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Title: Organizational Characteristics of High- and Low-Clozapine-Utilization Clinics in the Veterans Health Administration

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Objective: Treatment-resistance schizophrenia occurs in 20-30% of patients. Clozapine is the only medication proven effective for treatment-resistant schizophrenia. However, less than 25% of treatment-resistant schizophrenia patients receive clozapine in most settings. Therefore, this study was conducted to identify facilitators and barriers to clozapine use, to inform development of interventions to maximize appropriate clozapine-utilization.

Methods: Seventy semi-structured phone interviews were conducted with five high- and five low-utilization VA Medical Centers, from different US regions including urban and rural areas. Interviewees were key informants of clozapine processes, including mental health leadership, psychiatrists, clinical pharmacists and advanced practice nurses. Interviews were analyzed using an emergent thematic strategy to identify barriers and facilitators to clozapine prescribing.

Results: Key elements associated with high-utilization included integration of non-physician psychiatric providers and clear organizational processes and infrastructure for treatment of severe mental illness (e.g. clozapine clinics, larger mental health intensive case management services). Low-utilization was associated with lack of champions to support clozapine processes and limited-capacity care systems. Obstacles identified at both high- and low-utilization sites included complex time-consuming paperwork, reliance on few individuals to facilitate processes, and issues related to transportation for patients living far from care facilities.

Conclusions: Implementation efforts to organize, streamline and simplify clozapine processes, development of a multidisciplinary clozapine clinic, increasing the size and capacity of existing clinics, and provision of transportation are reasonable targets to increase clozapine utilization.

Schizophrenia is one of the most disabling disorders. Although effective treatment is available, 20-30% of patients fail to respond to at least two antipsychotic medications, and are deemed to have treatment-resistant schizophrenia.¹ Clozapine has been proved superior to other antipsychotics for treatment-resistant schizophrenia.²⁻⁴ Accordingly, evidence-based treatment-guidelines and Veterans Affairs (VA) policies agree that patients who do not respond to adequate trials of two antipsychotics should be offered clozapine.⁵⁻¹⁰ However, clozapine is associated with side effects including significant weight gain, diabetes and myocarditis.^{11,12} Clozapine is also subject to an FDA-mandated Risk Evaluation and Mitigation Strategy (REMS) program due to the risk of agranulocytosis. Monitoring requirements vary but many countries have similar requirements making this study relevant across healthcare systems. The FDA REMS program requires registration of the physician, patient and pharmacy, and frequent monitoring and reporting of white blood cell and absolute neutrophil counts (ANC), although the reporting of the ANC alone is now required.^{11,12} Thus, clozapine is both uniquely effective and uniquely inconvenient, leading to an imperative to use it as much as possible, combined with a “bother” factor that induces clinicians to avoid its use. Therefore, clozapine underutilization may persist on the clinician side, in part, due to the increased prescribing complexity compared with other antipsychotics. However, clozapine-utilization rates vary between facilities, suggesting it is possible to achieve higher clozapine-utilization rates despite these challenges.¹³⁻¹⁴

Because clozapine is prescribed for a small minority of patients most treatment-resistant schizophrenia patients receive less effective antipsychotics.¹³⁻¹⁶ Another concern is the substitution of clozapine with supra-therapeutic antipsychotic doses and polypharmacy of non-clozapine antipsychotics, strategies generally found to be less effective than clozapine.^{13,16,17,18,19} Thus, by under-using clozapine, the most vulnerable patients are being prescribed less effective treatment. It therefore seems worthwhile to consider how clozapine use might be increased, despite the known challenges.

While there is no consensus on what proportion of patients should be treated with clozapine, all treatment refractory patients should be offered clozapine unless there is an absolute contraindication (e.g. history of myocarditis or clozapine-induced agranulocytosis).²⁰ Since up to 30% of patients have treatment-resistant schizophrenia and recognizing that not all patients are appropriate candidates or willing to take clozapine, one could estimate clozapine-utilization should approach 20% of patients with schizophrenia. Indeed, one study reported 69% of patients with treatment-resistant schizophrenia, roughly 20% of all patients with schizophrenia, accepted clozapine treatment when offered. However, clozapine-utilization rates of less than 5% are reported in multiple settings.^{13,14,18-20} While the challenges of the clozapine REMS and the side effect profile undoubtedly contribute to low-utilization, nationwide VA data indicate some sites approach 20% utilization, despite these challenges.¹⁵ Thus, low-utilization rates may not lie solely in patient refusal or contraindications to clozapine.

