mhc
MENTAL HEALTH CLINICIAN

ORIGINAL RESEARCH Open Access

Comparison of clozapine monitoring and adverse event management in a psychiatrist-only and a clinical pharmacist-psychiatrist collaborative clinic

Samantha Maryan, PharmD[1]; Michelle Harms, PharmD, BCPP[2]; Erin McAllister, PharmD, BCPP[3]; Beth DeJongh, PharmD, BCPS, BCPP[4]

How to cite: Maryan S, Harms M, McAllister E, DeJongh B. Comparison of clozapine monitoring and adverse event management in a psychiatrist-only and a clinical pharmacist-psychiatrist collaborative clinic. Ment Health Clin [Internet]. 2019;9(2):70-5. DOI: 10.9740/mhc.2019.03.070.

Abstract

Introduction: In an effort to establish clinical support for providers prescribing clozapine and to help reverse the national decline in clozapine utilization, a clinical pharmacist began seeing half the clozapine clinic patients, preceding the psychiatrist, at this facility in July 2017. The other half of the clozapine clinic patients continued being seen by the psychiatrist only. The purpose was to determine the impact of the pharmacist on clozapine management and identify barriers to clozapine use to potentially increase its utilization.

Methods: Baseline data (clozapine dose, number of antipsychotics and other psychotropics, A1c, lipids, pulse, body mass index, weight, blood pressure, and number of medications for adverse effects) were collected via chart review from the first clinic visit and each follow-up visit. A provider survey was used to identify barriers and solutions to prescribing clozapine.

Results: There were no statistically significant differences from baseline in patient outcomes between the collaborative and psychiatrist-only group. In the prepharmacist to postpharmacist analysis, there was a decrease in number of antipsychotics (−0.27 ± 0.65), number of other psychotropics (−0.18 ± 0.41), A1c (−0.04% ± 0.25%), clozapine dose (−7.96 mg ± 19.58 mg), and total cholesterol (−15.73 mg/dL ± 42.31 mg/dL). There were more pharmacologic (71 vs 19) and nonpharmacologic (154 vs 3) interventions documented in the collaborative group compared to the psychiatrist-only group. Eleven providers (69%) completed the survey. Providers' perception of patient refusal of monitoring was the barrier that received the most responses (54%). A pharmacist seeing every clozapine clinic patient was the solution that received the most responses (90%).

Discussion: Trends were seen for decreasing the number of antipsychotics, other psychotropics, A1c, and total cholesterol as well as an increased number of nonpharmacologic and pharmacologic interventions documented in the collaborative group. Providers identified that pharmacists seeing every clozapine clinic patient would be a solution to clozapine underutilization, which demonstrates the perceived value of pharmacist involvement.

Keywords: clozapine clinic, pharmacist intervention, pharmacist monitoring, clozapine underutilization

[1] Postgraduate Year 1 Pharmacy Resident, Clement J. Zablocki Veterans Affairs Medical Center, Milwaukee, Wisconsin, ORCID: https://orcid.org/0000-0002-9291-4250; [2] Mental Health Clinical Pharmacy Specialist, Clement J. Zablocki Veterans Affairs Medical Center, Milwaukee, Wisconsin, ORCID: https://orcid.org/0000-0002-4915-6810; [3] Mental Health Clinical Pharmacy Specialist, Clement J. Zablocki Veterans Affairs Medical Center, Milwaukee, Wisconsin, ORCID: https://orcid.org/0000-0002-2452-3282; [4] (Corresponding author) Associate Professor of Pharmacy Practice, Concordia University, Wisconsin School of Pharmacy, Mequon, Wisconsin, beth.dejongh@cuw.edu, ORCID: https://orcid.org/0000-0002-0964-3788

Disclosures: There are no actual or potential conflicts of interest by any authors of this article.

