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## Clozapine-induced myocarditis in Russia: Animal studies but no clinical studies



### Miocarditis inducida por clozapina en Rusia: estudios animales pero no clínicos

Dear Editor:

In 1980, Vesterby et al.<sup>1</sup> published the first case of clozapine-induced myocarditis during an overdose. In 1990, after another case of clozapine-induced myocarditis during an overdose, Meeker et al.<sup>2</sup> described a case of eosinophilic myocarditis characterized by an infiltration of eosinophils. Eosinophilic myocarditis is the typical presentation of clozapine-induced myocarditis and is indicative of a drug hypersensitivity reaction.<sup>3</sup>

During the 1990s, the national drug agencies started paying attention to this clozapine adverse drug reaction (ADR).<sup>4</sup> Vigibase, the database of the World Health Organization, receives data from the national drug agencies. In early 2021, a Vigibase search identified more than 3000 cases of clozapine-induced myocarditis associated with a 5% mortality rate (178/3572). Almost all the cases of myocarditis in clozapine patients appeared early in treatment with 84% (1309/1560) in the first month and another 5% (82/1560) in the second month, which is compatible with clozapine uptitration that was too rapid for the metabolism of that specific patient.<sup>4</sup> The occasional cases of myocarditis following clozapine overdose have the same mechanism. In the Vigibase search, there were no reports of clozapine-induced myocarditis from the Russian drug agency.

Clozapine started being used in Russia in 1973. In a cross-sectional study on a governmental database, 51% (22,676/44,836) of outpatients with schizophrenia were taking clozapine.<sup>5</sup> In 2010, Slyundin et al.<sup>6</sup> reported that clozapine ranked first in drug intoxication in the forensic studies that occurred in Moscow during the period from 2003 to 2009.

Thus, we decided to do a systematic search of clozapine-induced myocarditis in the Russian scientific literature. On August 14, 2021, the first author, using clozapine as the key word, found 185 articles. After a careful review of all of them only 17 of them provided any reference to clozapine-induced myocarditis. Most of them were review articles. Babkina et al.<sup>7</sup> mentioned the involvement of immuno-

logical mechanisms in clozapine-induced myocarditis. We found no articles describing clinical cases after overdoses or rapid titration, but we found three articles on animal studies<sup>8-10</sup> modeling clozapine intoxications completed by the same research group. The first study<sup>8</sup> included 14 Wistar male rats divided into 3 groups (I: saline solution, II: clozapine 150 mg/kg plus saline solution and III: clozapine 150 mg/kg in a 40% ethyl alcohol solution) studied after 4 h. They described the myocardium of the rats receiving clozapine as having hypereosinophilic areas. The second and third studies, completed after 24 h, described similar myocardial changes.<sup>9,10</sup>

In summary, the limited Russian literature suggests that clozapine intoxication is a relevant problem in Russia and that Russian authors are aware of the risk of clozapine-induced myocarditis, but there is no clinical data on whether or not this ADR is frequent in Russia. Russian psychiatrists may need to be aware of this ADR and report it to the Russian drug agencies.<sup>11</sup> They also need to start publishing cases of clozapine-induced myocarditis in medical journals and consider the possibility that slow personalized titration may contribute to decreasing its incidence.<sup>12</sup>

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## Conflict of interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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## References

- Vesterby A, Pedersen JH, Kaempe B, Thomsen NJ. Pludselig død under behandling med klozapin (Leponex) [Sudden death during treatment with clozapine (Leponex)]. *Ugeskr Laeger*. 1980;142:170-1 [Article in Danish].
- Meeker JE, Herrmann PW, Som CW, Reynolds PC. Clozapine tissue concentrations following an apparent suicide.

- dal overdose of Clozaril. *J Anal Toxicol.* 1992;16:54–6, <http://dx.doi.org/10.1093/jat/16.1.54>.
3. Chopra N, de Leon J. Clozapine-induced myocarditis may be associated with rapid titration: a case report verified with autopsy. *Int J Psychiatry Med.* 2016;51:104–15, <http://dx.doi.org/10.1111/j.1600-0447.1985.tb01268.x>.
  4. De las Cuevas C, Sanz EJ, Norén N, Ruan CJ, de Leon J. Clozapine-associated myocarditis in the World Health Organization's pharmacovigilance database: focus on reports from various countries. *Rev Psiquiatr Salud Ment.* 2021 Jul 20, <http://dx.doi.org/10.1016/j.rpsm.2021.07.004>. S1888-9891(21)00070-7.
  5. Kostev K, Osina G, Konrad M. Treatment patterns of patients with schizophrenia based on the data from 44,836 outpatients in Russia. *Heart Mind.* 2019;3:161–4, [http://dx.doi.org/10.4103/hm.hm\\_73\\_19](http://dx.doi.org/10.4103/hm.hm_73_19).
  6. Slyundin DG, Livanov AS, Anuchin VV, Merkin AG, Bobrinskaya IG, Gutova EV. Specific features of psychopathological manifestations in criminal clozapine intoxications. *Neurol Neuropsychiatry Psychosom.* 2010;2:57–63, <http://dx.doi.org/10.14412/2074-2711-2010-102> [Article in Russian].
  7. Babkina AS, Golubev AM, Sundukov DV, Bashirova AR, Golubev MA. Clozapine: mechanisms of toxicity and side effects. *Gen Reanimotol.* 2018;14:35–45, <http://dx.doi.org/10.15360/1813-9779-2018-2-35-45> [Article in Russian].
  8. Romanova OL, Sundukov DV, Golubev AM, Babkina AS, Golubev MA. Morphological changes in the heart with clozapine poisoning (experimental study). *Gen Reanimotol.* 2017;13:6–13, <http://dx.doi.org/10.15360/1813-9779-2017-2-6-13> [Article in Russian].
  9. Babkina AS, Ryzhkov IA, Antonova VV, Tsokolaeva ZI, Asanov AR, Kalabushev SN, et al. Morphological and functional alterations of the cardiovascular system during clozapine poisoning (experimental study). *Gen Reanimotol.* 2019;15:67–75, <http://dx.doi.org/10.15360/1813-9779-2019-4-67-75> [Article in Russian].
  10. Ryzhkov IA, Babkina AS, Tsokolaeva ZI, Kalabushev SN, Antonova VV, Sergeeva MV, et al. [Morphological and function of myocardium and skin microcirculation 24 hours after clozapine poisoning (experimental study)]. *Gen Reanimotol.* 2020;16:56–75, <http://dx.doi.org/10.15360/1813-9779-2020-5-56-64> [Article in Russian].
  11. Kirilochev OO, Dorfman IP, Umerova AR. Monitoring drug safety in Astrakhan, Russia. *Int J Risk Saf Med.* 2015;27 Suppl. 1:533–4, <http://dx.doi.org/10.3233/JRS-150680>.
  12. de Leon J, Ruan CJ, Schoretsanitis G, De Las Cuevas C. A rational use of clozapine based on adverse drug reactions, pharmacokinetics, and clinical pharmacopsychology. *Psychother Psychosom.* 2020;89:200–4, <http://dx.doi.org/10.1159/000507638>.
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