Therefore, we conducted a qualitative study to identify facilitators and barriers to clozapine use in the VA, at sites with the highest- and lowest clozapine-utilization. This focus on outlier sites has the potential to help identify strategies that are both effective and at least moderately feasible, since some sites have already succeeded in adopting them.²¹⁻¹³ This in turn can help inform a feasible and effective strategy for implementing changes to improve clozapine-utilization.

METHODS

Conceptual Model: The Consolidated Framework for Implementation Research (CFIR) and an emergent thematic analysis strategy were used to inform our research and to develop interview guides and for high- and low-utilization sites.²⁴⁻²⁹ CFIR is composed of five domains: intervention characteristics, outer-setting, inner-setting, characteristics of individuals involved, and process

of implementation as well as 39 constructs and sub-constructs to identify and track barriers and facilitators to change in complex medical systems.^{27,28} Framing the research with CFIR assisted in designing and conducting a rigorous assessment of organizational characteristics of sites.²⁹

Study Sites: Using FY2013 VA prescribing data, facility-level clozapine-utilization rates were calculated for patients with schizophrenia or schizoaffective disorder receiving clozapine at each VA facility. The denominator was the total number of patients at the site with a diagnosis of schizophrenia or schizoaffective disorder (ICD-9 code 295.x), and the numerator was the proportion of these patients who received clozapine from a VA pharmacy during FY13. Using this definition, clozapine-utilization across the entire VA system was 4%. Five high- and 5 low-utilization sites were requested to participate. Sites with non-zero rates of utilization were contacted, as personnel at sites with zero-utilization might not be able to contribute useful information. Sites were generally of different sizes, geographic regions, etc. This was easier to accomplish with low-outliers due to the many sites fitting that description. Sites were not informed of their utilization status.

Key Informants: Purposeful and chain-referral sampling approaches were used to identify participants with expertise related to clozapine prescribing, policy and practice.^{30,31} The Chief of Psychiatry was contacted at each site to identify potential participants. Potential participants identified by the Chief were contacted to request their participation and to ask them to identify potential participants involved in local clozapine policies, processes and prescribing (chain-referral sampling). Chain referral sampling was also used to confirm interview subjects were considered experts on clozapine policy and practice by staff.^{32,33} Participants were divided into leadership figures and front-line clinicians. Leadership figures may not directly prescribe or manage clozapine, but are involved in creating, influencing or implementing policies or managing departments integral to clozapine processes (i.e. laboratory, information technology,

psychiatry and pharmacy). Front-line clinicians were directly responsible for prescribing or managing patients receiving clozapine (i.e. psychiatrists, advanced practice nurses, clinical pharmacists).

Interviews: Semi-structured telephone interviews were conducted between September 2014 and May 2015. Participants provided informed consent prior to the interview. Interview guides were informed by CFIR and relevant literature.^{27,28} Interviews focused on perceptions of clozapine risks and benefits, local and national clozapine policies and processes (formal and informal), departmental interfaces regarding clozapine-utilization, sources of clozapine policies and procedures, and patient perceptions of clozapine.

Data Analysis: Coding and analysis of interview transcripts was completed by experts in qualitative research methods (RE and MM) and experts in medicine and psychiatry with qualitative research experience (JG and AR). All coders conducted interviews. The codebook was developed using inductively-informed grounded thematic analysis.²⁴⁻²⁶ The finalized codebook identified broad themes relating to “domains” regarding clozapine beliefs, policies, practices and processes. Once the codebook was finalized, interrater consensus was reached through an iterative process with four interviews coded by all four team members. The remaining interviews were coded by one investigator except for two interviews coded by all four to ensure continued inter-rater reliability. Each investigator coded interviews from different sites and job roles. Next each facility was assigned to one investigator, who independently reviewed all coded interviews for that site and synthesized data into a profile of that site’s organizational structure, clozapine management policies and procedures, and beliefs related to clozapine. Thus interviewee data was triangulated so provider perceptions of individual and organizational structures and processes of care could be analyzed and contextualized within site and across sites. Quote tables containing representative quotes from sites were developed for each

domain. Finally, looking across site profiles, the team identified thematic domains that defined the differences between high- and low-utilization sites. All data were coded and analyzed using NVivo 10.

