

# Perceived Barriers and Facilitators of Clozapine Use: A National Survey of Veterans Affairs Prescribers

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Although health care providers report that the frequent laboratory monitoring requirement is an unavoidable concern, other barriers, such as logistical concerns and the administrative burden that accompanies clozapine use, can be addressed.

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Clozapine is an atypical antipsychotic that the US Food and Drug Administration (FDA) approved for use in schizophrenia and suicidality associated with schizophrenia or schizoaffective disorder. Clozapine has been shown to be superior to other antipsychotic treatment for treatment resistant schizophrenia (TRS), which is defined as failure of 2 adequate trials of antipsychotic therapy.<sup>1</sup> Up to 30% of patients with schizophrenia are classified as treatment resistant.<sup>2</sup>

Clozapine is considered the drug of choice for patients with TRS in both the US Department of Veterans Affairs (VA) policies and other evidence-based guidelines and remains the only antipsychotic with FDA approval for TRS.<sup>2-5</sup> Patients treated with clozapine have fewer psychiatric hospitalizations, fewer suicide attempts, lower rates of nonadherence, and less antipsychotic polypharmacy compared with patients who are treated with other antipsychotic therapy.<sup>6,7</sup> A 2016 study by Gören and colleagues found that in addition to the clinical benefits, there is the potential for cost savings of \$22,000 for each veteran switched to and treated with clozapine for 1 year even when accounting for the cost of monitoring and potential adverse event management.<sup>8</sup> This translates to a total savings of > \$80 million if current utilization were doubled and half of those patients continued treatment for 1 year within the Veterans Health Administration (VHA). However, despite evidence supporting use, < 10% of Medicaid-eligible patients and only 4% of patients with schizophrenia in the VHA are prescribed clozapine.<sup>8,9</sup>

Clozapine is underutilized for a variety of reasons, including intensive monitoring requirements, potential for severe adverse drug reactions, and concern for patient adherence.<sup>8</sup>

Common adverse effects (AEs) can range from mild to severe and include weight gain, constipation, sedation, orthostatic hypotension, and excessive salivation. Clozapine also carries a boxed warning for agranulocytosis, seizures, myocarditis, other cardiovascular and respiratory AEs (including orthostatic hypotension), and increased mortality in elderly patients with dementia.

Severe agranulocytosis occurs in between 0.05% and 0.86% of patients, which led the FDA to implement a Risk Evaluation and Mitigation Strategy (REMS) program for clozapine prescribing in 2015. Prior to the REMS program, each of the 6 clozapine manufacturers were required to maintain a registry to monitor for agranulocytosis. Per the REMS program requirements, health care providers (HCPs), dispensing pharmacies, and patients must be enrolled in the program and provide an updated absolute neutrophil count (ANC) prior to prescribing or dispensing clozapine. This is potentially time consuming, particularly during the first 6 months of treatment when the ANC must be monitored weekly and prescriptions are restricted to a 7-day supply. With recent changes to the REMS program, pharmacists are no longer permitted to enroll patients in the REMS system. This adds to the administrative burden on HCPs and may decrease further the likelihood of prescribing clozapine due to lack of time for these tasks. Within the VHA, a separate entity, the VA National Clozapine Coordinating Center (NCCC), reduces the administrative burden on HCPs by monitoring laboratory values, controlling dispensing, and communicating data electronically to the FDA REMS program.<sup>10</sup>

Despite the various administrative and clinical barriers and facilitators to prescribing that exist,

previous studies have found that certain organizational characteristics also may influence clozapine prescribing rates. Gören and colleagues found that utilization at VHA facilities ranged from < 5% to about 20% of patients with schizophrenia. In this study, facilities with higher utilization of clozapine were more likely to have integrated nonphysician psychiatric providers in clinics and to have clear organizational structure and processes for the treatment of severe mental illness, while facilities with lower utilization rates were less likely to have a point person for clozapine management.<sup>11</sup>

Although many national efforts have been made to increase clozapine use in recent years, no study has examined HCP perception of barriers and facilitators of clozapine use in the VHA. The objective of this study is to identify barriers and facilitators of clozapine use within the VHA as perceived by HCPs so that these may be addressed to increase appropriate utilization of clozapine in veterans with TRS.