Introduction

Clozapine utilization continues to decline nationally, despite documented evidence endorsing its use as the gold standard in treatment refractory schizophrenia.[1] About 30% of patients with schizophrenia have treatment-resistant symptoms; however, only a small percentage of these patients are prescribed clozapine.[2-5] A study by Stroup et al[6] found that clozapine was only utilized in 5.5% of patients with treatment-resistant schizophrenia across 45 states. Clozapine is the only antipsychotic with an indication from the US Food and Drug Administration for treatment-resistant schizophrenia and is considered the medication of choice for patients without a satisfactory response to standard medication treatment due to its efficacy in controlling symptoms.[7-10] Several guidelines support clozapine use for treatment-resistant schizophrenia, and it is typically recommended to trial clozapine in patients whose mental illness has had an inadequate, partial, or no response after trying at least 2 different antipsychotics at maximally tolerated therapeutic doses with at least 1 trial being a second-generation antipsychotic.[11-13]

Potential barriers to clozapine use include its significant adverse effect (AE) profile, clinicians' perception of poor patient adherence, and the clozapine risk evaluation and mitigation strategies program requirements.[14,15] Common AEs include fatigue, dizziness, weight gain, hypersalivation, dry mouth, hypotension, nausea, and constipation. More severe AEs that merit black box warnings from the US Food and Drug Administration include the risk for severe neutropenia, seizures, myocarditis, cardiomyopathy, orthostatic hypotension, bradycardia, and syncope as well as increased mortality in elderly patients with dementia-related psychosis.[16] Although these potential AEs are concerning, providers tend to overestimate patient discontent with clozapine.[17-19] There are discrepancies between mental health (MH) providers' beliefs and what patients actually report in regard to displeasure with the required monitoring and AEs. Clinicians tend to overestimate the prevalence of some AEs, such as sedation and muscle stiffness, while underestimating others, such as sialorrhea. Clinicians also tend to overestimate patient dissatisfaction with the required blood draws for AE monitoring. A study by Taylor et al[20] found almost 90% of patients preferred clozapine over changing to another antipsychotic, and 86% reported feeling better on clozapine. In regard to the barriers to clozapine use, less than 30% of patients listed frequent blood draws and only 1.6% listed blood draws as a motive to discontinue clozapine. Shedding light on these discrepancies and including a pharmacist on the team to aid in AE management and laboratory monitoring could be a solution to clozapine underutilization.[21]

The clozapine clinic at the Clement J. Zablocki Veterans Affairs Medical Center (ZVAMC) was historically run by attending psychiatrists only. A collaborative clozapine clinic was established in July 2017 in an attempt to improve clozapine utilization and help manage patients taking clozapine. The purpose of this quality-assurance project was to determine the impact of a clinical MH pharmacist on clozapine management and identify barriers to clozapine prescribing to potentially increase its utilization.

Methods

A clinical MH pharmacist began seeing half of the clozapine clinic patients, directly preceding the psychiatrist, to help with AE management and laboratory monitoring. The pharmacist only practices at the ZVAMC on Wednesdays and Fridays and, therefore, only worked with patients who attended the clozapine clinic held on Wednesdays. Those not seen by the pharmacist continued to be evaluated by the psychiatrist only during the Thursday clozapine clinic. The patients were consistently seen in the same clinic and did not switch between the collaborative and psychiatrist-only clinic. All patients in the clozapine clinics were included in this project.

A prospective chart review was performed from July 1, 2017, through February 28, 2018, using a computerized patient record system to identify patients 18 years and older who were prescribed clozapine. The primary outcome was to compare interventions and safety outcomes of recommended monitoring and AE management of patients prescribed clozapine in the psychiatrist-only and psychiatrist-pharmacist collaborative clinic as well as to compare prepharmacist to postpharmacist intervention within the collaborative clinic. The secondary outcome was to discover the barriers to clozapine use at the ZVAMC and potential solutions through distribution and assessment of a MH provider survey.

