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SHORT - TERM KETAMINE ADMINISTRATION IN TREATMENT - RESISTANT DEPRESSION: FOCUS ON CARDIOVASCULAR SAFETY

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To the Editor,

We read with interest the review *Short- term ketamine administration in treatment- resistant depression: focus on cardiovascular safety* by Szarmach et al. 2019 published in Psychiatria Danubina, 2019; Vol. 31, Suppl. 3, pp 585-590 that discuss the cardiovascular adverse effects and safety risks regarding the use of short-term ketamine for patients with major depression disorder. We would like to congratulate the authors for the review. However, we think that some information may be misleading and need to be revised by the authors. In the article, on table 4, page S588, a study by Loo et al. (2016) is mentioned as a study with intravenous esketamine, that originated a transient cardiovascular adverse effect of blood pressure increase thus in the original article (Loo et al. 2016), the drug administrated is not esketamine, but ketamine. The article explores the differences of safety and effectives of different routes of ketamine administration (intravenous (IV) (n=4), intramuscular (IM) (n=5) and subcutaneous (SC) (n=6)) injections with dosing titration from 0.1 mg/kg up to 0.5 mg/kg. The results demonstrated that there were a transient increase in heart rate, systolic and diastolic blood pressure in all routes of administration (IV, SC, IM) that reached its peak at 5–10 min after ketamine injection in the IV group, and 10–15 min after ketamine injection in the IM and SC groups. In all groups, there was a heart rate increase thus not exceeding 120% of baseline, except in three participants (one each in IV, IM and SC groups) as well as for the mean arterial pressure (MAP) that did not exceed 120% from pre dosing, except for four patients (none in the SC group). This study concluded that the SC route had the least cardiovascular effects and was the simplest and most advantageous when compared to other routes. Moreover, on the same table and page, there is another reference that lacks accuracy, the author has mentioned a study by Singh et al. 2015 that aimed to assess the efficacy and safety, among other outcomes, of intravenous esketamine infusion in treatment-resistant depression (TRD) patients. It has reported that esketamine was relatively safe according to cardiovascular parameters since there were no deaths reports as well as no clinically significant changes in cardiovascular safety parameters (laboratory tests, electrocardiograms, and physical examinations). The author emphasis that the only clinically significant vital sign abnormalities was a single case of transient high blood pressure and irregular breathing (both with esketamine 0.40 mg/kg dosing) that resolved within 2 hours without intervention. However, the author has mistakenly demonstrated these results as a study by Singh et al. 2015 when actually, they are from the study by Singh published in 2016 (Singh et al. 2016). Furthermore, we would like to point out that both articles were missing their proper citation in the references, the only mention to the author Singh was on the article by Zarate et al. 2006 (14th reference) and, unfortunately there was no mention of Loo et al. in any reference cited at all.

Overall, we praise the authors for writing such a review that helps shed light in the cardiovascular safety of ketamine and its enantiomers. Depression is the leading cause of disability worldwide, fortunately, the range of treatment options available for TRD patients is growing faster than the previous decade, and newer agents are being investigated. Although the efficacy of subanesthetic doses of both ketamine and esketamine for the treatment of TRD has been established by numerous studies, major concerns persist regarding the safety (cardiovascular, psychotomimetic, cognitive and the risk for drug abuse) of such treatment protocols. Therefore, it is a very important issue and needs robust clinical protocols to manage short and long-term cardiovascular side-effects for the safety of our patients.

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References

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