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LETTER TO THE EDITOR

Comment on: "Clinical Pharmacokinetics of Atypical Antipsychotics: An Update"

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Dear Editor,

We would like to comment on some aspects regarding cariprazine (CRP) pharmacokinetics in the article by Mauri et al. [1].

Regarding Sect. 16, we would like to emphasize that CRP is metabolized to two major active metabolites which have in vitro receptor binding profiles that are similar to the parent drug. This is important as efficacy is driven by all active moieties, not just CRP. In fact, the active metabolite didesmethyl-CRP (DDCRP) is more abundant at steady state than CRP.

Regarding the first sentence of the second paragraph of Sect. 16.1, the steady-state pharmacokinetic profile was dose proportional in the therapeutic range (1.5–6 mg/day) in patients [2–4].

Regarding Sect. 16.2 and Table 8, it is not appropriate to discuss correlation of efficacy versus CRP concentration alone, but rather against the total active moieties (sum of CRP, desmethyl-CRP [DCRP], and DDCRP concentrations). A correlation between total CRP (sum of all three active moieties, in nM) plasma concentration and therapeutic response does exist; this was presented as a poster at the American Psychiatric Association 2016 annual meeting [5] and a manuscript has been submitted. The approved therapeutic dose range is 1.5–6 mg daily [3]. The concentration of total active moieties at steady state, as per Figure 2D of the Nakamura et al. [2] publication, is between 100 and 150 nM for the 6 mg dose [6].

Regarding the last sentence of Sect. 16.2 and Table 1, we acknowledge that the therapeutic plasma concentration range of 10–20 ng/mL for therapeutic drug monitoring (TDM) comes from Hiemke et al. [7], though it is still not clear to us how it was determined. The approved doses of CRP are in the range of 1.5–6 mg/day. The CRP therapeutic plasma concentration range of 10–20 ng/mL [7] seems to reflect mean minimum concentration (C_{min}) and maximum concentration (C_{max}) values for the highest approved dose of CRP of 6 mg/day. However, plasma concentrations of CRP below this range have been shown to be effective. For example, doses of 1.5 and 3 mg/day of CRP result in steady-state average plasma concentrations of CRP that are below 10 ng/mL, and both of these doses demonstrated efficacy in patients with schizophrenia and/or bipolar I disorder [3]. CRP is assigned "3—useful" in the Table 1 column on the level (1–4) of recommendation to use TDM and this text also appears in Sect. 16.2. However, we are not aware of any recommendation for TDM for CRP or evidence that it would be necessary to monitor CRP and metabolite concentrations. Furthermore, the Vraylar® (cariprazine) prescribing information does not recommend plasma concentration monitoring.

Compliance with Ethical Standards

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Conflict of interest Antonia Periclou and Todd Riccobene are employees of Allergan plc. and Margit Kapás and István Laszlovszky are employees of Gedeon Richter Plc.

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References

1. Mauri MC, Paletta S, Di Pace C, Reggiori A, Cirnigliaro G, Valli I, et al. Clinical pharmacokinetics of atypical antipsychotics: an update. Clin Pharmacokinet. 2018;57:1493–528. https://doi.org/10.1007/s40262-018-0664-3.
2. Nakamura T, Kubota T, Iwakaji A, Imada M, Kapás M, Morio Y. Clinical pharmacology study of cariprazine (MP-214) in patients with schizophrenia (12-week treatment). Drug Des Devel Ther. 2016;10:327–38.
3. Allergan. VRAYLAR® (cariprazine). Full prescribing information. Allergan; 2019.
4. European Medicines Agency. Reagila product information; 2019. https://www.ema.europa.eu/en/documents/product-information/reagila-epar-product-information_en.pdf. Accessed 26 June 2019.
5. Carrothers T, Willavize S, Jaworowicz D, Passarell J, Periclou A, Ghahramani P, et al. Relationship of cariprazine plasma concentration to efficacy and safety in patients with schizophrenia or bipolar mania [poster]. American Psychiatric Association (APA) Annual Meeting; 14–18 May 2016; Atlanta.
6. Allergan, Data on file.
7. Hiemke C, Bergemann N, Clement HW, Conca A, Deckert J, Domschke K, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. Pharmacopsychiatry. 2018;51(1–02):9–62.