Risk Evaluation and Mitigation Strategy programs: How they can be improved

Health care professionals suggest ways to enhance the REMS of 3 psychotropics

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JIM FRAZIER

A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program the FDA can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks (***Box***,[1] ***page 16***). The FDA may require medication guides, patient package inserts, communication plans for health care professionals, and/or certain packaging and safe disposal technologies for medications that pose a serious risk of abuse or overdose. The FDA may also require elements to assure safe use and/or an implementation system be included in the REMS. Pharmaceutical manufacturers then develop a proposed REMS for FDA review.[2] If the FDA approves the proposed REMS, the manufacturer is responsible for implementing the REMS requirements.

The REMS program for clozapine[3] has been the subject of much discussion in the psychiatric community. The adverse impact of the 2015 update to the clozapine REMS program was emphasized at meetings of both the American Psychiatric Association and the College of Psychiatric and Neurologic Pharmacists. A white paper published by the National Association of State Mental Health Program Directors shortly after the 2015 update concluded, "clozapine is underused due to a variety of barriers related to the drug and its properties, the health care system, regulatory requirements, and reimbursement issues."[4] After an update to the clozapine REMS program in 2021, the FDA temporarily suspended enforcement of certain requirements due to concerns from health care professionals about patient access to the medication because of problems with implementing the clozapine REMS program.[5,6] In November 2022, the FDA issued a second announcement of enforcement discretion related to additional

Improving REMS

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A REMS can help ensure the benefits of a medication outweigh its risks

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Box

What is a Risk Evaluation and Mitigation Strategy?

The FDA provides this description of a Risk Evaluation and Mitigation Strategy (REMS):

"A [REMS] is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks. REMS are designed to reinforce medication use behaviors and actions that support the safe use of that medication. While all medications have labeling that informs health care stakeholders about medication risks, only a few medications require a REMS. REMS are not designed to mitigate all the adverse events of a medication, these are communicated to health care providers in the medication's prescribing information. Rather, REMS focus on preventing, monitoring and/or managing a specific serious risk by informing, educating and/or reinforcing actions to reduce the frequency and/or severity of the event."[1]

requirements of the REMS program.[5] The FDA had previously announced a decision to not take action regarding adherence to REMS requirements for certain laboratory tests in March 2020, during the COVID-19 pandemic.[7]

REMS programs for other psychiatric medications may also present challenges. The REMS programs for esketamine[8] and olanzapine for extended-release (ER) injectable suspension[9] include certain risks that require postadministration monitoring. Some facilities have had to dedicate additional space and clinician time to ensure REMS requirements are met.

To further understand health care professionals' perspectives regarding the value and burden of these REMS programs, a collaborative effort of the University of Maryland (College Park and Baltimore campuses) Center of Excellence in Regulatory Science and Innovation with the FDA was undertaken. The REMS for clozapine, olanzapine for ER injectable suspension, and esketamine were examined to develop recommendations for improving patient access while ensuring safe medication use and limiting the impact on health care professionals.

Assessing the REMS programs

Focus groups were held with health care professionals nominated by professional organizations to gather their perspectives on the REMS requirements. There was 1 focus group for each of the 3 medications. A facilitator's guide was developed that contained the details of how to conduct the focus group along with the medication-specific questions. The questions were based on the REMS requirements as of May 2021 and assessed the impact of the REMS on patient safety, patient access, and health care professional workload; effects from the COVID-19 pandemic; and suggestions to improve the REMS programs. The University of Maryland Institutional Review Board reviewed the materials and processes and made the determination of exempt.

Health care professionals were eligible to participate in a focus group if they had ≥1 year of experience working with patients who use the specific medication and ≥6 months of experience within the past year working with the REMS program for that medication. Participants were excluded if they were employed by a pharmaceutical manufacturer or the FDA. The focus groups were conducted virtually using an online conferencing service during summer 2021 and were scheduled for 90 minutes. Prior to the focus group, participants received information from the "Goals" and "Summary" tabs of the FDA REMS website[10] for the specific medication along with patient/caregiver guides, which were available for clozapine and olanzapine for ER injectable suspension. For each focus group, there was a target sample size of 6 to 9 participants. However, there were only 4 participants in the olanzapine for ER injectable suspension focus group, which we believed was due to lower national utilization of this medication. Individuals were only able to participate in 1 focus group, so the unique participant count for all 3 focus groups totaled 17 (***Table 1, page 17***).