This study was approved by Edith Nourse Rogers Memorial Veterans Hospital, Bedford, Massachusetts Institutional Review Board.

RESULTS

Seventy interviews were conducted five sites in the top 10% for clozapine-utilization (> 8% of all patients with schizophrenia) and five sites with lower than median utilization (< 4%) (Tables 1&2).

Five thematic domains related to clozapine-utilization were identified. (Table 3) Domains were conceptualized based on potential to develop interventions unique to each domain. Each domain is discussed in detail below, with Table 4 providing representative quotes from each domain.

Transportation: The most pervasive issue was patients' needs and resources related to transportation for weekly visits and laboratory monitoring. Lack of reliable transportation was mentioned by low- and high-utilization sites, even at sites located in environments with adequate public transportation. Reasons cited included disorganized patients' inability to navigate public transit, patients too paranoid to ride public transit, and cost of transportation. Patients living far from care facilities were not considered clozapine candidates, regardless of clinical need, because of perceptions patients could not attend weekly visits. Sites with higher clozapine-utilization often had greater availability of transportation services (e.g. van to bring patients to appointments). Transportation services were often located within mental health intensive case management

(MHICM) services; while all sites had MHICM, more clozapine patients were enrolled in MHICM at high-utilization sites. However, even high-utilization sites struggled to provide clozapine for patients living far from care.

Capacity: Clozapine prescription requires multiple administrative processes including registration of physician, patient, and pharmacy, review of informed consent, and weekly visits. Thus, there must be adequate clinician availability to accommodate increased visit frequency and complete required paperwork, processes, monitoring and reporting. Low-utilization sites cited increased prescriber burden as a primary barrier to clozapine-utilization.

Both high- and low-utilization sites expressed concerns over capacity to accommodate increased prescribing burden associated with clozapine. Even among high-utilization sites, only three achieved clozapine prescribing rates above 10%. Low-utilization sites reported limited capacity prevented meaningful clozapine use. High-utilization sites often reported the clozapine clinic was functioning at or above capacity.

Multi-disciplinary teams: From analysis of capacity it was clear that a related but independent thematic domain was the issue of multi-disciplinary teams. In this theme data were captured and analyzed on the use of non-physician providers as well as the gaps and strains at sites that relied solely on physicians.

High-utilization sites addressed capacity issues in part through integration of non-physician staff into the clozapine team. Advanced practice nurses and clinical pharmacists completed clozapine related tasks (e.g. registration, ordering and monitoring laboratories, evaluating side). Low-utilization sites relied on physicians to complete these tasks. Low-utilization sites expressed the

need for more clinical pharmacists in mental health care in general, but especially to facilitate the clozapine use.

Care Coordination: While all providers are required to follow the REMS monitoring parameters, the process of care was significantly different at high- and low-utilization sites. For example, high-utilization sites often had a clearly defined point person or clinic system to organize clozapine care. Multiple entities, including the clozapine registry, psychiatry, laboratory, and pharmacy, all play a role in clozapine prescription, necessitating considerable coordination among departments and often with the patient or patient's family. In addition, these steps must happen in a specific sequence within narrow timelines. High-utilization sites addressed these issues through development of clozapine clinics to coordinate care. Clozapine clinics were largely defined by the presence of multi-disciplinary teams, adequate time to accommodate increased visit frequency and dedicated support staff. Clozapine clinics were seen as integral to providing clozapine care, with high-utilization sites unable to imagine providing clozapine without a clozapine clinic.

While having a clozapine clinic was beneficial, it still limited patient access. Once the capacity of a clinic was reached, a decision would need to be made to expand the clinic, often by adding an additional session requiring allocation of resources or having additional patients treated outside the clinic, meaning a much greater burden for physicians.

Maintaining adequate psychiatric staff is an ongoing issue for many facilities, but particularly for low-utilization sites. Frequent staff turnover was reported by some as a barrier to the continuity of care necessary to ensure coordination of clozapine treatment.

Another barrier was the accumulation of many small process delays, which added up to bigger delays for patients. At some facilities a weekly clozapine visit was an all day affair, due to delays

before blood draws, processing laboratory results, clinic visits and dispensing the prescription or limited access to transportation. Lack of coordination made it difficult to accommodate patients who lived far away and had difficulty getting to the medical facility on clozapine clinic days. High-utilization sites were more flexible in terms of scheduling outside of clinic hours, offering walk in hours or same day appointments.