Baseline data were collected from the first clinic visit within this time frame and were obtained after each follow-up visit. The following data were collected: patient demographics, clozapine dose, number of antipsychotics and other psychotropic medications prescribed, metabolic parameters (weight, A1c, total cholesterol [TC], low density lipoprotein [LDL], high density lipoprotein [HDL], triglycerides, blood pressure [BP], body mass index [BMI]), pharmacologic interventions (medication changes), nonpharmacologic interventions (specific diet and exercise recommendations, nonpharmacologic AE management), and safety measures (AE management, clozapine discontinuation rate and reason, number of MH-related emergency visits and hospitalizations). The pharmacist used the Glasgow Antipsychotic Side-effects Scale for Clozapine

TABLE 1: Example of the paper-based provider survey

Possible Answers	Votes	Percent
1. Which of the following barriers prevent you from prescribing clozapine to patients with treatment resistant schizophrenia? Select all that apply.		
Patient refusal about obtaining baseline blood tests	4	36.36
Patient refusal about required regular blood monitoring	6	54.54
Burden of ANC collection and reporting to pharmacy in a timely manner	4	36.36
Patient concerns about tolerability/side effects	4	36.36
Provider concerns about tolerability/side effects	4	36.36
Lack of knowledge on how to manage side effects if they arise	3	27.27
Lack of familiarity with clozapine clinic and how to consult	2	18.18
Process of registering in REMS program (administrative responsibilities)	0	0
Lack of educational written materials to give to patients	2	18.18
Need for hospital admission	4	36.36
Lack of experience prescribing clozapine	5	45.45
Lack of familiarity with guidelines related to clozapine prescribing	2	18.18
Other	3	27.27
2. Which of the following potential interventions would increase your likelihood of prescribing clozapine for a patient with treatment-resistant schizophrenia? Select all that apply.		
In-service presentations for continued education on clozapine	8	72.72
Webinar or video training on clozapine that could be completed on own time	0	0
Additional administrative support with REMS registry and clozapine initiation	4	36.36
Pharmacist seeing every patient, in conjunction with psychiatrist, to help with side effect management and lab monitoring	10	90.90
Other	0	0

ANC = absolute neutrophil count; REMS = risk evaluation and mitigation strategies.

score to assess the severity of AEs related to clozapine.[22] The psychiatrist did not utilize this tool.

An anonymous paper-based survey was distributed to 16 psychiatrists assessing the barriers to clozapine use and potential solutions (Table 1). The survey was administered 1 time during an in-person provider meeting and once via email. The survey was considered exempt by the institutional review board. Providers were asked to return completed surveys to a designated mailbox. Only 1 of the psychiatrists practices in the clozapine clinic.

TABLE 2: Patient demographics of the 2 groups in the study

	Collaborative Clinic (n = 11)	Psychiatrist Only (n = 11)	*P* Value
	Mean ± SD		
Average age, y	53.6 ± 12.4	59.6 ± 13.6	.32708
	Percent		
Male	81.8	100	.4902
White	81.8	63.6	.50926
African American	9.1	27.3	.50926
Hispanic	9.1	0	.50926
American Indian	0	9.1	.50926
Smoker	54.5	45.5	.7414
Diabetes	81.8	45.5	.15854
Hypertension	36.4	54.5	.4902
Hyperlipidemia	81.8	72.7	.7414

The Mann-Whitney *U* test via statistical package for the social sciences version 24 was utilized for the statistical analysis with a *P* value $<.05$ considered statistically significant. The ZVAMC Institutional Review Board considered this project exempt from approval because it was conducted for quality improvement purposes.

Results

Eleven patients were seen in the collaborative clinic (104 pharmacist visits), and 11 were seen in the psychiatrist-only clinic (54 psychiatrist visits; $P<.01$). Baseline demographics were similar between the 2 groups, but the collaborative clinic had more women, less racial diversity, and more patients with diabetes (Table 2). There were no statistically significant differences in the data collected at baseline between the 2 groups of patients other than higher pulse in the collaborative group ($P=.02$; Table 3).

