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Clozapine and hematologic adverse reactions: Impact of the Risk Evaluation and Mitigation Strategy program

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Abstract

Introduction: In October 2015, the Food and Drug Administration (FDA) instituted an update to the mandatory Risk Evaluation and Mitigation Strategy (REMS) program for clozapine to improve safety monitoring of hematologic events. However, the impact of the clozapine REMS program on reporting of hematologic adverse events has not been quantified.

Methods: We assessed adverse event reports for agranulocytosis, granulocytopenia, leukopenia, and neutropenia from the FDA Adverse Event Reporting System (FAERS) for a 1-year time period before (October 2014 to September 2015, pre-REMS) and after (October 2015 to September 2016, post-REMS) the implementation of the clozapine REMS program. The AERSMine platform was used to capture historical effect estimates (October 2004 to September 2014). Reporting odds ratios (ROR), proportional reporting ratios (PRR), and corresponding Taylor series 95% confidence intervals (CIs) were calculated for hematologic events with clozapine compared with all other medications using OpenEpi.

Results: Reporting rates for agranulocytosis, granulocytopenia, leukopenia, and neutropenia with clozapine all increased from the pre-REMS to post-REMS time frames, ranging from a 2-fold increase with leukopenia to a 40-fold increase with neutropenia; the composite measure of all hematologic reports had a 12-fold increase. During the post-REMS time frame, the ROR increased by 1691% (111.4, 95% CI 100.6-123.4) compared with the pre-REMS time frame (7.1, 95% CI 5.2-9.6), and the PRR increased by 1280% (83.1, 95% CI 76.8-90.0 vs 6.9, 95% CI 5.1-9.4) for the composite outcome.

Discussion: We observed significant increases in reports of hematologic adverse events with clozapine after the introduction of the clozapine REMS program. Future research should explore the impact of the less stringent exclusionary and discontinuation criteria on utilization (eg, expanded access) and clinical outcomes (eg, treatment effectiveness and adverse events).

Keywords: clozapine, neutropenia, pharmacovigilance, drug safety, agranulocytosis, granulocytopenia, leukopenia, Risk Evaluation and Mitigation Strategy Program

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Introduction

Clozapine is an atypical antipsychotic medication first approved in the United States in 1989. US Food and Drug Administration (FDA) approved indications include treatment-resistant schizophrenia as well as suicidal behavior in schizophrenia or schizoaffective disorder.[1] Clozapine has been shown to be 1 of the most effective treatment options available for these 2 indications and is recommended as a potential first-line treatment option.[2-4] Even with clozapine's documented effectiveness, it is considered to be underutilized, in part due to its severe side effect profile.[5] Clozapine has several black box warnings regarding potential severe adverse drug reactions (ADRs), including hematologic abnormalities.[1] Although the label specifically mentions neutropenia, there are 3 additional hematologic abnormalities that are clinically similar but have different defining parameters: agranulocytosis, granulocytopenia, and leukopenia. Agranulocytosis is defined as having an absolute neutrophil count (ANC) below 500/μL.[6] Granulocytopenia is defined as an ANC between 500/μL and 1000/μL.[7] Leukopenia is defined as have a total white blood cell (WBC) count of less than 4000/μL.[8] Neutropenia is defined as having an ANC below 1500/μL.[9]

The mechanism of action that causes these hematologic changes is unknown and has not been shown to be dose dependent.[1] Risk of these reactions is greatest during the first 18 weeks of therapy with subsequent decreases in risk thereafter.[1] With the body's inability to properly protect against pathogens, this can result in increased risk of infections.[10] Further, as the duration of these hematologic reactions increases, the risk of infection increases, and therefore, clinically managing these decreased WBC counts becomes more difficult.[10] In the event of hematologic abnormalities necessitating clozapine discontinuation, it has been reported that discontinuation may be associated with worsening psychiatric symptoms, reduced quality of life, and increased risk of suicide.[11-13]