Overreliance on a Few: This domain pinpoints a systems and processes issue noted at high- and low-utilization sites. While having committed clozapine champions was essential, it was not sufficient to ensure access to clozapine. Many sites relied on 1-2 clozapine champions. However, overreliance on too few people left sites vulnerable when staff were away due to illness, annual leave, or retirement. Even high-utilization sites were vulnerable in this way, though they usually relied on 3-4 people, rather than one or two as was the case at low-utilization sites.

DISCUSSION

We interviewed key informants at high- and low-clozapine-utilization facilities, to understand what specific factors prevented or facilitated clozapine-utilization. Via triangulation of key informant data within and across sites, we identified barriers that actually exist versus barriers that are only perceived. Through this analysis we found that high-utilization sites had commonalities, among them providing access to transportation, having sufficient capacity to enroll patients, utilization of multidisciplinary teams including non-physician providers, better coordination of care, and creation of systems to reduce reliance on too few individuals.

These findings suggest that clozapine clinics staffed by a multidisciplinary team, with adequate time to accommodate increased visit frequency and prescribing burden of clozapine, could improve access to evidence-based care for patients with treatment-resistant schizophrenia. This would include development of clozapine clinics at sites without one, and expansion of clozapine

clinics where one already exists. Clearly defined clinical structure and staff roles may improve the effectiveness of clinics.³⁴ In addition, this study suggests that the straight forward act of providing transportation for patients to and from clozapine appointments has the potential to greatly expand the pool of patients who would be able to receive this potentially life-changing medication. Home visits have been a successful tool for some clozapine programs and could also address this issue.²⁰

There have been other similar studies using qualitative interviews of outlier sites to gain insight into how to organize care to achieve the best results.^{22,23} Some of our findings echo earlier studies. In particular, previous studies reported the importance of adequate staffing and effective integration of non-physicians into patient care are key ingredients in the success of programs as diverse as anticoagulation clinics and hospital teams caring for patients with acute coronary syndromes.^{22,23} In a study of clozapine patients, multi-disciplinary teams were associated with improved medical monitoring.³⁵ Thus, a more effective use of multidisciplinary teams could improve access and outcomes across a multitude of settings.

One of the strengths of this study is the focus on strategies that work well within the current system and rules, rather than ideas that rely on changing those rules, which may not be possible.²⁰ While all of the changes or initiatives suggested by this study may be feasible (i.e. allowed under the rules), some of these changes would require commitment of resources. However, data suggest cost-savings with incremental increases in clozapine-utilization. Thus increased outpatient costs may be outweighed by cost-savings from reduced inpatient hospitalizations.^{36,37} In a companion study published in this issue of Psychiatric Services, we demonstrated incremental increases in clozapine-utilization could result in substantial cost-savings, primarily through decreased use of inpatient admissions. Thus, implementation of

interventions derived from this study could more than pay for themselves, if they succeed in increasing clozapine-utilization for treatment-resistant schizophrenia.

Patients who live far from clinics are a unique and difficult group to reach, and are not well served even by the highest-utilization sites studied. This means that a fairly large subset of patients essentially has no access to clozapine. Some of the solutions discussed above would help to reach this population as well. The most feasible solution would involve providing transportation or home-based care to patients who live far from clinics, which would admittedly be more expensive and laborious than providing these services to patients living closer. Some other solutions, like increased use of outside laboratories or point-of-care testing for blood count monitoring, would be difficult to implement within VA, because they may require national policy change. However, point-of-care testing should be considered as clozapine patients report it to be more convenient and less painful than traditional venipuncture.³⁸

This study does have some limitations. First, the VA limits clozapine prescribing to psychiatrists and neurologists. Thus some obstacles encountered in the VA may not be an issue for other care settings. Second, telephone interviews may be suboptimal in some cases, in part because of missing non-verbal cues and difficulty developing rapport. However, many of the interviews were much longer than anticipated, suggesting that participants felt comfortable sharing their experiences. Additionally, surveys of clinicians have reported similar findings.³⁹ Thirdly, what we deemed high-utilization may not reflect optimal-utilization as this optimal rate has not been defined. Lastly, VA sites may not be representative of other healthcare systems. However, the side effects, FDA REMS requirements and low-utilization for clozapine are the same inside and outside VA, suggesting the challenges that need to be overcome in other systems are similar to those faced by the sites we studied. This is true even in light of the changes to the clozapine REMS program, which still requires registration of physician, patient and pharmacies, frequent

monitoring, and limitations on days supplied. These interventions may prove useful in other countries with similar monitoring requirements.