There were no statistically significant differences in the patient outcomes (A1c, BMI, weight, TC, LDL, HDL, triglycerides, BP, pulse, number of antipsychotics, number of psychotropics, number of medications for clozapine AEs, and clozapine dose) from baseline to end point between the collaborative group and the psychiatrist-only group (n = 22) or in the prepharmacist to postpharmacist analysis (n = 11). In the prepharmacist to postpharmacist analysis of the collaborative group, there was a decrease in the number of antipsychotics (-0.27 ± 0.65), number of other psychotropics

TABLE 3: Medication and metabolic parameter changes from baseline

	Collaborative Clinic (104 visits)		Psychiatrist Only (54 visits)				
	Mean ± SD				*P* Value		
Average	Baseline	Change From Baseline	Baseline	Change From Baseline	Baseline (n = 22)	Change From Baseline (n = 22)	Prepharmacist to Postpharmacist (n = 11)
No. of antipsychotics	1.64 ± 0.81	−0.27 ± 0.65	1.55 ± 0.52	−0.09 ± 0.30	1	.70	.47
No. of other psychotropics	1.55 ± 1.63	−0.18 ± 0.41	1.18 ± 1.08	0.09 ± 0.70	.74	.52	.87
A1c, %	5.71 ± 0.66	−0.04 ± 0.25	6.17 ± 0.93	0.05 ± 0.31	.58	.40	.74
BMI, kg/m^2	31.15 ± 4.83	1.29 ± 2.19	30.94 ± 6.48	0.47 ± 2.14	.79	.08	.50
Weight, kg	99.65 ± 19.78	3.2 ± .14	99.03 ± 26.45	1.05 ± 5.18	.94	.19	.69
TC, mg/dL	181.64 ± 40.20	−15.73 ± 42.31	166.64 ± 36.40	−2.18 ± 13.97	.37	.85	.41
LDL, mg/dL	100.73 ± 30.40	−6.64 ± 37.31	87 ± 30.20	0.36 ± 6.50	.29	.85	.45
HDL, mg/dL	39.36 ± 10.60	−2.27 ± 7.86	49.09 ± 18.10	−3.45 ± 8.26	.14	.80	.66
TG, mg/dL	281.27 ± 189.10	4.55 ± 199.83	215.36 ± 190.20	5.09 ± 30.02	.21	.75	.84
BP, mmHg	121/79 ± 14/8	5.6/5.1 ± 9.3/8.6	127/78 ± 2/6	11.3/1.4 ± 17.0/7.3	.40	.27	.55
Pulse, beats/min	94.27 ± 7.81	0.27 ± 7.88	80.73 ± 16.40	5.82 ± 13.45	.0232	.61	.71
No. of medications for adverse effects	1.91 ± 1.30	0.18 ± 1.08	1.55 ± 1.03	−0.09 ± 0.30	.74	.37	.64
Clozapine dose administered, mg	375 ± 195.5	−7.96 ± 19.58	345.45 ± 200.80	9.10 ± 16.86	.79	.12	.94

BMI = body mass index; BP = blood pressure; HDL = high density lipoprotein; LDL = low density lipoprotein; TC = total cholesterol; TG = triglycerides.

(−0.18 ± 0.41), A1c (−0.04% ± 0.25%), clozapine dose (−7.96 mg ± 19.58 mg), and TC (−15.73 mg/dL ± 42.31 mg/dL) after 8 months of pharmacist intervention. In the psychiatrist-only group, there was a decrease in TC (−2.18 mg/dL ± 13.97 mg/dL) and number of antipsychotics (−0.09 ± 0.30). Body mass index, weight, HDL, triglycerides, BP, and pulse did not show improvement from baseline in either group.