In October 2015, the mandatory FDA Risk Evaluation and Mitigation Strategy (REMS) program for clozapine was modified to improve safety monitoring in patients treated with clozapine. A REMS program is a risk management program that mandates safety monitoring activities that may prevent occurrence of the event, reduce severity, or identify the adverse event sooner.[14] The clozapine REMS program replaced the 6 existing prescribing registries that were maintained by individual manufacturers of clozapine.[15] The modified REMS program is shared by prescribers, pharmacies, and patients in 1 centralized program. Both prescribers and pharmacies must be certified in the program in order to prescribe and dispense clozapine, respectively. A requirement of the clozapine REMS program is the monitoring of ANC before each prescription of clozapine can be dispensed.[15] Some additional components of this modified REMS program include lowering the discontinuation threshold from an ANC of less than 1500/μL to an ANC of less than 1000/μL as well as allowing patients with benign ethnic neutropenia to be treated with clozapine (Table 1). The purpose of initiating this new mandatory REMS program was "to address continuing safety concerns and current knowledge about a serious blood condition called severe neutropenia."[15(p1)] The impact of the REMS program on addressing safety concerns with neutropenia is not well defined. Therefore, the objective of our study was to assess adverse event reporting rates of hematologic events with clozapine before and after the implementation of the clozapine REMS program.

Methods

We reviewed reports submitted to the FDA's Adverse Event Reporting System (FAERS) for a 1-year time period before (October 2014 through September 2015, pre-REMS) and after (October 2015 through September 2016, post-REMS) the implementation of the clozapine REMS program.[16] We only included initial reports and excluded reports missing all 3 of the following: event date, sex, and age. The AERSMine platform was also analyzed for the time period of October 2004 through September 2014 to capture historical effect estimates.[17] We identified reactions from adverse event reports using the MedRA terms (medical dictionary for regulatory activities) *agranulocytosis*, *granulocytopenia*, *leukopenia*, *neutropenia*, and *neutropenic*, and subsequent listings of adverse events were reviewed for inclusion. Reports were assessed for mention of either the brand names Clozaril, Fazaclo, Leponex, and Versacloz or the generic drug name clozapine. The reporting odds ratio (ROR), proportional reporting ratio (PRR),[18] and corresponding Taylor series 95% confidence intervals (CIs) were calculated using OpenEpi[19] for all 3 time frames comparing clozapine hematologic reports with all other medications. Although the FDA label broadly refers to these hematologic reactions as neutropenia, we assessed agranulocytosis, granulocytopenia, leukopenia, and neutropenia individually and also as a composite reaction.

Results

During the 1-year pre-REMS time frame, there were 765 185 total adverse event reports, and clozapine was listed in 0.27% of these reports (n = 2048; Table 2). In the 1-year post-REMS time frame, there were 881 184 total adverse event reports with clozapine comprising 0.26% of reports (n = 2248). In the 11-year historical time frame

TABLE 1: Changes in the clozapine Risk Evaluation and Mitigation Strategy (REMS) program (October 2015)[15]

	Pre-REMS[a]	Post-REMS[a]
WBC count monitoring	Dose discontinuation recommended if WBC <3000	No WBC count monitoring
ANC	Dose discontinuation recommended if ANC <1500	Dose discontinuation recommended if ANC <1000
NNRMF	Patients were listed in the NNRMF if they had WBC <2000 or ANC <1000	The NNRMF was discontinued
Patients with BEN	Patients are not able to receive treatment	Patients are able to receive treatment; dose discontinuation recommended if ANC <500
Rechallenge	Not allowed if WBC <2000 or ANC <1000	Is not recommended, but prescribers are allowed to if they determine the benefit outweighs the risk

ANC = absolute neutrophil count; BEN = benign ethnic neutropenia; NNRMF = national non-rechallenge master file; WBC = white blood cell.
[a]Units in cells/μL.

prior to REMS, there were 5 828 458 total adverse event reports, and 0.76% included clozapine (n = 44 164).