Themes extracted from qualitative analysis of the focus group responses were the value of the REMS programs; registration/enrollment processes and REMS websites;

Table 1

Characteristics of focus group participants

Characteristic	Clozapine[a] (n = 7)	Olanzapine for ER injectable suspension (n = 4)	Esketamine (n = 6)
Profession, n (%)			
Pharmacist	3 (42.9)	2 (50)	3 (50)
Physician	3 (42.9)	1 (25)	2 (33.3)
Nurse	1 (14.3)	1 (25)	1 (16.7)
Years practicing in health care role, median (IQR)	12.5 (8.3, 21)	5 (2.9, 15.8)	8.0 (3.1,17.8)
Years working with REMS, median (IQR)	9.5 (8, 12.3)	2.8 (2.4, 3.8)	1.8 (1.5, 2.0)
Current involvement with clozapine REMS, n (%)			
Prescribing	5 (71.4)	1 (25)	2 (33.3)
Dispensing	1 (14.3)	1 (25)	2 (33.3)
Medication administration	0	2 (50)	1 (16.7)
Monitoring	4 (57.1)	1 (25)	2 (33.3)
Education	5 (71.4)	2 (50)	2 (33.3)
Program or practice site administrative	2 (28.6)	3 (75)	3 (50)
Data entry	2 (28.6)	2 (50)	1 (16.7)
Hours per week providing REMS-related services, n (%)			
<4 hours	4 (57.1)	4 (100)	3 (50)
5 to 8 hours	1 (14.3)	0	1 (16.7)
>16 hours	2 (28.6)	0	2 (33.3)
Average number of patients per month, n (%)			
1 to 5	1 (14.3)	1 (25)	1 (16.7)
6 to 10	1 (14.3)	1 (25)	2 (33.3)
11 to 20	1 (14.3)	2 (50)	1 (16.7)
>20	4 (57.1)	0	2 (33.3)

[a]Clozapine focus group was held prior to the July 2021 announcement that the FDA had approved a modification to the clozapine REMS

ER: extended-release; IQR: interquartile range; REMS: Risk Evaluation and Mitigation Strategy

monitoring requirements; care transitions; and COVID considerations (***Table 2, page 18***). While the REMS programs were perceived to increase practitioner and patient awareness of potential harms, discussions centered on the relative cost-to-benefit of the required reporting and other REMS requirements. There were challenges with the registration/enrollment processes and REMS websites that also affected patient care during transitions to different health care settings or clinicians. Patient access was affected by disparities in care related to monitoring requirements and clinician availability.

COVID impacted all REMS programs. Physical distancing was an issue for medications that required extensive postadministration monitoring (ie, esketamine and olanzapine for ER injectable suspension). Access to laboratory services was an issue for clozapine.

Medication-specific themes are listed in ***Table 3*** (***page 22***) and relate to terms and descriptions in the REMS or additional regulatory requirements from the Drug Enforcement Agency (DEA). Suggestions for improvement to the REMS are presented in ***Table 4*** (***page 24***).

Recommendations for improving REMS

A group consisting of health care professionals, policy experts, and mental health

Clinical Point

Focus groups assessed the impact of REMS on patient safety, patient access, and health care professional workload

Improving REMS

Clinical Point

REMS were perceived to increase practitioner and patient awareness of potential harms

