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LETTER TO THE EDITOR Open Access

Response to comment on the recently published article "An update on recently approved long-acting injectable second-generation antipsychotics: Knowns and unknowns regarding their use"

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Dear Editor:

Thank you for the opportunity to respond to the letter submitted by Dr. Still and colleagues[1] regarding the December 2022 article entitled "An update on recently approved long-acting injectable second-generation antipsychotics: Knowns and unknowns regarding their use."[2] The purpose of that article was to review key clinical pearls of newer long-acting injectable (LAI) second-generation antipsychotics informed by clinical evidence, pharmacokinetic properties, and clinical experience using these products in practice since the first risperidone LAI came to market. An additional aim was to provide a succinct case-based framework for clinicians to apply to multiple medications in day-to-day practice. Hence, some of the more complex, nuanced pharmacokinetic data were not discussed in detail.

First, regarding the differences in dose: A common misconception the author has encountered is that labeled doses of aripiprazole lauroxil (AL) and aripiprazole monohydrate (AM) are similar on a milligram per milligram basis, which has the potential for dosing errors. The statement that "The difference in molecular weight drives much of the difference in dose between" AM and AL is not contradictory to Dr. Still's statements regarding proprietary dissolution technology and the impact on dosing interval. The molecular weights are, in fact, 41% different, and total labeled dose for each product reflects different effective doses required to obtain therapeutic levels of aripiprazole. This has been a simple means to partially explain the difference in dose between products in practice without an in-depth review of pharmacokinetics. The FDA has previously guided manufacturers to label products based on strength of drug substance rather than active portion to avoid potential medication errors.[3] Hence, paliperidone palmitate is labeled for the strength of the palmitate rather than base paliperidone (eg, 156 mg paliperidone palmitate rather than 100 mg paliperidone mg equivalent). This was not included in the original article as there was not a comparable alternative paliperidone formulation that would generate confusion as with AL and AM. The FDA has not applied the same guidance to prodrugs, like AL, which can make it difficult for providers to determine comparable doses between products. Looked at a different way, in data reviewed by the FDA for approval of AL, the relative bioavailability of AL was reported as 58% compared with aripiprazole tablets.[4] This compares to AM, which, per documents submitted to the FDA, is "completely bioavailable" from intramuscular injection sites.[5]

Second, regarding the statement that "in pharmacokinetic studies, higher serum concentrations were achieved with AM vs all labeled AL dosing strategies"[2]: This was not intended to imply that head-to-head studies are available, similar to Dr. Still's statement: "Peak-to-trough ratios of serum aripiprazole concentrations are smaller with AL than with AM."[1] The statement regarding serum concentrations was referring to steady state concentrations (C_{ss}), not maximum/minimum concentrations. Mean C_{ss} were projected in the new drug application (NDA) for AL to be 117 ng/mL, 178 ng/mL, 225 ng/mL, and 150 ng/mL for 441 mg monthly, 662 mg monthly, 882 mg monthly, and 882 mg every 6 weeks, respectively.[4] This compares with AM, where the NDA provides mean C_{ss} of 208 ng/mL and 242 ng/mL for the 300 mg every 4 weeks and 400 mg every 4 weeks gluteal injections, respectively.[5]

Peak-to-trough ratios were not discussed for any medications in the article, rather mentioned in general concept: "Clinically, this prolonged action is expected to minimize fluctuations in serum concentrations to maximize tolerability and minimize risk of symptom recurrence in the event of delayed doses."[2] Differences in peak-to-trough ratio vary across studies and are dependent upon factors including injection site (gluteal vs deltoid) as well as differences in CYP activity. Injection site was addressed as a general concept in a section discussing paliperidone ("In the case of wearing off, however, the gluteal site should be considered regardless of weight as the $t_{1/2}$ of elimination is

prolonged compared to deltoid injections." In-depth analysis of the PK studies for various LAI products was outside the scope of this article, though I agree that the full concentration-time curve—considering administration site and CYP phenotype—is critical to understanding a patient's aripiprazole LAI exposure.

Third, regarding more frequent doses of AL 1064 mg rather than monthly 884 mg doses for patients with high dose requirements, this is merely one example of off-label dosing that has been used in practice. One of the draws of the labeled dosing regimen of 1064 mg every 8 weeks over 884 mg every 6 weeks as options for conversion from oral aripiprazole 15 mg daily is the extended interval. If a patient requires a higher dose and can be stabilized on an off-label regimen of 1064 mg every 6 weeks, this may be more favorable for logistics and patient/provider satisfaction than monthly 884 mg doses. As the Pearls product is intended to include real-world experience outside of clinical trial settings, this is one example of off-label dosing that may be considered to help a patient who prefers extended intervals maintain stability.

Thank you for this opportunity to further clarify concepts from the clinical pearl. This discussion further demonstrates the complexities of managing patients on LAIAs and how use of these products in practice may differ from clinical trial protocols.

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