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LETTER TO THE EDITOR Open Access

High frequency of clozapine-associated myocarditis and troponin elevation: Need for slower titration prospective studies

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Dear Editor:

We read with great interest the paper by Nuebel et al, "Evaluation of major adverse events of clozapine based on accordance to an international titration guideline."[1] The authors concluded that more aggressive clozapine dose relationships did not increase the incidence of adverse drug reactions (ADRs) in their small chart review of mostly white males. This conclusion was drawn from the finding of an inverse correlation between the cumulative dose of clozapine in the last week of hospitalization and the probability of ADRs. However, we want to point out that this result may have been incorrectly derived due to sampling bias and methodological issues. Before the end of the second week, 10 of the 14 patients with ADRs dropped out of the analysis, possibly due in part to ADRs. When ADRs occur, clinicians tend to reduce or discontinue clozapine doses. Therefore, recording the end-of-the-week dose does not consider that the dose may have been higher earlier in the week but was lowered (or the titration was halted) after the emergence of an ADR. As the authors pointed out, it is also possible that clinicians may have chosen a slower titration in patients who were estimated to be at a higher risk for ADRs at the time of clozapine initiation. This is supported by the higher frequency of both baseline and week 1 C-reactive protein measurements in patients with ADR compared with those without ADR. For a more rigorous analysis, the dose should be compared with the International Clozapine Titration Guideline (ICTG)–recommended dose up to the date of the first symptom of ADR, not at the end of the week. Patients with ADRs had a lower percentage of accordance at the end of week 1 than those without ADRs (142.1 versus 181). However, the week 1 dose for both groups was considerably higher than the ICTG-recommended doses. Under this condition, the incidence of clozapine discontinuation was 26% (11/43), myocarditis was 4.6% (2/43), and troponin elevation was 7.0% (3/43) (the combined incidence of myocarditis and troponin elevation was 11.6% [5/43]), suggesting a high incidence of inflammatory ADRs. In our previous paper, inflammatory side effects were less frequent in the slower titration group (approximately 60% to 70% of the ICTG-recommended titration rate) than in the faster titration group (approximately 130% of the ICTG-recommended titration rate).[2] Thus, in the Nuebel et al study, most patients corresponded more closely to our faster titration group, and few corresponded to our slower titration comparison group. To clarify these findings, a prospective study is needed that uses a slow titration that increases to approximately 60% to 70% of the ICTG-recommended titration rate.

Finally, regardless of the small sample size and the limitations stated herein, it was remarkable that this study observed an increased risk of ADRs among obese patients. Recently, a larger scale study conducted in the Hunter region of Australia provided a suggestion that obesity is a risk factor for the high prevalence of myocarditis as discussed in *Schizophrenia Research*.[3-5] We hope that a more extensive study will validate the impact of obesity on the inflammatory side effects of clozapine.

Yuki Kikuchi, MD[1]
[1] *(Corresponding author) Psychiatrist, Department of Psychiatry, Graduate School of Medicine, Tohoku University, Sendai, Miyagi, Japan; Department of Psychiatry, Kodama Hospital, Ishinomaki, Miyagi, Japan, ykikuchi@sand.ocn.ne.jp, ORCID: https://orcid.org/0000-0002-1184-8918*

Bunichiro Onodera, MD[2]
[2] *Psychiatrist, Department of Psychiatry, Graduate School of Medicine, Tohoku University, Sendai, Miyagi, Japan; Department of Psychiatry, Kodama Hospital, Ishinomaki, Miyagi, Japan, ORCID: https://orcid.org/0009-0004-9354-3457*

Hiroshi Komatsu, MD, PhD[3]
[3] *Lecturer, Department of Psychiatry, Tohoku University Hospital, Sendai, Miyagi, Japan, ORCID: https://orcid.org/0000-0002-7602-0281*

Hiroaki Tomita, MD, PhD[4]
[4] *Professor, Department of Psychiatry, Graduate School of Medicine, Tohoku University, Sendai, Miyagi, Japan, ORCID: https://orcid.org/0000-0003-2628-880X*

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