Table 2

Themes from focus group interviews: representative quotes

Theme	Clozapine[a]
Value of REMS requirements on patient safety	The CBC always looks a little funky during those first 6 to 8 months. After the 1-year mark, it's stable. There's very little change in their CBC So, I don't know that it's really worth it, but I struggle to really come out and say I don't think there should be any monitoring. Probably some should be early on
Impact of registration processes and REMS website on health care professional workload	You can't go into a patient's record and then do everything that you need to in there. You go into a patient's record … and you enter an ANC … and then you go back to the home screen … then you go back into the patient's record to look at the history … and once you go out of that you go back to the home screen to go back into the record. There's so many steps, just to do a few things to look at a single patient When I call REMS, I've been told that the patient actually has multiple charts through them. I think that part of that [discrepancy] is because (I could be wrong) they're using the ZIP code as one of the identifiers. So, especially in our population where we have a lot of people who are homeless living in group homes and moving frequently, they may have 4 different REMS charts out there
Impact of monitoring requirements	I would almost argue, look at it in the opposite. I think it could negatively impact safety in the sense that in my patients, if a patient misses their clozapine, they're almost definitely getting hospitalized. So, anything that makes it hard for them to get clozapine puts them at risk for being hospitalized I agree with that. If patients are missing the lab work and not able to get the medication for a couple days, we're seeing that leading to relapse, to rehospitalization, to suicides in some instances
Impact of disparities, clinician availability, and monitoring requirements on patient access	I also think it's an equity issue ... your higher socioeconomic patients with more social support are going to have an easier time getting to the lab My mobile treatment patients who are homeless, there's no way they're going to get their blood drawn. We're not even going to try it; those are the people that don't get it

Olanzapine for ER injectable suspension	Esketamine
[The REMS] is an inconvenience and a burden that does not seem to have any immediately apparent changes in outcomes, other than the requirement that providers monitor for 3 hours, which could and should be part of responsible and accountable practice without needing a REMS to monitor I don't know how the information that I put in the REMS program every week, week after week, necessarily adds any value to the REMS program or to patient safety, other than … that initial setup that ensures the doctor who's prescribing and the nurses who are monitoring understand the risks to the patient	I think the REMS is way too much to be monitored and entered To me it seems really over the top in terms of what is really a rather safe drug Is there any access to the data from REMS like pertaining to outcomes or anything that is shared?
The registration process is a big one. It's not intuitive. There is some flow type of sheet on the Zyprexa Relprevv patient care program site, but it has multiple boxes and arrows going every which direction so it's not super intuitive. I think that allowing a registration to be bundled (perhaps like provider, facility, representative, delegates) all together would be helpful instead of these 4 separate sheets that no one really understands what they are If [patients] would be linked to the clinic with maybe a dropdown menu of the providers at the clinic who are approved, you could select it each time with a different script. It would save everybody a lot of time	The portal has to be more effective with the enrollments and with the patient monitoring forms. We're still faxing it because we feel it's faster There's too much paperwork that you have to fax. And sometimes they don't receive it and tell you you're not compliant. Then you tell them you sent it in a couple of times. Many conversations back and forth. They have to have a smoother [process]
We have had a couple of events (PDSS). Certainly, from a patient safety aspect, them being monitored and onsite, they received help that I'm not sure if they had left and been in the community they would have gotten the follow-up care that they needed. Patients … have had events of postinjection delirium and sedation syndrome	Basically, [the time is when] the patient's clinically ready to be discharged. I don't know if even having a time frame … What is the difference between 1 hour, hour and a half? I think the patient needs to be clinically ready, the majority are clinically ready by 90 minutes. You're going to have some maybe a little bit sooner, some a little bit later. The time frame alone I feel like the clinic is able to make that decision based off of their procedures and protocols The 60- to 90-minute marker is plenty of time. I also agree that it could totally be up to the clinic to make that decision, especially on a patient-to-patient basis, because some of our patients really do need that 2-hour. But it typically is related to other factors, so it really could be an hour for the majority
I find that the paperwork associated with it and the registration process can be a barrier to people actually implementing a Relprevv program The barrier that I see with [setting up Relprevv clinic] is understanding the process to enroll. When one goes on the [web]site and sees it, they're throwing hands up and saying, "forget it, I'm not going to do that"	You have somebody traveling hours to get to a clinic when if it was made more accessible, or the limitations were released a little bit, you would have other individuals establishing or providing Spravato to their patients Two-hour requirement, we didn't realize the impact it can have on how many patients you can see at one time

continued

Clinical Point

Challenges with the registration/ enrollment processes and REMS websites affected patient care during transitions

Clinical Point

Each REMS should have a section providing justification for its existence and specific quantifiable outcomes