There was an increase in the number of medications used for AEs in the collaborative group (0.18 ± 1.08). There was a statistically significant difference in the number of pharmacologic (71 vs 19) and nonpharmacologic (154 vs 3) interventions documented in the collaborative group compared to the psychiatrist-only group ($P = .02$ and $P < .01$, respectively) from baseline to end of data collection. The pharmacist operates under a scope of practice and has prescribing privileges, but all recommendations were discussed with the psychiatrist and accepted. The number of MH-related emergency room visits (7 collaborative vs 4 psychiatrist only) and clozapine discontinuation (1 collaborative vs 2 psychiatrist only) were similar between the 2 groups ($P = .62$ and $P = .74$, respectively).

Eleven providers (69%) completed the clozapine survey. Providers' perception of patient refusal of required blood monitoring was the barrier that received the most responses (54%), followed by providers' lack of experience prescribing clozapine (45%), and provider/patient concerns about tolerability/AEs (36%; Table 1). Having a pharmacist see every patient in conjunction with the psychiatrist to help with AE management and lab monitoring was the solution that received the most responses (90%) followed by in-service presentations for continued education on clozapine (72%; Table 1).

Discussion

Although no statistically significant differences were found in the patient outcomes between the 2 groups or the prepharmacist to postpharmacist data, this pilot was not powered to detect such a difference. Yet it is important to note the outcomes that showed improvement with pharmacist intervention. A decrease was observed in the average clozapine dose, number of antipsychotics, number of other psychotropics, A1c, and TC in the collaborative group. Clinically, a decrease in the number of antipsychotics and psychotropics may indicate a more streamlined medication regimen with less potential for AEs and interactions. Overall, an increase in BMI, weight, triglycerides, BP, and pulse were identified in the collaborative clinic. One explanation for the weight and BMI increase is that 2 of the patients were new clozapine starts and gained a significant amount of weight

relatively quickly. These patients declined the addition of metformin to their medication regimen to potentially help with attenuation of weight gain despite recommendations by the pharmacist. The discontinuation rate and reason for stopping clozapine were similar between the 2 groups with two-thirds discontinuing due to refusal to continue taking clozapine for no specific or apparent reason. One third discontinued due to lack of adherence with clozapine and were transitioned to long-acting injectable antipsychotics.

One of the main benefits of pharmacy involvement in the collaborative clinic was the increase in time to talk to the patient about the therapy. The pharmacist scheduled 30 minutes for each appointment and focused on AE assessment and management, and the psychiatrist was able to focus more on psychiatric symptoms and other patient concerns. Identifying and addressing AEs of clozapine may help build a stronger patient-provider relationship as well as improve quality of life for these patients. The number of medications to manage AEs of clozapine slightly increased in the collaborative clinic, which may be due to the extra time allowed for assessment and intervention. There was a statistically significant difference in the number of pharmacologic and nonpharmacologic interventions documented in the collaborative group compared to the psychiatrist-only group. Common interventions documented by the pharmacist included specific diet and exercise recommendations, pumping legs and clenching fists prior to changing position to prevent dizziness, and utilizing sugarless hard candy to combat dry mouth and/or sialorrhea. The pharmacist assessed the patient and made recommendations related to MH and non-MH disease states. This comprehensive approach may benefit the patient's overall health and potentially prevent complications, which may be an area for future study. The quantity of documented pharmacist interventions supports the utility of a clinical pharmacist in a collaborative clozapine clinic.

The high completion rate of this survey will help guide future improvements that are mutually agreed upon by a majority of MH providers. The preferred solution of having more pharmacy involvement with clozapine patients led to pharmacists seeing all of the clozapine patients at the ZVAMC. This positive response of involving more MH pharmacists may further increase AE management, decrease clozapine discontinuation rates, and increase medication adherence. Barriers identified include lack of experience prescribing clozapine, absolute neutrophil count collection, and patient/provider concerns about AEs/tolerability. To overcome these barriers, providers acknowledged that continued clozapine education, such as in-service presentations, could be beneficial. Mental health providers feeling more confident with the appropriate use of this antipsychotic may have the potential to reverse the decline in its prescribing. Future directions include creating educational materials for MH providers and patients and surveying patients to identify discrepancies between providers' perception of AE and what patients actually report. These steps may assist with increasing clozapine prescribing and expanding the collaborative clozapine clinic in the future.