## METHODS

This study was conducted as a national survey of mental health providers within the VHA who had a scope of practice that allowed clozapine prescribing. Any HCP in a solely administrative role was excluded. The survey tool was reviewed by clinical pharmacy specialists at the Lexington VA Health Care System for content and ease of administration. Following appropriate institutional review board approval, the survey was submitted to the organizational assessment subcommittee and the 5 national VA unions for approval per VA policy. The survey tool was built and administered through REDCap (Nashville, Tennessee) software. An electronic link was sent out to the national VA psychiatric pharmacist and national psychiatry chief listservs for dissemination to the psychiatric providers at each facility with weekly reminders sent out during the 4-week study period to maximize participation. The 29-item survey was developed to assess demographic information, HCP characteristics, perceived barriers and facilitators of clozapine use, and general clozapine knowledge. Knowledge-based questions included appropriate indications, starting dose, baseline ANC requirement, ANC monitoring requirements, and possible AEs.

Primary outcomes assessed were perceived barriers to clozapine prescribing, opinions of potential interventions to facilitate clozapine prescribing, knowledge regarding clozapine, and

**TABLE 1**  
**Survey Respondent Characteristics (N = 97)**

Characteristics	No. (%)
Prescribing credentials	
Doctor	85 (87.6)
Advanced practice registered nurse	9 (9.3)
Physician Assistant	3 (3.1)
Practice setting	
Inpatient psychiatry	13 (13.4)
Outpatient psychiatry (main campus)	59 (60.8)
Outpatient psychiatry	25 (25.8)
Time in practice	
1-5 y	10 (10.3)
6-10 y	18 (18.5)
11-15 y	13 (13.4)
> 15 y	56 (57.7)
Time in direct patient care	
1%-24%	9 (9.3)
25%-49%	8 (8.2)
50%-74%	22 (22.7)
75%-100%	58 (59.8)
Academic medical center affiliation	75 (77.3)
Current clozapine prescriber	48 (49.5)

the impact of medication management clinics on clozapine prescribing. For the purposes of this study, a clozapine clinic was defined as an interdisciplinary team dedicated to clozapine prescribing and monitoring.

Secondary outcomes included a comparison of clozapine prescribing rates among different subgroups of HCPs. Subgroups included HCP discipline, geographic region, presence of academic affiliation, level of comfort or familiarity with clozapine, and percentage of time spent in direct patient care. The regional Veterans Integrated Service Networks (VISN) were used to evaluate the effect of geographic region on prescribing practices.

Results of the survey were analyzed using descriptive statistics. The Mann-Whitney U test was utilized to compare ordinal data from questions that were scored on a Likert scale, and nominal data was compared utilizing the  $\chi^2$  test. For all objectives, an  $\alpha$  of < .05 was considered significant.

## RESULTS

Ninety-eight HCPs from 17 VISNs responded during the 4-week survey period. One participant was excluded due to a solely administrative role. HCP characteristics and

**TABLE 2**  
**Perceived Barriers to Prescribing (N = 97)**

Response	Lack of Experience, No. (%)	Monitoring Requirements, No. (%)	Logistics of Prescribing, No. (%)	Other Pharmacotherapy Preferred, No. (%)	Concern Regarding ADRs, No. (%)
Not a barrier	43 (44.3)	24 (24.7)	28 (28.9)	38 (39.2)	21 (21.6)
Somewhat of a barrier	28 (28.9)	30 (30.9)	37 (38.1)	31 (31.9)	45 (46.4)
Significant barrier	19 (19.5)	42 (43.3)	31 (31.9)	27 (27.8)	31 (31.9)
Not applicable	7 (7.2)	1 (1)	1 (1)	1 (1)	-

Abbreviation: ADRs, adverse drug reactions.

**TABLE 3**  
**Perceived Facilitators to Prescribing (N = 97)**

Response	Clozapine Clinic, No. (%)	Specified REMS Contact, No. (%)	Educational Sessions, No. (%)	Outside Laboratory Monitoring, No. (%)
Highly unlikely	-	12.4 (12)	20 (20.1)	11 (11.3)
Somewhat unlikely	7 (7.2)	6 (6.1)	10 (10.3)	12 (12.4)
Somewhat likely	41 (42.2)	31 (31.9)	31 (34)	41 (42.2)
Highly likely	28 (27.8)	26 (26.8)	25 (25.8)	27 (27.8)
Not applicable	22 (22.6)	22 (22.6)	8 (8.2)	5 (5.2)

Abbreviation: REMS, Risk Evaluation and Mitigation Strategy.

demographics are described in Table 1. The majority of respondents practice in an outpatient mental health setting either at the main VA campus or at a community-based outpatient clinic (CBOC).