Table 2

Themes from focus group interviews: representative quotes

continued from page 19

Theme	Clozapine[a]
Impact of care transitions on patient access and health care professional workload	If a patient leaves our clinic and goes to another state where we don't often have referrals, it can be really hard to find someone who prescribes clozapine. We're always trying to figure out if they have to move in a given time frame, how do we handle that gap? Because there may not be someone in their state who prescribes clozapine. We also see that trying to discharge people from the inpatient unit. It's hard to find people who write for clozapine The notion of clozapine patients moving from outpatient to inpatient back to outpatient, I think that process should be looked at. For example, a patient being plucked out of their outpatient providers list, inserted into an inpatient providers list, when they get discharged, someone has to notify the outpatient provider to add them back in. If that doesn't take place, then that patient potentially gets lost in that transition of care, which is already a problem with all of our behavioral health patients
Impact of COVID	The pandemic really opened my eyes to the relevance of [the need for testing] because the FDA allowed the CBC override and all these patients have gone a year, sometimes longer, without monthly CBC checks. And they are questioning like, "Why do you want me to come back monthly if I've been okay?" So it really makes me question the relevance of it I feel like clozapine monitoring is the only thing that COVID made better

[a]Clozapine focus group was held prior to the July 2021 announcement that the FDA had approved a modification to the clozapine REMS

ANC: absolute neutrophil count; CBC: complete blood count; ER: extended-release; PDSS: postinjection delirium/sedation syndrome; REMS: Risk Evaluation and Mitigation Strategy

advocates reviewed the information provided by the focus groups and developed the following recommendations.

Overarching recommendations

Each REMS should include a section providing justification for its existence, including a risk analysis of the data regarding the risk the REMS is designed to mitigate. This analysis should be repeated on a regular basis as scientific evidence regarding the risk and its epidemiology evolves. This additional section should also explain how the program requirements of the REMS as implemented (or planned) will achieve the aims of the REMS and weigh the potential benefits of the REMS requirements as implemented (or planned) by the manufacturer vs the potential risks of the REMS requirements as implemented (or planned) by the manufacturer.

Each REMS should have specific quantifiable outcomes. For example, it should specify a reduction in occurrence of the rate of the concerned risk by a specified amount.

Ensure adequate stakeholder input during the REMS development and real-world testing in multiple environments before implementing the REMS to identify unanticipated consequences that might impact patient access, patient safety, and health care professional burden. Implementation testing should explore issues such as purchasing and procurement, billing and reimbursement, and relevant factors such as other

	Olanzapine for ER injectable suspension	Esketamine
	If there's a provider out of town then you've got to re-register the person … all these processes. Goodness forbid you have someone go into an inpatient unit who needs an injection while they're in there. Then I'm transferring someone from clinic over to an inpatient unit, and they have to redo all of that. They get it on an inpatient unit and then, when they come back, do it all again. And heaven forbid someone has a guardian and you have to scan all those documents back and forth and can't just get a signature. [REMS processes] greatly impact access. I have had people not be able to get it because of these barriers As soon as someone's out of town, [the prescription] comes in from a new provider. If the office didn't anticipate that, then all of a sudden there's a registration issue. And patients go without their medications	
	We didn't have the space We doubled the number of clinics that we hosted for Relprevv administration and halved the number of people in each clinic	It delayed them from actually starting their esketamine clinic. It would have been started earlier if not for [the pandemic] One of the issues we ran into was the designation by different systems if this is a needed procedure. From our perspective, we felt that offering the service was absolutely still necessary. There were a couple clinics around us that actually stopped seeing patients and stopped treatments. Those patients ended up getting referred to us because we continued to do so

federal regulations or requirements (eg, the DEA or Medicare).

Ensure harmonization of the REMS forms and processes (eg, initiation and monitoring) for different medications where possible. A prescriber, pharmacist, or system should not face additional barriers to participate in a REMS based on REMS-specific intricacies (ie, prescription systems, data submission systems, or ordering systems). This streamlining will likely decrease clinical inertia to initiate care with the REMS medication, decrease health care professional burden, and improve compliance with REMS requirements.

REMS should anticipate the need for care transitions and employ provisions to ensure seamless care. Considerations should be given to transitions that occur due to:

- Different care settings (eg, inpatient, outpatient, or long-term care)
- Different geographies (eg, patient moves)
- Changes in clinicians, including leaves or absences
- Changes in facilities (eg, pharmacies).