There were strengths to the design of this project. Data collection began when the collaborative clinic was first established, capturing all interventions from the beginning. There was consistency with only 1 clinical MH pharmacist seeing all the collaborative clinic patients and only one pharmacist collecting and analyzing the data.

Limitations include the small sample size and short duration of data collection. Significant changes in the project outcomes might have been apparent if the study period were longer. The short data-collection period may also have led to the increase in metabolic outcomes without time for lifestyle modification effects to be realized. For example, if a patient were started on statin therapy or counseled on lifestyle modification by the pharmacist during the data-collection window, there might not have been enough time to capture the full effect on LDL, weight, and BMI. Data collected on interventions were contingent on direct documentation in the patient's electronic health record. More interventions may have been made in the psychiatrist-only clinic but not documented. The pharmacist had nearly twice the amount of clinic visits eligible to make interventions compared to the psychiatrist. This imbalance was a result of more patients in the collaborative clinic being seen weekly due to recent initiation of clozapine and their status in the clozapine risk evaluation and mitigation strategies program. More patients in the psychiatrist-only clinic were on clozapine for more than a year and were only seen monthly.

Clinical MH pharmacist involvement in clozapine management may be useful for providing the necessary AE management and laboratory monitoring these patients require. A greater number of documented pharmacologic and nonpharmacologic interventions in the collaborative clinic, indicating an increased number of identified and addressed adverse effects, offers a starting point for advocating for more pharmacy involvement in the management of clozapine clinic patients. Additionally, the positive results from the survey, indicating providers would like all of the clozapine clinic patients to be seen by a pharmacist, validate current pharmacy involvement with clozapine monitoring and AE management and resulted in expansion of the collaborative clozapine clinic at the ZVAMC.