### Primary Outcomes

#### *Perceived Barriers to Prescribing*

The majority of survey respondents rated all factors listed as at least somewhat of a barrier to prescribing. Table 2 describes the perception of these various factors as barriers to clozapine prescribing. Along with prespecified variables, a free text box was available to participants to identify other perceived barriers not listed. Among other concerns listed in this text box were patient buy-in (11.3%), process/coordination of prescribing (8.2%), time restrictions (7.2%), prescriber restrictions (7.2%), access (3.1%), credentialing problems (2.1%), and lack of clear education materials (1%).

#### *Perceived Facilitators to Prescribing*

When asked to consider the potential for increased prescribing with various interventions,

most participants reported that all identified facilitators would be at least somewhat likely to increase their clozapine utilization. Table 3 describes the perception of these various factors as facilitators to clozapine prescribing. Other identified facilitators included nursing or pharmacy support for follow-ups (4.1%), advanced practice registered nurse credentialing for VHA prescribing (3.1%), utilization of national REMS program without the NCCC (3.1%), outside pharmacy use during titration phase (2.1%), prespecified coverage for HCPs while on leave (1%), and increased access to specialty consults for AEs (1%).

#### *Clozapine Knowledge Assessment*

Overall, the average score on the clozapine knowledge assessment portion of the survey was 85.6%. The most commonly missed questions concerned the minimum ANC required to initiate clozapine and the appropriate starting dose for clozapine (Table 4). No significant difference was seen in clozapine utilization based on the clozapine knowledge assessment score when HCPs who scored  $\leq 60\%$  were compared with those who scored  $\geq 80\%$  ( $P = .29$ ).

#### *Clozapine Clinic*

No statistically significant difference was found ( $P = .35$ ) when rates of prescribing between facilities with or without a dedicated clozapine clinic were compared (Table 5). Additionally, the involvement of a pharmacist in clozapine management clinics did not lead to a statistically significant difference in utilization rates ( $P = .45$ ).

## Secondary Outcomes

Self-rated level of comfort with clozapine prescribing was significantly associated with rates of clozapine prescribing ( $P < .01$ ). HCPs who rated themselves as somewhat or very comfortable were significantly more likely to prescribe clozapine (Table 6). Providers who rated themselves as very familiar with clozapine monitoring requirements (Table 7) were significantly more likely to prescribe clozapine ( $P < .01$ ). This significance remained when comparing HCPs who rated themselves as very familiar to those who ranked themselves as somewhat familiar ( $P = .01$ ). There was no statistically significant difference in clozapine prescribing based on academic medical center affiliation, time spent in direct patient care, or geographic location.

## DISCUSSION

This survey targeted VHA HCPs who were licensed to prescribe clozapine to identify barriers and facilitators of use, along with HCP characteristics that may impact clozapine utilization. The findings of this study indicate that even though HCPs may perceive many legitimate barriers to clozapine prescribing, such as the frequent laboratory monitoring requirements, some factors may increase their willingness to prescribe clozapine. Many of these facilitators involve addressing logistical concerns and the administrative burden that accompanies clozapine use. These findings echo previous studies done within and outside the VHA.<sup>8,9</sup>

While some identified barriers would require national policy changes to address, others could be addressed at VHA facilities. It may be prudent for each VA facility to identify a HCP who is familiar with clozapine to serve as a subject matter expert. This would be beneficial to those HCPs who feel their patients may benefit from clozapine, but who lack experience in prescribing, or for those with concerns about appropriateness of a specific patient. Additionally, this point of contact could be a valuable resource for concerns regarding administrative issues that may arise with the laboratory reporting system. In some facilities, it may be beneficial to set aside dedicated prescriber time in a clinic designed for clozapine management. Many HCPs in this survey identified the establishment of a clozapine clinic as an intervention that would increase their likelihood of prescribing clozapine. This type of clinic may alleviate some of the concerns regarding appointment availability for weekly or bimonthly

**TABLE 4**  
**Clozapine Knowledge Assessment (N = 97)**

	Indication, No. (%)	Starting Dose, No. (%)	Initial Monitoring, No. (%)	Minimum ANC, No. (%)	ADRs, No. (%)
Score	94 (97)	75 (77)	92 (94.8)	71 (73.2)	84 (86.6)

Abbreviations: ADRs, adverse drug reactions; ANC, absolute neutrophil count

**TABLE 5**  
**Clozapine Clinics (N = 97)**

Response	Current Clozapine Prescriber, No. (%)	Not Prescribing Clozapine, No. (%)
No clozapine clinic	28 (18.6)	23 (23.7)
Clozapine clinic	30 (30.1)	26 (26.8)

appointments early in therapy by having additional staff and time dedicated to accommodating the need for frequent visits.