In a separate study we found some relatively straightforward changes are associated with higher clozapine-utilization within the VA. Among these are having a dedicated clozapine clinic, ensuring the clinic has sufficient capacity to accommodate all patients with TRS and adequate levels of staffing in the clinic by non-physicians including RNs and pharmacists and providing transportation for appointments for clozapine patient. While all of these strategies are allowable under VA rules and regulations, and are currently done at some sites, they are not without cost. It is hoped that the present study can provide an impetus to make these relatively straightforward, if not inexpensive changes. Extrapolating from our findings here, an average sized VA site (managing 700 patients with schizophrenia) could expect to have a population of 140 patients with TRS. Increasing the proportion of patients treated with clozapine from 20% to 40% would save the facility greater than \$625,000 in the first year. It is difficult to imagine the cost of implementing our recommendations could approach this figure. Thus, even a modest increase in clozapine-utilization, achieved at a very high cost, and could still result in a net cost savings for VA.

CONCLUSIONS

Using qualitative research methods, we examined differences between VA sites that use clozapine at the highest and lowest rates. We found that a number of strategies already pursued by high-outlier sites would be feasible to implement in a broad variety of settings. These strategies included starting a clozapine clinic where none exists, ensuring that clozapine clinics have sufficient capacity to handle the number of patients for whom clozapine is indicated, providing transportation to all patients receiving clozapine and ensuring adequate staffing, and integration of non-physician clinicians within clozapine clinics. While other strategies could also

be considered, in many cases they would require national-level policy changes that could prove challenging to pursue. Used in combination, and pursued diligently, the more feasible strategies identified in this study would likely be sufficient to reach the goal of providing clozapine to all appropriate patients.

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References:

1. Hasan A, Falkai P, Wobrock T, et al: World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, part 1: update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. World Journal of Biologic Psychiatry 13:318-378, 2012
2. Kane J, Honigfeld G, Singer J, et al: Clozapine for the treatment-resistant schizophrenic: A double-blind comparison with chlorpromazine. Archives of General Psychiatry 45:789-796, 1988
3. Meltzer HY, Alphas L, Green AI, et al: Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). Archives of General Psychiatry. 60:82-91, 2003
4. Volavka J, Czobor P, Nolan K, et al: Overt aggression and psychotic symptoms in patients with schizophrenia treated with clozapine, olanzapine, risperidone, or haloperidol. Journal of Clinical Psychopharmacology 24:225-228, 2004
5. VA Pharmacy Benefits Management. Recommendations for antipsychotic selection in schizophrenia and schizoaffective disorders. June 2012. Available at <http://www.pbm.va.gov/clinicalguidance/clinicalrecommendations.asp>. Accessed September 21, 2015
6. Veterans Health Administration Mental Health Handbook. 1160.02. December 23, 2008.
7. American Psychiatric Association: Practice guideline for the treatment of patients with schizophrenia, second addition. American Journal of Psychiatry 161:1-56, 2004
8. Kreyenbuhl J, Buchanan RW, Dickerson FB, et al: The schizophrenia patient outcomes research team (PORT): Updated treatment recommendations 2009. Schizophrenia Bulletin 36(1):94-103, 2010

