AMERICAN ACADEMY OF CHILD & ADOLESCENT PSYCHIATRY

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November 4, 2024

Psychopharmacologic Drugs Advisory Committee
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

RE: Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Psychopharmacologic Drugs Advisory Committee: Public Docket for Clozapine Risk Evaluation and Mitigation Strategy (REMS)

Dear Members of the Drug Safety and Risk Management Advisory Committee and Psychopharmacologic Drugs Advisory Committee:

The American Academy of Child and Adolescent Psychiatry (AACAP) represents more than 11,000 child and adolescent psychiatrists, fellows, residents, and medical students. A large number of AACAP members and their patients are negatively affected by the overly stringent clozapine REMS requirements, which we would like to address here.

Studies have shown that 12.3% of adult individuals diagnosed with schizophrenia-spectrum and primary psychotic disorders developed full threshold psychosis before the age of 18 years old, and 3% of individuals developed this before the age of 14 years old[i]. Child and adolescent psychiatrists are often tasked with working with individuals experiencing early onset psychosis (the development of psychosis before the age of 18 years old). Child psychiatrists often consider using clozapine for pediatric age individuals who have not responded favorably to two prior adequate antipsychotic trials given the robustness of evidence for efficacy in this population.

Clozapine is one of the most effective medications for pediatric individuals living with treatment refractory schizophrenia or other primary psychotic illness. In children and adolescents living with psychotic disorders, clozapine has been shown to have superior efficacy compared to other antipsychotics, leading to shorter hospital stays, and has low rates of discontinuation in pediatric populations[ii]. Clozapine is also FDA-approved for suicidality in schizophrenia and schizoaffective disorder. In one systematic review and meta-analysis, neutropenia was seen in 6%-15% of cases and agranulocytosis was seen in less than 0.1%. When accessed in a timely fashion, clozapine can meaningfully change the developmental

trajectory of a young individual living with psychosis such that they are able to achieve meaningful recovery from psychosis that is highly personal to them, including pursuing their goals, returning to school, and pursuing higher education or employment.

Despite its efficacy, the clozapine REMS program imposes substantial barriers that disproportionately affect young people, particularly those from marginalized or underserved communities. The stringent monitoring and logistical hurdles of the current REMS system make it difficult for young people and their families to access this potentially life-saving treatment.

Specific barriers include:

1. Frequent lab monitoring: The requirement for frequent blood tests to monitor for the exceedingly rare side effect of agranulocytosis (<1%) is often not feasible for most families, regardless of socioeconomic status, due to the burden of traveling to appointments for laboratory testing. This involves additional barriers for the parents of young individuals taking clozapine due to lack of ability to take time off from work, having consistent access to transportation, living in a rural area without close proximity to a lab, or other factors. While lab monitoring is important for safety monitoring, it is also important to acknowledge that the frequency of lab testing required for medication refills disproportionately impacts those with limited financial or logistical support, or those who face language barriers.

2. Pharmacy issues: Due to the requirement for pharmacies to be enrolled in REMS to be able to receive and dispense clozapine, some pharmacies opt out of carrying this medication altogether. Those that do may be staffed by pharmacists who are not familiar with the REMS program, or struggle with balancing the demands of managing the various tasks in their pharmacy in addition to the additional step of checking the REMS before filling and dispensing clozapine for patients. Patients and families encountering pharmacies with these issues may struggle to advocate or navigate this situation, leading to undue stress, anxiety, discontinuation, or missed doses. Families facing socioeconomic challenges like limited access to transportation may not have opportunities to return to the pharmacy at a time when a particular pharmacist familiar with REMS is available.

3. Health system navigation: The complexity of the current clozapine REMS requires coordination between prescribers, pharmacists and laboratories, and the current system places undue burden on patients and families to navigate this complex system. For example, some families may agree to start clozapine for their child living with schizophrenia, but due to pharmacy issues such as pharmacists not being aware of REMS or how to check if the absolute neutrophil count (ANC) was uploaded, may not be able to access the medication. Families with limited healthcare literacy or language barriers face significant challenges in managing these complexities, leading to delays in treatment, missed doses requiring re-titration, or decision to never initiate clozapine.