REMS should mirror normal health care professional workflow, including how monitoring data are collected and how and with which frequency pharmacies fill prescriptions.

Enhanced information technology to support REMS programs is needed. For example, REMS should be integrated with major electronic patient health record and pharmacy systems to reduce the effort required for clinicians to supply data and automate REMS processes.

continued

Clinical Point

REMS should anticipate the need for care transitions and employ provisions to ensure seamless care

Clinical Point

REMS should be required to meet all standards of all applicable agencies (eg, the CDC or DEA) with a single system

Table 3

Medication-specific themes from focus group interviews

Medication	Theme	Representative quotes
Clozapine[a]	Designating "benign ethnic neutropenia" improves patient safety and patient access	The access has increased quite a bit. I don't know that more patients are receiving clozapine, but patients are being able to receive it longer BEN made it easier to not need to add things like lithium to try to bump the ANC
Clozapine[a]	Understanding "benign ethnic neutropenia" can improve patient access	I think that's something the REMS could do better … giving guidance on how to identify somebody who's BEN Yeah, that's a good point. I even question how they define BEN and what I would think is more realistic. I don't know, I'm not even 100% sure, honestly, what they consider BEN. What I think they consider BEN seems pretty extreme
Olanzapine for ER injectable suspension	Understanding "ready access" can improve patient access	We called and spoke to Relprevv REMS about [ready access], and the answer that we received is that all that that means is that the clinic must be able to dial 911 and be serviced by EMS at that particular address. So there does not need to be anybody trained with BLS, ACLS, defibrillators, anything like that, but I think a lot of providers don't know that. So that's one of the things that people find as a barrier. They see that or hear that, and they think it means there has to be someone on site who can perform ACLS with the defibrillator and that's not the case [Ready access] can be perceived as scary when one hears that that's the requirement
Esketamine	Additional regulatory challenges affect health care professional workload	The primary cause of delaying setting up the site and getting running is figuring out the logistics of pharmacy. One, it's a controlled substance, and two, a REMS medication, and then figuring out who's willing to sign their name on that representative form and be willing to take on those rules. It definitely prevented us from getting started earlier ... and other sites I have spoken with that are in the process still of getting up and running, even having a pharmacy on-site Our provider had a different address on a DEA number, and she had to switch that over—that took a day. Then you have to call the REMS program, send in your form. That took another week before they could get that fixed. And nothing happens until that form is in place

[a]Clozapine focus group was held prior to the July 2021 announcement that the FDA had approved a modification to the clozapine REMS

ACLS: advanced cardiac life support; ANC: absolute neutrophil count; BEN: benign ethnic neutropenia; BLS: basic life support; DEA: Drug Enforcement Administration; EMS: emergency medical services; ER: extended-release; REMS: Risk Evaluation and Mitigation Strategy

For medications that are subject to other agencies and their regulations (eg, the CDC, Centers for Medicare & Medicaid Services, or the DEA), REMS should be required to meet all standards of all agencies with a single system that accommodates normal health care professional workflow.

REMS should have a standard disclaimer that allows the health care professional to waive certain provisions of the REMS in cases when the specific provisions of the REMS pose a greater risk to the patient than the risk posed by waiving the requirement.

Assure the actions implemented by the industry to meet the requirements for each REMS program are based on peer-reviewed evidence and provide a reasonable expectation to achieve the anticipated benefit.

Ensure that manufacturers make all accumulated REMS data available in a deidentified manner for use by qualified scientific researchers. Additionally, each REMS should have a plan for data access

upon initiation and termination of the REMS.

Each REMS should collect data on the performance of the centers and/or personnel who operate the REMS and submit this data for review by qualified outside reviewers. Parameters to assess could include:

- timeliness of response
- timeliness of problem resolution
- data availability and its helpfulness to patient care
- adequacy of resources.

Recommendations for clozapine REMS

These comments relate to the clozapine REMS program prior to the July 2021 announcement that FDA had approved a modification.

Provide a clear definition for "benign ethnic neutropenia."