References

1. Warnez S, Alessi-Severini S. Clozapine: a review of clinical practice guidelines and prescribing trends. BMC Psychiatry. 2014;14:102. DOI: 10.1186/1471-244X-14-102. PubMed PMID: 24708834; PubMed Central PMCID: PMC3999500.
2. Meltzer HY. Treatment-resistant schizophrenia—the role of clozapine. Curr Med Res Opin. 1997;14(1):1-20. DOI: 10.1185/03007999709113338. PubMed PMID: 9524789.
3. Meltzer HY. New trends in the treatment of schizophrenia. CNS Neurol Disord Drug Targets. 2018;16(8):900-6. DOI: 10.2174/1871527316666170728165355. PubMed PMID: 28758583.
4. Lally J, Gaughran F, Timms P, Curran S. Treatment-resistant schizophrenia: current insights on the pharmacogenomics of antipsychotics. Pharmgenomics Pers Med. 2016;9:117-29. DOI: 10.2147/PGPM.S115741. PubMed PMID: 27853387; PubMed Central PMCID: PMC5106233.
5. Kelly D, Wehring H, Vyas G. Current status of clozapine in the United States. Shanghai Arch Psychiatry. 2012;24:110-3. DOI: 10.3969/j.issn.1002-0829.2012.02.007. PubMed PMID: 25324612.
6. Stroup TS, Gerhard T, Crystal S, Huang C, Olfson M. Geographic and clinical variation in clozapine use in the United States. Psychiatr Serv. 2014;65(2):186-92. DOI: 10.1176/appi.ps.201300180. PubMed PMID: 24233347.
7. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Arch Gen Psychiatry. 1988;45(9):789-96. PubMed PMID: 3046553.
8. Conley RR, Tamminga CA, Kelly DL, Richardson CM. Treatment-resistant schizophrenic patients respond to clozapine after olanzapine non-response. Biol Psychiatry. 1999;46(1):73-7. PubMed PMID: 10394475.
9. McEvoy JP, Lieberman JA, Stroup TS, Davis SM, Meltzer HY, Rosenheck RA, et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. Am J Psychiatry. 2006;163(4):600-10. DOI: 10.1176/appi.ajp.163.4.600. PubMed PMID: 16585434.
10. Azorin J-M, Spiegel R, Remington G, Vanelle J-M, Péré J-J, Giguere M, et al. A double-blind comparative study of clozapine and risperidone in the management of severe chronic schizophrenia. Am J Psychiatry. 2001;158(8):1305-13. DOI: 10.1176/appi.ajp.158.8.1305. PubMed PMID: 11481167.
11. Taylor M, Perera U. NICE CG178 Psychosis and Schizophrenia in Adults: Treatment and Management—an evidence-based guideline? Br J Psychiatry. 2015;206(5):357-9. DOI: 10.1192/bjp.bp.114.155945. PubMed PMID: 25934299.
12. Lehman AF, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, et al. Practice guideline for the treatment of patients with schizophrenia. 2nd ed. Am J Psychiatry. 2004;161(2 Suppl):1-56. PubMed PMID: 15000267.
13. Buchanan RW, Kreyenbuhl J, Kelly DL, Noel JM, Boggs DL, Fischer BA, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. Schizophr Bull. 2010;36(1):71-93. DOI: 10.1093/schbul/sbp116. PubMed PMID: 19955390.
14. Stahl SM. Clozapine: is now the time for more clinicians to adopt this orphan? CNS Spectr. 2014;19(4):279-81. DOI: 10.1017/S1092852914000418. PubMed PMID: 25267329.
15. Gee S, Vergunst F, Howes O, Taylor D. Practitioner attitudes to clozapine initiation. Acta Psychiatr Scand. 2014;130(1):16-24. DOI: 10.1111/acps.12193. PubMed PMID: 24004162.
16. Clozaril (clozapine) package insert. Durham (NC): Accord Healthcare, Inc [cited 2017 Jun 29]. DailyMed [Internet]. National Library of Medicine (US). Available from: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=a243ce25-2aa0-4879-86ec-455db3a63c5e
17. Nielsen J, Dahm M, Lublin H, Taylor D. Psychiatrists' attitude towards and knowledge of clozapine treatment. J Psychopharmacol. 2010;24(7):965-71. DOI: 10.1177/0269881108100320. PubMed PMID: 19164499.
18. Kim J-H, Kim S-Y, Ahn YM, Kim YS. Subjective response to clozapine and risperidone treatment in outpatients with schizophrenia. Prog Neuro Psychopharmacol Biol Psychiatry. 2006;30(2):301-5. DOI: 10.1016/j.pnpbp.2005.10.006. PubMed PMID: 16309807.
19. Hodge K, Jespersen S. Side-effects and treatment with clozapine: a comparison between the views of consumers and their clinicians. Int J Ment Health Nurs. 2008;17(1):2-8. DOI: 10.1111/j.1447-0349.2007.00506.x. PubMed PMID: 18211398.
20. Taylor D, Shapland L, Laverick G, Bond J, Munro J. Clozapine – a survey of patient perceptions. Psychiatr Bull. 2000;24(12):450-2. DOI: 10.1192/pb.24.12.450.
21. Gören JL, Rose AJ, Engle RL, Smith EG, Christopher MLD, Rickles NM, et al. Organizational characteristics of veterans affairs clinics with high and low utilization of clozapine. Psychiatr Serv. 2016;67(11):1189-96. DOI: 10.1176/appi.ps.201500506. PubMed PMID: 27301765.
22. Hynes C, Keating D, McWilliams S, Madigan K, Kinsella A, Maidment I, et al. Glasgow antipsychotic side-effects scale for clozapine—development and validation of a clozapine-specific side-effects scale. Schizophr Res. 2015;168(1-2):505-13. DOI: 10.1016/j.schres.2015.07.052. PubMed PMID: 26276305.