During the pre-REMS time frame, the ROR for agranulocytosis with clozapine was 29.3 (95% CI 19.1-44.8) and a PRR of 29.0 (95% CI 19.0-44.2), which were similar to the historical time frame (ROR 23.2, 95% CI 21.6-24.8; PRR 22.7, 95% CI 21.2-24.3; Table 3). During the post-REMS time frame, the ROR increased by 397% (116.2, 95% CI 93.0-145.2) compared with the pre-REMS time frame, and the PRR increased by 382% (110.9, 95% CI 89.5-137.5).

For granulocytopenia, the pre-REMS ROR was 168.4 (95% CI 76.6-370.3), and the PRR was 167.7 (95% CI 76.5-367.8), which were 1.7 times lower than the historical reporting rates (ROR 292.7, 95% CI 272.2-314.7; PRR 277.4, 95% CI 258.3-297.9). During the post-REMS time frame, there was more than a 13.4-fold increase in the ROR (2261.3, 95% CI 1546.0-3306.0) and a 12.5-fold increase in the PRR (2089.3, 95% CI 1436.0-3041.0) compared with the pre-REMS reporting rates.

The pre-REMS reporting rates for leukopenia with clozapine were almost 3 times lower with an ROR of 4.5 (95% CI 1.7-12.0) and a PRR of 4.5 (95% CI 1.7-12.0) than the historical reporting rates (ROR 13.6, 95% CI 13.0-14.3; PRR 13.1, 95% CI 12.5-13.8). The post-REMS reporting rates were more than double those of the pre-REMS time frame but slightly lower than the historical reporting rates with an ROR of 10.3 (95% CI 5.1-20.9) and a PRR of 10.3 (95% CI 5.1-20.7).

The pre-REMS and historical reporting rates for neutropenia with clozapine were lower than with the other reactions (pre-REMS ROR 1.4, 95% CI 0.6-3.1; PRR 1.4, 95% CI 0.6-3.1; historical ROR 10.8, 95% CI 10.5-11.2; PRR 9.8, 95% CI 9.5-10.1). During the post-REMS time frame, there was a 41-fold increase in reporting rates compared with the pre-REMS time frames with an ROR of 65.6 (95% CI 57.6-74.8) and a PRR of 57.2 (95% CI 51.0-64.2).

The composite measure of all hematologic reactions with clozapine produced a historical estimate with an ROR of

TABLE 2: Clozapine adverse reactions in the Food and Drug Administration Adverse Event Reporting System

	Historical: Oct 2004 to Sept 2014	Pre-REMS: Oct 2014 to Sept 2015	Post-REMS: Oct 2015 to Sept 2016
Total reactions	5 828 458	765 185	881 184
Total clozapine reactions	44 168	2048	2248
Total agranulocytosis reactions	6468	319	466
Clozapine agranuloytosis reactions	955	23	103
Total granulocytopenia reactions	3408	29	203
Clozapine granulocytopenia reactions	2315	9	171
Total leukopenia reactions	19 641	337	312
Clozapine leukopenia reactions	1787	4	8
Total neutropenia reactions	68 722	1615	2304
Clozapine neutropenia reactions	4772	6	294
Total hematologic reactions	98 239	2300	3285
Clozapine hematologic reactions	9829	42	576

REMS = Risk Evaluation and Mitigation Strategy.

TABLE 3: Risk estimates with corresponding 95% confidence intervals for hematologic adverse reactions with clozapine in the Food and Drug Administration Adverse Event Reporting System