Ensure the REMS includes patient-specific adjustments to allow flexibility for monitoring. During COVID, the FDA allowed clinicians to "use their best medical judgment in weighing the benefits and risks of continuing treatment in the absence of laboratory testing."[7] This guidance, which allowed flexibility to absolute neutrophil count (ANC) monitoring, was perceived as positive and safe. Before the changes in the REMS requirements, patients with benign ethnic neutropenia were restricted from accessing their medication or encountered harm from additional pharmacotherapy to mitigate ANC levels.

Recommendations for olanzapine for ER injectable suspension REMS

Provide clear explicit instructions on what is required to have "ready access to emergency services."

Ensure the REMS include patient-specific adjustments to allow flexibility for postadministration monitoring (eg, sedation or blood pressure). Specific patient groups may have differential access to certain types of facilities, transportation, or other resources. For example, consider the administration of olanzapine for ER injectable suspension by a mobile treatment team with an adequate protocol (eg, via videoconferencing or phone calls).

Ensure actions with peer-reviewed evidence demonstrating efficacy/effectiveness are included in the REMS. How was the 3-hour cut-point determined? Has it been reevaluated?

Ensure the REMS requirements allow for seamless care during transitions, particularly when clinicians are on vacation.

Recommendations for esketamine REMS

Ensure the REMS includes patient-specific adjustments to allow flexibility for post-administration monitoring. Specific patient groups may have differential access to certain types of facilities, transportation, or other resources. For example, consider the administration of esketamine by a mobile treatment team with an adequate protocol (eg, via videoconferencing or phone calls).

Ensure actions with peer-reviewed evidence demonstrating efficacy/effectiveness of requirements are included in the REMS. How was the 2-hour cut-point determined? Has it been reevaluated?

Ensure that the REMS meet all standards of the DEA, with a single system that accommodates normal health care professional workflow.

A summary of the findings

Overall, the REMS programs for these 3 medications were positively perceived for raising awareness of safe medication use for clinicians and patients. Monitoring patients for safety concerns is important and REMS requirements provide accountability.

The use of a single shared REMS system for documenting requirements for clozapine (compared to separate systems for each manufacturer) was a positive move forward in implementation. The focus group welcomed the increased awareness of benign ethnic neutropenia as a result of this condition being incorporated in the revised monitoring requirements of the clozapine REMS.

Focus group participants raised the issue of the real-world efficiency of the REMS programs (reduced access and increased clinician workload) vs the benefits (patient safety). They noted that excessive workload could lead to clinicians becoming unwilling

Clinical Point

All 3 of these REMS could benefit from including patient-specific adjustments to allow flexibility for monitoring

Improving REMS

Clinical Point

Increased workload could lead to clinicians becoming unwilling to use a medication that requires a REMS program

Table 4

Suggestions for improving the REMS

Clozapine[a]	Olanzapine for ER injectable suspension
• Reduce the amount of paperwork – Have 1 simple form for registration • Reduce/suspend ANC monitoring based on: – Duration of use – Genetic markers – Patient- and clinician-signed waiver – Allowable exceptions • Provide guidance on identifying patients with BEN • During inpatient care: – Allow patients to remain in outpatient prescriber's database (eg, create temporary inpatient queue for inpatient clinician) – Remove need to obtain an approval number, especially for acutely psychotic patients • Make website more user-friendly – Smoother navigation – Enable ability to print a report of patients who are due for labs – Enable ability to delete all past email messages all together – Enable ability to find current prescriber, contact information, and clozapine dose • Information technology enhancements include: – EMR automatically pushes the ANC to REMS – E-prescription automatically includes the latest ANC count on prescription	• REMS could include just registration, training, and acknowledging "ready access to emergency services" • Reduce the amount of paperwork – Allow registration to be bundled together (eg, clinician, facility, representative, or delegates) instead of separate forms – Allow patient to be registered to a clinic instead of a specific prescriber (eg, with a dropdown menu of approved prescribers) – Follow clozapine REMS processes regarding transferring facilities, clinicians, and delegates – For non-PDSS hospital admissions, reduce paperwork to checking a box stating "not related to PDSS" • Clarify meaning of "ready access to emergency services" (eg, the ability to dial 911 and be serviced by EMS) • Make website more user-friendly – Smoother navigation (eg, sort and search functions) – Exchange information about pharmacy dispensing and medication administration to enable viewing by pharmacies and prescribers

[a]Clozapine focus group was held prior to the July 2021 announcement that the FDA had approved a modification to clozapine REMS

ANC: absolute neutrophil count; BEN: benign ethnic neutropenia; EMR: electronic medical record; EMS: emergency medical services; ER: extended-release; PDSS: postinjection delirium/sedation syndrome; REMS: Risk Evaluation and Mitigation Strategy

to use a medication that requires a REMS. Clinician workload may be further compromised when REMS logistics disrupt the normal workflow and transitions of care between clinicians or settings. This latter aspect is of particular concern for clozapine.

