

Psychiatric pharmacist's role in overcoming barriers to clozapine use and improving management

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How to cite: Kelly DL, Love RC. Psychiatric pharmacist's role in overcoming barriers to clozapine use and improving management. *Ment Health Clin* [Internet]. 2019;9(2):64-9. DOI: 10.9740/mhc.2019.03.064.

Abstract

Clozapine is an antipsychotic that exhibits superior efficacy and effectiveness for those with schizophrenia and other serious mental illness. However, its side-effect profile and administrative burdens present challenges to its use. In the United States, the medication is grossly underused even though it may improve outcomes and reduce costs. Current barriers to use include lack of prescriber knowledge and confidence, negative prescriber attitudes, special monitoring requirements, administrative factors, lack of clozapine on formularies, lack of support and infrastructure to use the medication within many health systems, and inadequate understanding or acknowledgement of clozapine prescribing and risks by policy makers and payers. Approaches using interprofessional models of care, which include pharmacists specializing in psychiatric care, can help meet the needs of patients receiving clozapine. This article lays out the big picture of barriers to clozapine and how psychiatric pharmacists could play a role in improving access.

Keywords: clozapine, barriers, pharmacists

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Disclosures: D.L.K. is on the advisory board for Lundbeck and a consultant for HLS Therapeutics. R.C.L. received a speaking fee for the Nevada Psychiatric Association and received an honorarium for the American Pharmacists Association Advisory Board on Pharmacist Administration of Medication from the National Alliance of State Pharmacy Associations for developing a white paper on medication administration by pharmacists.

Clozapine was the first antipsychotic found to be superior for treatment-resistant schizophrenia (TRS)^{1,2} and continues to be the most effective antipsychotic for patients with schizophrenia who do not respond to treatment with 2 adequate trials of different antipsychotics.³ Several meta-analyses of controlled trials, effectiveness trials, and

systematic reviews of clozapine provide evidence of its superiority.⁴⁻¹⁰ The most recent meta-analysis¹¹ reported clozapine was almost twice as efficacious as other available antipsychotics (effect size relative to placebo = 0.88). Furthermore, clozapine is recommended for TRS by the American Psychiatric Association¹²; the Texas Medication Algorithm Project, Schizophrenia^{13,14}; Patient Outcomes Research Team (PORT)¹⁵; the Harvard South Shore Program Algorithm¹⁶; the British Association for Psychopharmacology Guidelines¹⁷; the National Institute for Health, and Care Excellence (NICE) Clinical Guidelines¹⁸; and the Canadian Clinical Practice Guidelines for Schizophrenia.¹⁹ Early clozapine use is critical for young people with schizophrenia who have TRS as data shows us that it provides hope for symptom improvement despite failed earlier trials with other antipsychotics¹ and may offer a chance for improvement and course stabilization as the basis for recovery.²⁰

Clozapine is also used off label for a variety of other indications and in increasingly younger populations.²¹⁻²⁸ Clozapine is the only antipsychotic with a Food and Drug

Administration indication for reducing suicidality in schizophrenia. In addition, there is a lower mortality rate with clozapine compared with other antipsychotics²⁹ as well as a cost-saving potential compared with antipsychotic polypharmacy, a nonevidence-based strategy for TRS.³⁰

Although it has a better efficacy profile than other antipsychotics, clozapine is associated with a variety of side effects, some of which are potentially serious. Common side effects include hypersalivation, tachycardia, enuresis, sweating, eosinophilia, metabolic syndrome, and constipation.³¹⁻³³ Among the more serious side effects of clozapine are an approximately 3% risk of myocarditis,³⁴ 0.1% risk of cardiomyopathy,³⁵ dose-dependent 1% to 3% risk of seizures,³⁶ and 0.05% to 0.86% risk of severe neutropenia.³⁷⁻⁴¹ The risk of severe neutropenia led the Food and Drug Administration to mandate regular blood draws to monitor the absolute neutrophil count and patient, provider, and pharmacy registration with the risk evaluation and mitigation strategies program. Due to these potentially serious side effects, the decision to use clozapine in any given patient requires a thorough consideration of both its risks and benefits, a thoughtful patient-centered approach, and a system that facilitates safe and appropriate use.⁴² Often ignored in risk-benefit discussions are the psychiatric and medical risks of not using clozapine and the risks of antipsychotic polypharmacy.⁴³

Despite the overwhelming evidence of clozapine's superior efficacy and effectiveness and its availability in generic form, clozapine is prescribed infrequently in the United States at a rate considerably lower than the estimated prevalence of TRS.⁴⁴⁻⁴⁸ The use of clozapine in the United States has steadily declined from 11% of all antipsychotic prescriptions in 1999 to about 4% in 2008.²⁹ In contrast, it is more frequently used in other countries (eg, percentage of antipsychotic market share among all antipsychotics, 36% to 38% in Australia, 26% in China, 20% to 30% in Taiwan).^{45,49} Despite the lack of evidence to support antipsychotic polypharmacy for TRS, antipsychotic polypharmacy is prescribed more frequently than clozapine monotherapy.^{50,51} To fully understand the widespread low use, a study⁵² of Medicaid and pharmacy prescription data from all 50 states was completed and published in 2015. Based on this study, Washington, Colorado, South Dakota, Connecticut, Vermont, and Maine used clozapine at the a rate of 10% or higher, and states using the least amount employed it in less than 3% of cases (these states included Oregon, Nevada, Arizona, Mississippi, Kentucky, North Carolina, Georgia, Alabama, and Louisiana).⁵² In addition to underusing clozapine, clinicians frequently wait years to initiate clozapine. Patients often undergo multiple failed antipsy-

chotic trials rather than the 2 trials recommended before employing clozapine.^{53,54}