	Historical: Oct 2004 to Sept 2014		Pre-REMS: Oct 2014 to Sept 2015		Post-REMS: Oct 2015 to Sept 2016	
	ROR	PRR	ROR	PRR	ROR	PRR
Agranulocytosis	23.2 (21.6-24.8)	22.7 (21.2-24.3)	29.3 (19.1-44.8)	29.0 (19.0-44.2)	116.2 (93.0-145.2)	110.9 (89.5-137.5)
Granulocytopenia	292.7 (272.2-314.7)	277.4 (258.3-297.9)	168.4 (76.6-370.3)	167.7 (76.5-367.8)	2261.3 (1546.0-3306.0)	2089.3 (1436.0-3041.0)
Leukopenia	13.6 (13.0-14.3)	13.1 (12.5-13.8)	4.5 (1.7-12.0)	4.5 (1.7-12.0)	10.3 (5.1-20.9)	10.3 (5.1-20.7)
Neutropenia	10.8 (10.5-11.2)	9.8 (9.5-10.1)	1.4 (0.6-3.1)	1.4 (0.6-3.1)	65.6 (57.6-74.8)	57.2 (51.0-64.2)
Composite	18.4 (18.0-18.9)	14.6 (14.3-14.8)	7.1 (5.2-9.6(	6.9 (5.1-9.4)	111.4 (100.6-123.4)	83.1 (76.8-90.0)

PRR = proportional reporting ratio; REMS = Risk Evaluation and Mitigation Strategy; ROR = reporting odds ratio.

18.4 (95% CI 18.0-18.9) and a PRR of 14.6 (95% CI 14.3-14.8) and a pre-REMS ROR of 7.1 (95% CI 5.2-9.6) and a PRR of 6.9 (95% CI 5.1-9.4). During the post-REMS time frame, the ROR increased by 1569% (111.4, 95% CI 100.6-123.4) compared with the pre-REMS time frame, and the PRR increased by 1204% (83.1, 95% CI 76.8-90.0).

Three of the adverse reactions assessed had statistically significant increases in effect estimates of at least a 4-fold increase and nonoverlapping confidence intervals from the historical time frame to the post-REMS time frame although leukopenia had a decrease. Neutropenia had the largest increase from the pre-REMS to the post-REMS time frame with a greater than 40-fold increase in the measures of association (ROR: 65.6; PRR: 57.2 vs ROR: 1.4; PRR: 1.4). The composite measure of all hematologic reactions had greater than a 5-fold increase in the post-REMS study period compared with the historical period and greater than a 12-fold increase compared with the 1-year pre-REMS period.

Discussion

To our knowledge, ours is the first study to assess hematologic adverse event reports with clozapine following the implementation of the clozapine REMS program. Our study showed significant increases in reports of hematologic adverse events with clozapine after the introduction of the clozapine REMS program. Reporting rates for agranulocytosis, granulocytopenia, leukopenia, and neutropenia with clozapine all increased from the pre-REMS to post-REMS time frames, ranging from a 2-fold increase with leukopenia to a 40-fold increase with neutropenia, and the composite measure of all hematologic reports had a 12-fold increase.

Conversion to a centralized clozapine REMS program now allows pharmacies and prescribers to monitor patients within a single, centralized system, eliminating reporting burden and potential confusion and discrepancies when there were 6 separate registries. There are several possible explanations for the significant increase in reporting rates of these adverse reactions since implementation of the revised REMS program, including changes in exclusionary criteria, monitoring parameters, and renewed attention to safety monitoring with clozapine. For example, under to the clozapine REMS program, providers are instructed to report clozapine-related adverse events directly to the Clozapine REMS Program Contact Center. Providers are also encouraged to submit an adverse event report to the FDA MedWatch Reporting System. Therefore, submission of adverse event reports to the Clozapine REMS Program Contact Center may increase voluntary reporting to the FDA MedWatch Reporting System.

The clozapine REMS program requires monitoring for neutropenia only by ANC before each prescription dispensing, whereas previously it was monitored by ANC in conjunction with WBC count (Table 1).[15] Although the frequency of this monitoring has remained the same, the clozapine REMS program amended the discontinuation threshold for patients from an ANC of less than 1500/μL to an ANC of less than 1000/μL. Another update is that patients who have benign ethnic neutropenia are now able to be treated with clozapine although they were not eligible prior to the modified REMS program. Another change is that prescribers are allowed to rechallenge patients if they believe the benefits outweigh the risks, whereas previously, patients with either a WBC count of less than 2000/μL or ANC less than 1000/μL were placed on the National Non-Rechallenge Master File list and were not allowed to rechallenge.