9. National Institute of Health and Clinical Excellence. Core interventions in the treatment and management of schizophrenia in primary and secondary care (CG82). March 2009. Accessed 9/21/2015 at <http://guidance.nice.org.uk/CG82>.
10. Moore TA, Buchanan RW, Buckley PF, et al: The Texas medication algorithm for schizophrenia: 2006 update. *Journal of Clinical Psychiatry* 68:983-990, 2007
11. Clozaril® [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation, 2015
12. Clozaril® [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation, 2014
13. Gören JL, Meterko M, Williams S, et al: Antipsychotic prescribing pathways, polypharmacy, and clozapine use in treatment of schizophrenia. *Psychiatric Services* 64:527-533, 2013
14. Kelly DL, Dixon LB, Kreyenbuhl JA, et al: Clozapine utilization and outcomes by race in a public mental health system: 1994-2000. *Journal of Clinical Psychiatry* 67:1404-1411, 2006
15. Veterans Affairs National Psychosis Registry. Ann Arbor, MI 2009
16. Taylor DM, Young C, Paton C: Prior antipsychotic prescribing in patients currently receiving clozapine: a case note review. *Journal of Clinical Psychiatry* 64:30-34, 2003
17. Tsutsumi C, Uchida H, Suzuki T, et al: The evolution of antipsychotic switch and polypharmacy in natural practice. *Schizophrenia Research* 130:40-46, 2011
18. Harrison J, Janlov M, Wheeler AJ: Patterns of clozapine prescribing in a mental health service in New Zealand. *Pharmacy World Science* 32:503-511, 2010
19. Moore TA, Covell NH, Essock SM, Miller AL: Real-world antipsychotic treatment practices. *Psychiatric Clinics North Am* 30(3):401-416, 2007
20. Beck K, McCutcheon R, Bloomfield MAP, Gaughran F, Reis Marques T, MacCabe J, Selvaraj S, Taylor D, Howes OD. The practical management of refractory schizophrenia-the Maudsley Team Review and Assessment Team Service approach. *Acta Psychiatrica Scandinavica* 2014;130:427-438.

21. Bradley EH, Curry LA, Ramanadhan S, Rowe L, Nembhard IM, Krumholz HM: Research in action: using positive deviance to improve quality of health care. *Implementation Science* 4:25, 2009
22. Curry LA, Spatz E, Cherlin E, et al: What distinguishes top-performing hospitals in acute myocardial infarction mortality rates? A qualitative study. *Annals of Internal Medicine* 154:384-390, 2011
23. Rose AJ, Petrakis BA, Callahan P, et al: Organizational characteristics of high- and low-performing anticoagulation clinics in the Veterans Health Administration. *Health Services Research* 47:1541-1560, 2012
24. Aronson J: A pragmatic view of thematic analysis. *Qualitative Report* 2(1):1-3, 1995
Available from: <http://nsuworks.nova.edu/tqr/vol2/iss1/3>
25. Boyatzis RE: Transforming qualitative information: thematic analyses and code development. Thousand Oaks, London & New Delhi, Sage Publications 1998.
26. Fereday J, Muir-Cochrane E: Demonstrating rigor using thematic analysis: A hybrid approach of inductive and deductive coding and theme development. *International Journal of Qualitative Methods* 5(1):80-92, 2008
27. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC: Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. *Implementation Science* 4:50, 2009
28. Damschroder LJ, Lowery JC: Evaluation of a large-scale weight management program using the consolidated framework for implementation research (CFIR). *Implementation Science* 8(1):51, 2013
29. Stetler CB, Legro MW, Wallace CM, et al: The role of formative evaluation in implementation research and the QUERI experience. *Journal of General Internal Medicine* 21(S2):S1-S8, 2006

30. Bernard HR: Research Methods In Anthropology: Qualitative and Quantitative Approaches, 4th Edition. Lanham, MD, AltaMira Press, 2006
31. Patton MQ: Qualitative Research and Evaluation Methods, 3rd edition. Thousand Oaks, CA, Sage Publications, 2002
32. Christopoulos D: Peer Esteem Snowballing: A methodology for expert surveys. Brussels, Eurostat Conference for the New Techniques and Technologies for statistics, Brussels, p171-179, 2010.
33. Penrod J, Preston DB, Cain RE, Starks MT: A Discussion of Chain Referral As a Method of Sampling Hard-to-Reach Populations. *Journal of Transcultural Nursing* 14(2):100-107, 2003
34. Sutton J, Family H, Scott JA, Taylor DA. The influence of organizational climate on care of patients with schizophrenia: a qualitative analysis of health care professionals' views. *International Journal of Clinical Pharmacy* 2016; [Epub ahead of print] Jan 21
35. Gage H, Family H, Murphy F, Williams P, Sutton J, Taylor D. Comparison of sole nurse and team-delivered community clozapine services for people with treatment-resistant schizophrenia. *J Advanced Nursing* 71(3):547-558:2014
36. Oh P, Iskedjian M, Addis A, Lanctot K, Einarson TR. Pharmacoeconomic evaluation of clozapine in treatment-resistant schizophrenia: a cost-utility analysis. *Canadian Journal of Clinical Pharmacology* 8(4):199-206, 2001
37. Stroup TS, Gerhard T, Crystal S, Huang Cm Olfson M: Comparative effectiveness of clozapine and standard antipsychotic treatment in adults with schizophrenia/ *American Journal of Psychiatry* 2015 Nov 6 [Epub ahead of print] Available at <http://ajp.psychiatryonline.org/doi/abs/10.1176/appi.ajp.2015.15030332>
38. Nielsen J, Thide D, Stenager E, Anderson KO, Sondrup U, Hansen TN, Munk AM, Lykkegaard S, Gosviq A, Pterov I, Le Quach P. Hematological clozapine monitoring with a