4. Impact of climate change and weather disruptions/natural disasters: Climate change has led to an increase in global temperatures, increasing the number of heat warnings in some regions. Due to the anticholinergic side effects of antipsychotic medications, many individuals taking these types of medications are encouraged to avoid being outside during such heat warnings. Some parts of the United States experience yearly hurricanes, flooding or wildfires which impact an individual's ability

to travel to complete required labs for clozapine REMS and can impact their ability to access the medication. While some pharmacies allow short term refills to prevent lapses in treatment, this is not a standard procedure, leaving some individuals without the medication for more than 48 hours, requiring re-titration.

5. Limited access to prescribers: The complexity of REMS has created a situation in which many psychiatric providers are reluctant to prescribe clozapine, particularly for children and adolescents. The excessive administrative burden related to the REMS enrollment requirements has resulted in a reduction in the number of clinicians willing to take on these patients. This limits the availability of clozapine for youth, especially in areas with limited psychiatric services. This also limits training opportunities for psychiatric residents and child and adolescent psychiatry fellows to gain experience prescribing clozapine to young individuals who meet the eligibility criteria for the medication, further compounding the access issues. In addition, when a child and adolescent psychiatrist is out of the office or on leave, the clozapine REMS requirements require the covering provider to be enrolled in the REMS, which also creates an undue burden for all individuals involved.

We urge your committee to consider the following recommendations:

1. During the COVID-19 pandemic, REMS requirements were temporarily unable to be met. This led to a natural experiment. We strongly recommend making de-identified REMS related data publicly available for studies to be conducted on the safety of reduced blood draw monitoring, especially in pediatric populations. This would allow for re-examining the risks of agranulocytosis related to clozapine.
2. Given there is a lack of evidence on the duration of blood draw monitoring related to clozapine in pediatric populations, we recommend studies be conducted using available data within clozapine REMS to determine whether the current ANC monitoring requirements are appropriate, especially for pediatric populations but also for adult populations.
3. Consider removing any restrictions for pharmacies to procure and keep clozapine in stock. This includes removing the requirement for pharmacies to enroll in the clozapine REMS OR requiring ALL pharmacies and pharmacists to enroll in clozapine REMS to improve access to the medication.
4. Consider removing any restrictions for pharmacies to dispense clozapine to adult and pediatric patients with a lawful prescription for this medication. Remove the requirement for pharmacists to check REMS prior to dispensing clozapine to a patient with a lawful prescription who can show that they have received their recommended ANC monitoring.
5. If the REMS system remains in place, allow parents/legal guardians of pediatric individuals, in addition to adults, to have their own REMS log in so that they can view their ANC lab results, and can help navigate systems issues related to receiving clozapine.
6. Support and pursue clinical trials for at home fingerstick blood draw for ANC monitoring for pediatric populations (example: Athelas machine which already has FDA approval in adult populations).
7. Allow covering prescribers to provide one-time prescriptions for clozapine to individuals who are already taking clozapine (continue titration prescription or provide refill to prevent missed doses) without requiring enrollment in the REMS.

We appreciate the opportunity to provide comments on this critical issue. Please do not hesitate to reach out to Karen Ferguson, Deputy Director of Clinical Practice at kferguson@aacap.org, with any follow-up questions you may have.

Sincerely,

Tami D. Benton, MD

President

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[i] Umbrella Review: Atlas of the Meta-Analytical Evidence of Early-Onset Psychosis - Journal of the American Academy of Child & Adolescent Psychiatry (jaacap.org)

[ii] Clozapine for Management of Childhood and Adolescent-Onset Schizophrenia: A Systematic Review and Meta-Analysis - PubMed (nih.gov)