain continuously below the cutoff value. Gaps in antipsychotic medication due to lack of adherence are associated with poor clinical outcomes in patients with schizophrenia [18, 19], but peaks and troughs in plasma drug levels over the LAI dosing interval are expected [6]. The use of a binary threshold does not take into account the differing effects on brain exposures or receptor occupancies associated with prolonged subtherapeutic exposure versus a dip in plasma drug concentration at a single timepoint.

Finally, some additional points affect the interpretation of the PK–PD analysis. The authors state that "according to expert opinion, in clinical practice, AL 441 mg and AM 300 mg are generally used only when patients do not tolerate higher doses" [1]. However, the cited source discusses AM 300 mg only [20], and that assertion is not true for AL 441 mg. On the contrary, AL can be initiated using any of the approved dosing regimens, including 441 mg monthly [17, 21]. Furthermore, Piena et al. included AL 1064 mg every 6 weeks in their analysis, which is not among the tested or approved AL dosing regimens [17]; therefore, any conclusions related to this dose are not meaningful.

In summary, because the input for the pharmacoeconomic model (probability of relapse) has no basis in AL clinical data and is not appropriate for modeling AL outcomes, no conclusions regarding AL can be drawn from the results reported. The AL 441 mg monthly and 1064 mg every 2 months dosing regimens have established efficacy in the treatment of adult patients with schizophrenia [14, 15, 21], and there is no evidence of clinically meaningful differences in efficacy between available AL doses [14]. All approved AL doses result in stable exposures that fall within the range of concentrations associated with the known efficacy of the AL 441 mg monthly and 882 mg monthly regimens [6, 16, 17]. A greater understanding of potential differences between LAI antipsychotics and their dosing regimens will be invaluable for clinicians prescribing for patients with schizophrenia; unfortunately, the Piena et al. report does not add to this understanding, especially as it relates to AL.

Declarations

Conflict of interest Bhaskar Rege, James McGrory, and Sabina Gasper are employees of Alkermes, Inc., and may be shareholders. David McDonnell is an employee of Alkermes Pharma Ireland Ltd. and may be a shareholder.

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Not applicable.

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