AMERICAN PSYCHIATRIC ASSOCIATION

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Dockets Management Staff (HFA-305)
Food and Drug Administration,
5630 Fishers Lane, Rm. 1061,
Rockville, MD 20852

Docket No. FDA-2024-N-3617 for "Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Psychopharmacologic Drugs Advisory Committee; Notice of Meeting; Establishment of a Public Docket; Request for Comments—Clozapine Risk Evaluation and Mitigation Strategy (REMS)

Dear Chairs Dr. Lo Re & Dr. Narendran,

On behalf of the American Psychiatric Association (APA), the national medical specialty society representing over 38,900 psychiatric physicians and their patients, we thank you for the opportunity to respond to the request for comments regarding Clozapine Risk Evaluation and Mitigation Strategy (REMS). Clozapine is a highly underutilized, potentially life-saving treatment for patients with treatment-resistant schizophrenia and among prescribers the Clozapine REMS system is perceived as an obstacle to increasing clozapine utilization. **APA recommends that the Advisory Committee on Drug Safety and Risk Management and the Advisory Committee on Psychopharmacologic Drugs consider reducing the scope of the current REMS program to focus on education only.**

Schizophrenia is a life-altering and potentially life-threatening disorder. Clozapine both reduces suicide and premature death in people diagnosed with schizophrenia. Lack of access to clozapine may result in violence, self-injury, inadvertent overdose, hospitalization, and death. Lack of access not only compromises the health of patients, it also deeply affects families, caregivers, healthcare providers and the public. The requirements set in place for the REMS are contradictory to the nature of the disease. For example, leaving home frequently for blood draws can be insurmountable and therefore, clozapine is not accessible to those patients.

Patients with treatment-resistant schizophrenia (TRS) should be treated with clozapine.[1] However, it is estimated that only 4.4 to 4.8 percent of individuals with

[1] American Psychiatric Association. (2020). "The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia, Third Edition." from https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines.

schizophrenia in the US are on clozapine.[2,3] That number is even lower for Black patients, even after adjustments for care access and social determinants of health a disparity is seen both in the US and abroad.[4] The goal of the Clozapine REMS program has been to ensure optimal patient monitoring for and management of clozapine-induced severe neutropenia.[5] Yet, research has shown that the prevalence of severe neutropenia due to clozapine is 0.4 percent, with peak incident typically within the first month.[6, 7] Modifications to the Clozapine REMS could aim to better balance monitoring the risk of neutropenia versus the administrative burden caused by the REMS system.

Psychiatrists are sufficiently capable and confident to appropriately monitor a patient's hematologic status and intervene when appropriate without central reporting. If the FDA continues the current REMS on clozapine, the burden of access and quality care will continue to exacerbate the healthcare disparities for minorities and individuals in rural areas. These individuals will continue to face unnecessary burdens of finding prescribers willing to participate in the complex REMS. In addition, they will have difficulties finding pharmacies that are certified or willing to participate in the REMS due to the lack of knowledge navigating this complex REM system, including the irregularities in dispensing limits and the inability to comply with the required monitoring.

Furthermore, with regards to the racial disparities touched on above, a systematic review revealed that Black and Hispanic patients in the UK and the USA are significantly less likely to receive clozapine than White/Caucasian service-users.[8] Benign ethic neutropenia, a naturally occurring condition in African American and people of Middle Eastern descent, has been cited as a reason for lower utilization, however even with an absolute neutrophil count that falls below the standards for clozapine use, their risk for agranulocytosis is no greater.[9] In fact, numerous studies indicate that there is less risk of agranulocytosis from clozapine than was thought when the drug was approved. Studies also indicate that an elevated risk may be time-limited, withing the first year, and that indefinite monitoring may not be required. Moreover, in a 2024 prospective study of 274 people of African descent, of the 227 that completed six months of clozapine treatment, one case of severe neutropenia occurred, fourteen patients discontinued due to adverse effects, and despite the high prevalence of ACKR1-null genotype, clozapine can be used safely in Black patients including those with benign ethnic neutropenia.[10] We believe that the REMS program as it

[2] Olfson M, Gerhard T, Crystal S, Stroup TS: Clozapine for Schizophrenia: State Variation in Evidence-Based Practice. PsychiatrServ 67:152, 2016

[3] Bareis N, OlfsonM, Wall M, Stroup TS: Variation in Psychotropic Medication Prescription for Adults With Schizophrenia in the United States. PsychiatrServ 73:492-500, 2022

[4] Barry, S., Jarskog, L. F., Xia, K., Torpunuri, R. S., Wu, X., & Zeng, X. (2024). Racial Disparities in Clozapine Prescription Patterns Among Patients With Schizophrenia. *Psychiatric Services*, *75*(8), 733–739. https://doi.org/10.1176/appi.ps.20230226

[5] https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/information-clozapine

[6] Li XH, Zhong XM, Lu L, et al: The prevalence of agranulocytosis and related death in clozapine-treated patients: a comprehensive meta-analysis of observational studies. Psychol Med 50:583-594, 2020

[7] Myles N, Myles H, Xia S, et al: Meta-analysis examining the epidemiology of clozapine-associated neutropenia. Acta PsychiatrScand138:101-109, 2018

[8] Ventura, A. M. B., Hayes, R. D., & Fonseca de Freitas, D. (2022). Ethnic disparities in clozapine prescription for service-users with schizophrenia-spectrum disorders: a systematic review. Psychological medicine, 52(12), 2212–2223

[9] Moran, M. (2018). More Minority Patients May Be Able to Safely Use Clozapine. *Psychopharmacology*, *4*(14). https://doi.org/10.1176/appi.pn.2018.pp10a3

[10] Kelly D., Glassman M., et al. Clozapine and neutrophil response in patients Barry, S., Jarskog, L. F., Xia, K., Torpunuri, R. S., Wu, X., & Zeng, X. (2024). Racial Disparities in Clozapine Prescription Patterns Among Patients With Schizophrenia. *Psychiatric Services*, *75*(8), 733–739. https://doi.org/10.1176/appi.ps.20230226

[10] https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/information-clozapine

is currently configured further contributes to these well-researched racial disparities. There needs to be a continued educational campaign to ensure prescribers are comfortable treating patients who have lower neutrophil counts upon initiation along with removing the other socioeconomic barriers to access such as the lack of flexibility regarding dispensing quantities of clozapine and stringent monitoring requirements.

As the Advisory Council reviews the evidence, APA encourages the members to consider reducing the scope of the current REMS program to focus on education only. Thank you for your review and consideration of these comments. If you have any questions, please contact Brooke Trainum (btrainum@psych.org), Senior Director, Practice Policy.

Sincerely,

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CEO and Medical Director
American Psychiatric Association

[10] Li XH, Zhong XM, Lu L, et al: The prevalence of agranulocytosis and related death in clozapine-treated patients: a comprehensive meta-analysis of observational studies. Psychol Med 50:583-594, 2020
[10] Myles N, Myles H, Xia S, et al: Meta-analysis examining the epidemiology of clozapine-associated neutropenia. Acta PsychiatrScand138:101-109, 2018
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[10] Moran, M. (2018). More Minority Patients May Be Able to Safely Use Clozapine. *Psychopharmacology*, *4*(14). https://doi.org/10.1176/appi.pn.2018.pp10a3
of African descent: A six-month, multinational, prospective, open-label clinical trial. Schizophrenia Research, Volume 268, 2024, Pages 312-322