A Summary of the FDA Joint Meeting on the Clozapine REMS

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On November 19, the FDA held a Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Psychopharmacologic Drugs Advisory Committee to consider the Risk Evaluation and Mitigation Strategy (REMS) for Clozapine Products. Three AAPP past presidents participated. Megan Ehret served as an ad hoc member of the advisory committee and Deanna Kelly and Ray Love presented during the public session.

Tiffany Farchione, MD, Director, Division of Psychiatry, FDA gave an overview of clozapine while Leah Hart, PharmD, Office of Medication Error Prevention and Risk Management (OMERPRM) reviewed the requirements, labeling changes, enforcement discretions and REMS that have affected clozapine since its approval in 1989.

Jason Gross, PharmD, John Kane, MD, Robert Cotes, MD and James Shamp presented on behalf of the Clozapine Product Manufacturers Group. Cynthia LaCivita, PharmD of OMEPRM presented FDA funded unpublished studies on prescriber experience, adherence to ANC monitoring, the risk of neutropenia and neutropenia related hospitalizations. Carolyn Tieu, PharmD, MPH of OMEPRM presented FDA's updated assessment of neutropenia and gaps in healthcare. The FDA slides are available at https://www.fda.gov/media/183654/download

There was consensus that clozapine was associated with a continued risk for neutropenia over an indefinite period of time, but that the greatest risk was in the first 18 weeks. In discussion, it was noted that some cases of neutropenia may have had other causes and just occurred in clozapine users. The FDA and CPMG continually noted that information was incomplete because of the "enforcement discretion" for many elements of the REMS.

CPMG did not report additional clozapine deaths. In a study using the FDA Sentinel system, no new neutropenia related deaths were reported. In a VA study conducted by the FDA (N = 6488) with up to 23

years of follow up, two neutropenia related deaths were noted. One of these occurred on the 23rd day of treatment; one that was noted to be "possibly related" occurred after five years of treatment.

Panel members also discussed the potential benefits of clozapine, considering the risk of suicide and mortality rate among those living with schizophrenia. One member pointed out that even without a precise analysis, the benefits appeared to outweigh the risks of neutropenia.

Dr. Love presented on behalf of AAPP and ASHP. He focused on the complex history of clozapine regulation, the numerous steps in the REMS where breakdowns may occur and the confusion among prescribers, pharmacists, patients and caregivers. He also addressed the contradictions and conflicts in REMS information, documents and guidances provided independently by the REMS Program, the CPMG and the FDA. Dr. Kelly reviewed her NIH funded clozapine education program and addressed provider knowledge and attitudes toward neutropenia and the REMS. In her study, the area that generated the greatest need for consultation was the REMS.

Numerous individuals receiving clozapine and family members also presented and detailed their struggles with REMS and the disastrous impact of interruptions in treatment. Some spoke of their inability to access clozapine due to the stigma concerning clozapine use and/or the resistance to the burden of the REMS.

Finally, several presenters focused on issues such as underutilization of clozapine in minorities, clozapine deserts and lack of knowledge regarding BEN.

The theme echoed by almost all of the public presenters was that "The greatest risk of clozapine is not getting clozapine."

The Joint Committees were presented with four questions to discuss and vote upon:

1. DISCUSSION: How reassured or concerned are you that current and potential clozapine health care providers have sufficient knowledge and access to resources about the risk of neutropenia and need for absolute neutrophil count (ANC) monitoring?
2. DISCUSSION: How reassured or concerned are you that current and potential clozapine health care providers will perform ANC monitoring without the requirements of the Risk Evaluation and Mitigation Strategy (REMS)?
3. VOTE: Are the requirements for the prescriber to document ANC results and the pharmacy to verify the ANC results through the REMS necessary to ensure safe use?
   a. Yes.
   b. No.

   Please provide your rationale for your vote.
4. VOTE: Is the requirement to educate health care providers through the REMS about the risk of severe neutropenia and the need for ANC monitoring necessary to ensure safe use?
   a. Yes.
   b. No.

   Please provide your rationale for your vote.

For questions 1 and 3, the vote was 1 vote yes and 14 votes no. The member who voted no stated that they were leaning towards a streamlined time limited REMS for 18 weeks at initiation of treatment only. The vote on question 4 was also 1 vote for yes and 14 votes for no.

FDA officials will now consider these votes and decide upon next steps. This could include changes to the REMS or "retiring" the REMS. In the case of changes to the REMS for isotretinoin, it took the FDA more than six months to act.

Several important themes seemed to emerge during the final discussions of the committee members:

- Clozapine REMS has caused an excessive focus on neutropenia that has negatively influenced use of clozapine and reduced consideration of other important toxic effects.
- There needs to be a consideration of how to best educate and "get the message out" concerning the positive benefits of clozapine.
- The FDA in their additional studies was asking the wrong questions. They focused on neutropenia rather than safe and effective use.
- REMS does not prevent neutropenia.
- Monitoring is still necessary, especially in the first 18 weeks, but this should be controlled by prescribers and health systems.
- No barrier to treatment is worth interrupting treatment.

Today's hearing resulted from years of work, publications, and meetings. During these efforts, AAPP played a prominent and sometimes pivotal leadership role. Even if the REMS is retired, psychiatric pharmacists will have major roles ahead in managing these changes, educating colleagues and continuing to assure the safe and effective use of clozapine.

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