The complexities of the registration and reporting system for olanzapine for ER injectable suspension and the lack of clarity about monitoring were noted to have discouraged the opening of treatment sites. This scarcity of sites may make clinicians hesitant to use this medication, and instead opt for alternative treatments in patients who may be appropriate candidates.

There has also been limited growth of esketamine treatment sites, especially in comparison to ketamine treatment sites.[11-14] Esketamine is FDA-approved for treatment-resistant depression in adults and for depressive symptoms in adults with major depressive disorder with acute suicidal ideation or behavior. Ketamine is not FDA-approved for treating depression but is being used off-label to treat this disorder.[15] The FDA determined that ketamine does not require a REMS to ensure the benefits outweigh the risks for its approved indications as an anesthetic agent, anesthesia-inducing agent, or supplement to anesthesia. Since ketamine has no REMS requirements, there may be a lower burden for its use. Thus, clinicians are treating patients for depression with this medication without needing to comply with a REMS.[16]

Technology plays a role in workload burden, and integrating health care processes within current workflow systems, such

Esketamine

- Reduce the amount of paperwork
- Facilitate registration
  - Allow filling out of paperwork on paper (eg, handwritten signature)
- Eliminate documentation of vital signs
- Allow flexibility in postadministration monitoring time
  - During maintenance phase
  - Ensure transportation
  - Patient-specific, as most ready by 90 minutes but some may need 2 hours
  - Analyze responses to question on patient monitoring form about when a patient is ready to leave

as using electronic patient health records and pharmacy systems, is recommended. The FDA has been exploring technologies to facilitate the completion of REMS requirements, including mandatory education within the prescribers' and pharmacists' workflow.[17] This is a complex task that requires multiple stakeholders with differing perspectives and incentives to align.

The data collected for the REMS program belongs to the medication's manufacturer. Current regulations do not require manufacturers to make this data available to qualified scientific researchers. A regulatory mandate to establish data sharing methods would improve transparency and enhance efforts to better understand the outcomes of the REMS programs.

A few caveats

Both the overarching and medication-specific recommendations were based on a small number of participants' discussions related to clozapine, olanzapine for ER injectable suspension, and esketamine. These recommendations do not include other medications with REMS that are used to treat psychiatric disorders, such as loxapine, buprenorphine ER, and buprenorphine transmucosal products. Larger-scale qualitative and quantitative research is needed to better understand health care professionals' perspectives. Lastly, some of the recommendations outlined in this article are beyond the current purview or

Related Resources

- FDA. Frequently asked questions (FAQs) about REMS. www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/frequently-asked-questions-faqs-about-rems

Drug Brand Names

Buprenorphine extended-release • Sublocade
Buprenorphine transmucosal • Subutex, Suboxone
Clozapine • Clozaril
Esketamine • Spravato
Ketamine • Ketalar
Lithium • Eskalith, Lithobid
Loxapine • Adasuve
Olanzapine extended-release injectable suspension • Zyprexa Relprevv

Clinical Point

A mandate to establish data sharing methods would enhance efforts to better understand the outcomes of REMS

Bottom Line

Risk Evaluation and Mitigation Strategy (REMS) programs are designed to help reduce the occurrence and/or severity of serious risks or to inform decision-making. However, REMS requirements may adversely impact patient access to certain REMS medications and clinician burden. Health care professionals can provide informed recommendations for improving the REMS programs for clozapine, olanzapine for extended-release injectable suspension, and esketamine.

Improving REMS

Clinical Point

Some of these recommendations may require legislative or regulatory action to implement

authority of the FDA and may require legislative or regulatory action to implement.

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