The majority of respondents to this survey were concerned about the logistics of clozapine monitoring and prescribing; however, this is largely dictated by FDA and VHA policies and regulations. Per national guidance, patients within the VHA should only receive prescriptions for clozapine from their local VA facility pharmacy. It takes many veterans  $\geq 1$  hour to travel to the closest VA hospital or CBOC. This is especially true for facilities with largely rural catchments. These patients often lack many resources that may be present in more urban areas, such as reliable public transportation. This creates challenges for both weekly laboratory monitoring and dispensing of weekly clozapine prescriptions early in therapy. The option to get clozapine from a local non-VA pharmacy and complete laboratory monitoring at a non-VA laboratory facility could make a clozapine trial more feasible for these veterans. Another consideration is increasing the availability of VA-funded transportation for these patients to assist them in getting to their appointments. Serious mental illness case workers or mental health intensive case management services also may prove useful in arranging for transportation for laboratory monitoring.

Providers with higher self-rated comfort and familiarity with monitoring requirements had a significantly increased likelihood of clozapine utilization. Lack of experience was commonly identified as a barrier to prescribing. Subsequently, the majority of respondents felt that educational

**TABLE 6**  
**Comfort with Clozapine Prescribing (N = 97)**

Response	Not a Current Prescriber, No. (%)	Current Prescriber, No. (%)
Very uncomfortable	4 (4.1)	3 (3.1)
Somewhat uncomfortable	8 (8.2)	1 (1)
Neutral	5 (5.2)	1 (1)
Somewhat comfortable	15 (15.5)	10 (10.3)
Very comfortable	17 (17.5)	33 (34)

**TABLE 7**  
**Familiarity with Clozapine Monitoring (N = 97)**

Response	Not a Current Prescriber, No. (%)	Current Prescriber, No. (%)
Very unfamiliar	1 (1)	0
Somewhat unfamiliar	6 (6.2)	2 (2.1)
Neutral	1 (1)	0
Somewhat familiar	22 (22.7)	7 (7.2)
Very familiar	19 (19.6)	40 (41.2)

sessions would increase their likelihood to prescribe clozapine. This could be addressed at both a facility and national level. As discussed above, a subject matter expert at each facility could provide some of this education and guidance for prescribers who have little or no experience with clozapine. Additionally, national educational presentations and academic detailing campaigns may be an efficient way to provide standardized education across the VHA. Dissemination of required education via the VA Talent Management System is another potential route that would ensure all providers received adequate training regarding the specific challenges of prescribing clozapine within the VA.

#### Strengths and Limitations

The strengths of this study lie in directly assessing HCP perceptions of barriers and facilitators. It is ultimately up to each individual HCP to decide to use clozapine. Addressing the concerns of these HCPs will be advantageous in efforts to increase clozapine utilization. Additionally, to the authors' knowledge this is the first study to assess provider characteristics and knowledge of clozapine in relation to utilization rates.

The method of distribution was a major limitation of this study. This survey was distributed via national e-mail listservs; however, no listserv exists within the VA that targets all psychiatric providers. This study relied on the psychiatry chiefs and psychiatric pharmacists within each facility to further disseminate the survey, which could have led to lower response rates than what may be gathered via more direct contact methods. In addition, targeting psychiatric section chiefs and pharmacists may have introduced response bias. Another limitation to this study was the small number of responses. It is possible that this study was not adequately powered to detect significant differences in clozapine prescribing based on HCP characteristics or clozapine clinic availability. Further studies investigating the impact of provider characteristics on clozapine utilization are warranted.

#### CONCLUSION

Even though clozapine is an effective medication for TRS, providers underutilize it for a variety of reasons. Commonly identified barriers to prescribing in this study included frequent monitoring requirements, logistics of prescribing (including the REMS program and transportation for laboratory monitoring), pharmacotherapy preferences, and concern about the potential AEs. Facilitators identified in this study included implementation of clozapine clinics, having a specified contact point within the facility to assist with administrative responsibility, educational sessions, and the ability to utilize outside laboratories.

While some of these barriers and facilitators cannot be fully addressed without national policy change, individual facilities should make every effort to identify institution-specific concerns and address these. Clozapine clinic implementation and educational sessions appear to be reasonable considerations. This study did not identify any HCP characteristics that significantly impacted the likelihood of prescribing clozapine aside from self-rated comfort and familiarity with clozapine. However, further studies are needed to fully assess the impact of provider characteristics on clozapine utilization.

#### Author disclosures

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