point-of –care device: a randomized cross-over trial. *European Neuropsychopharmacology* 2012;22(6):401-405.

39. Gee S, Vergunst F, Howes O, Taylor D. Practitioner attitudes to clozapine initiation. *Acta Psychiatrica Scandinavica* 2014;130(1):16-24, 2014

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Table 1: Key informants by position and number of interviews

Interviews	N
Mental health leadership	11
Pharmacy leadership	5
Psychiatrist	22
Clinical pharmacist specialist	12
Advanced practice nurse	4
Dispensing pharmacist	9
Laboratory staff	3
Other*	4
Total interviews	70

*RN, clinic coordinator, medical technologist, social worker

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Table 2: Site Characteristics

Facility	High /Low	Clozapine Utilization Rate*	Patients with Schizophrenia	Region	Number of Interviews	Clozapine Clinic	Multi-disciplinary	Significant Transport Support
A	High	10%	590	Midwest	8	Yes	Yes	Yes
B	High	8%	1080	Northeast	7	Yes	Yes	Yes
C	High	15%	290	Midwest	12	Yes	Yes	No
D	High	10%	450	West	7	Yes	Yes	Yes
E	High	9%	660	Southeast	4	Yes	Yes	No
F	Low	2%	550	Northeast	6	Yes	Yes	No
G	Low	4%	1170	West	9	Limited [#]	Yes	No
H	Low	1%	450	Southeast	8	No	No	Yes
I	Low	2%	1510	Southeast	6	No	No	No
J	Low	3%	1830	Midwest	3	No	No	No

*Percentage of patients with schizophrenia receiving clozapine in 2013

[#]Clozapine clinic was available but given limited capacity and rigidity regarding seeing patients outside of set clozapine clinic hours many clozapine patients were still treated by individual clinicians outside the clinic

Table 3: Thematic Domains and Definitions

Thematic Domain	Definition
Transportation	A multifaceted issue related to the need for transportation to frequent medical visits. The domain was directly related to the distance to and from medical centers as well as the distance between community based outpatient clinics and major medical centers.
Capacity	Multiple reasons account for sites' ability, or lack thereof, to prescribe clozapine. The domain was directly related to staffing and scheduling issues.
Multidisciplinary care teams	Availability and incorporation of non-physician staff impacted sites' ability to initiate patients on clozapine treatment as well as to prescribe clozapine for patients maintained on clozapine.
Care coordination	Oversight of clozapine prescribing process was a key component in sites' ability to use clozapine. The domain was related to champions, clear processes and ready identification of people "in charge" of clozapine.
Over-reliance on a few	Utilization of only a few people to facilitate clozapine processes left systems vulnerable when key personnel were away or unavailable.

Table 4: Representative Quotes From Each Domain

High Utilization Site	Low Utilization Site
Transportation	
<p><u>Site D: Clinical Pharmacist</u></p> <p>[Intensive case management staff] are either able to go and get them and bring them into clinic, or if there are residing out in an assisted living facility, we can coordinate with the facility to bring them in. All our [intensive case management] veterans do have a lot more supports in place to help them get into Clozaril Clinic without difficulty.</p>	<p><u>Site I: Psychiatrist</u></p> <p>[It's true that] not that many people like getting blood draws... [But] the frequent appointments, the distance, a lot of people come from an hour away and just the logistics of coming in for frequent monitoring sometimes is an issue. The side-effects doesn't usually seem to be the factor.</p>
Capacity	
<p><u>Site B: Pharmacist</u></p> <p>We had to tell inpatient team to stop referring to clozapine... because we were at capacity. So there were these two solutions – give us [staffing for] another day or we'll have to start discharging patients.</p>	<p><u>Site I: Mental Health Leadership</u></p> <p>People [staff] have full schedules; we are a huge facility and for a certain time over the past two years we grew up faster than we were able to record people and so there was time when people [didn't] have a next available appointment for another three or four months and I think availability and accessibility is definitely a factor and this is why [we are developing a] Clozaril Clinic, trying to diffuse... that ... barrier.</p>