Clozapine is an effective treatment option and may be 1 of the last options available for patients who have failed previous therapies. Under the clozapine REMS program, less stringent parameters for exclusion, discontinuation, and rechallenge (Table 1) may have expanded access to clozapine. One study[20] conducted in a single state psychiatric hospital found that clozapine prescribing had a nonsignificant increase in the 6 months following the REMS implementation. As such, our findings of increased hematologic adverse event reporting with clozapine after

the introduction of the clozapine REMS program may be due to increased utilization of clozapine.

In regards to the change in ANC level from pre-REMS to post-REMS, patients may now continue clozapine treatment when neutropenic as the discontinuation threshold was lowered to the level of granulocytopenia. The observed increases in granulocytopenia and agranulocytosis may be due, in part, to additional patients reaching these ANC parameters in the absence of discontinuation at the detection of neutropenia, resulting in progression to lower ANC levels. Another potential explanation for this increase could be the notoriety effect, which is an increase in reporting due to an ADR being highlighted in the literature or media.[21] With the introduction of the REMS program, prescribers and patients may have become more aware of these potential ADRs and more likely to report them to the FAERS database when they occurred. However, notoriety effects tend to wane over time, and increases in reporting may have leveled off in recent years.

The historical and pre-REMS reporting rates from our study were similar to others in the literature. A population-based case control study[22] conducted in Hong Kong reported a crude odds ratio of 36.0 (95% CI 4.6-284.2) for agranulocytosis with clozapine from January 2004 through December 2013. Another case control study,[23] conducted in Berlin from 2000 through 2010, reported an odds ratio of 49.7 (95% CI 6.0-999.0) for agranulocytosis with clozapine after adjusting for age and sex. As these case-control studies were small, the CIs were wide. However, the effect estimated indicates a large, statically significant increased risk of agranulocytosis with clozapine as we observed in our study.

The FDA has made further modifications to the clozapine REMS program. As part of this update, which took effect February 28, 2019, prescribers are not required to be certified in the REMS program in order to prescribe clozapine in the inpatient setting as long as the patient is already enrolled in the program.[24] In addition, pharmacies are no longer allowed to enroll patients in the clozapine REMS program, and only the prescriber or the prescriber's designee may enroll patients.[24] It is unclear how these changes to the program have affected adverse event reporting and is an area of further evaluation.

There were several limitations to our study in addition to the notoriety effect listed previously. First and foremost, neither incidence nor prevalence of either the exposure (clozapine) or the outcome (hematologic events) can be quantified from the FAERS database.[25-27] In addition, causality does not need to be established between the medication and ADR in order for it to be reported and documented in FAERS.[27] Underreporting of known ADRs is also a limitation of FAERS.[28] Another potential limitation is that the initial rollout of the REMS program resulted in technical issues that led to implementation complications for both prescribers and pharmacies.[29] This may have resulted in restricted access for patients who were eligible for clozapine therapy.

The centralized clozapine REMS program enhances tracking of patients and their laboratory values for all health care providers involved in an effort to improve patient outcomes. There was greater than a 2-fold increase in risk estimates for agranulocytosis, granulocytopenia, leukopenia, and neutropenia with the composite measure having a 12-fold increase after REMS introduction compared to the previous year's reporting rates. Although more hematologic events are being reported since the modified clozapine REMS program was initiated, it remains unclear how this REMS program may be impacting clinical outcomes in patients. With new requirements being added to the REMS program in February 2019, future research should evaluate the effect of the clozapine REMS program, including access and utilization as well as positive clinical outcomes, such as treatment effectiveness and early detection of safety events, and negative clinical outcomes, such as increased incidence of serious hematologic reactions and progression to more severe hematologic conditions.

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