<p><u>Site C: Psychiatrist</u></p> <p>I have a Clozapine Clinic, on Tuesday morning and then, I have...quite a bit of overflow on Mondays and I do it as a walk-in clinic.</p>	<p><u>Site H: Nurse Practitioner Intensive Case Management</u></p> <p>I think it's a very effective medication. In fact, I say when nothing else works, clozapine definitely will work, and it does keep 'em out of the hospital. I don't know that we have the staff that can monitor the face-to-face follow-up that is really needed.</p>
<p>Multi-Disciplinary Teams</p>	
<p><u>Site D: Clinical Pharmacist</u></p> <p>We have a number of different people in the clinic...we have one psychiatrist, Dr. X who is Head Psychiatrist over at the clinic. It's managed by a nurse, who keeps tabs on the patients who are supposed to be coming in for that day and prints us out a list of who those patients are. I serve as a provider in the clinic and we have another psychiatrist who serves as a provider and then when we have residents, we have them serve as providers for clinic. We meet together in the morning and we're given the list of patients that we'll be seeing for that day and then it's kind of an</p>	<p><u>Site G: Psychiatrist</u></p> <p>Once we had a clinical pharmacist on board it, made managing patients on clozapine...and getting new starts much, much easier... I basically would recommend that every mental health, outpatient clinic, have a [mental health] pharmacist assigned to them to help manage [clozapine] patients.</p>

<p>open clinic so the patients show up at their leisure. ...if I were to see a patient because I cannot write Clozaril orders, I would see the patient, do my evaluation and assessment and then I would [discuss the patient] with our chief psychiatrist and make my recommendations and then...[Dr. X] decides whether to take our recommendations or not and then puts in the orders for the patients.</p>	
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Care Coordination

<p><u>Site C: Clinical Pharmacist</u></p> <p>I think that it would be helpful to have a specific Clozapine clinic with providers who are more familiar with [clozapine]...[and people] who have the time to sit down with the patient and arrange for all of their lab appointments and their med renewals and everything...have somebody who focuses on that because it is time-consuming. There's a lot of paperwork and stuff that goes along with it.</p>	<p><u>Site F: Social Worker</u></p> <p>I don't know that I could treat more patients...who are on Clozapine because it's so labor-intensive... I have to worry where they are and track them down and make sure they come in. Has a blood test been ordered? Are their appointments in the computer? Is there somebody here to draw their blood? I mean, there [are] so many details that have to be seen to...it just doesn't all happen by itself.</p>
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<p><u>Site A: Pharmacist</u></p> <p>It worries me when ... there's not somebody coordinating it...if we didn't have our clinic downstairs I don't know how any of these guys could stay on track. I really don't know how that would work. So if there are VAs that don't [have a clozapine clinic], I can't imagine how they're doing [prescribing clozapine]. But maybe it's a requirement. Like I said... I'm not sure.</p>	<p><u>Site G: Psychiatrist</u></p> <p>Monitoring patients new to clozapine is kind of hard to do, especially when you're busy with a whole bunch of other patients. Checking to make [sure] their labs are okay and then writing the prescription every single week, I don't feel like I could have many patients on that kind of regime.</p>
<p>Over-Reliance on a Few</p>	
<p><u>Site E: Pharmacist</u></p> <p>[The clinical pharmacist] is trying to do everything good and smooth. ..she does a phenomenal job. She goes out of her way, she is always accessible. She leaves her phone number, even [when] she was out of country... so I can't really tell you...how smooth it [would go] without her.</p>	<p><u>Site G: Clinical Pharmacist</u></p> <p>[The other staff] just wait until I get back [from vacation]...There've been a couple of times when it's been delayed...several days, even up to a week.</p>
<p><u>Site A: Psychiatrist</u></p> <p>He does [play an integral part]. If he's not there and the nurse...[isn't] there I can sometimes get in his drawer and figure out where things are or go through the process</p>	

that we use [to prescribe clozapine].	
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