Many clinical and administrative barriers prevent optimized use of clozapine.⁵⁵ A recent publication sponsored by the National Association of State Mental Health Program Directors (NASHMPD)⁵⁶ provides a review of barriers, which include provider, patient, and family issues; resource availability; health system factors; and administrative burden. The NASHMPD-sponsored paper lays out recommendations from a workgroup as a call to action for all facets and key stakeholders to play a role in improving access to clozapine treatment.^{56,57} In fact, the field is beginning to recognize that, to overcome barriers and provide more effective care for patients with severe mental illness, every health care system should meet minimum requirements. These include providing easy access to clozapine, offering appropriate safety monitoring of patients receiving it, encouraging prescribers to consider its use when appropriate, and supporting prescribers in learning how to best use it. Furthermore, new and innovative multidisciplinary team strategies, clozapine clinics, and centers of excellence may provide much-needed support and infrastructure to help promote and manage this challenging agent effectively.⁵⁸⁻⁶²

Psychiatrists cannot do this alone. In fact, our nation is facing a shortage in psychiatric providers. Data shows the pool of psychiatrists working with the public sector for insured populations declined by 10% from 2003 to 2013.⁶³ Projections predict this shortage and critically low numbers of psychiatric providers is not expected to improve in the near future. In addition, fewer psychiatrists are available to serve rural and underserved populations.⁶³ In 2017, the Medical Director Institute from the National Council for Behavioral Health convened a range of stakeholders for a 2-day expert roundtable and made recommendations to address the psychiatric shortage. The recommendations suggest other trained disciplines, such as advance-practice nurse practitioners, psychiatric-trained physician assistants, and board-certified psychiatric pharmacists could help provide more access to psychiatric care.⁶⁴

Based on the impending shortage of psychiatrists, the known underutilization of clozapine, and a nation facing challenges in delivering evidence-based health care, the psychiatric pharmacist should be recognized for his or her ability to help educate about, advocate for, and assist in managing clozapine treatment. Innovative models for the management of those receiving clozapine (including models with clinically trained pharmacists) have existed for years. Data demonstrates that pharmacist-run or -assisted clozapine clinics in which they can play a role in the monitoring, recommendations, education, and other roles may lead to cost savings, high clozapine continuation rates, patient and

family satisfaction, and early intervention in cases of decompensation and suicidal ideation.^{62,65}

The role of the pharmacist may vary greatly depending on the clinical setting. For example, at Fairview Health Services in Minneapolis, Minnesota, pharmacists operate the Fairview Pharmacy Clozapine Monitoring Program. Roles in this program include managing initial enrollment in and ongoing monitoring through the clozapine risk evaluation and mitigation strategies program; coordination of all laboratory services, including mobile phlebotomy; reminder calls for both refills and laboratory tests; and interfacing with patients. They report that patients enrolled in their program are 4 times more likely to be persistent in their use.⁶⁶

Goren and colleagues⁶⁰ examined characteristics impacting the rate of clozapine utilization in Veterans Affairs (VA) clinics. They report that pharmacist-based registration, ordering and monitoring laboratory tests, and evaluation of side effects improved clinic utilization of clozapine. Williams and Purvis⁶² describe more extensive roles in their VA pharmacist-managed clozapine clinic. At their VA Sierra Nevada Health System clinic, pharmacists conduct initial patient evaluations; obtain informed consent; and educate patients, caregivers, and family members. They are also responsible for performing dosage adjustments and cross-tapering with other antipsychotics, monitoring for side effects, ordering laboratory tests, obtaining vital signs, assessing adherence, and administering standardized rating scales.

Psychiatric pharmacists also have extensive training and experience in addressing clozapine-related issues, such as adherence, smoking cessation, and drug interactions (primarily from cytochrome P450 1A2-inducing agents) and side effect management.⁶⁷⁻⁷⁰ A recent report⁷¹ highlighted one of the pharmacist roles in recognizing medication-related side effects, such as case of clozapine-associated neuroleptic malignant syndrome in an emergency department. These roles are consistent with the initial role delineation studies for psychiatric pharmacist specialty certification that included assessing; designing a pharmacotherapy plan; recommending or initiating pharmacotherapy; implementing a monitoring plan; outcomes; and predicting, preventing, and resolving drug-related problems.⁷²

Among the recommendations in NASMHPD's report on clozapine underutilization was the need to include clozapine on every hospital and health plan formulary. Psychiatric pharmacists can serve as effective advocates for this inclusion.⁷³ An emerging role for psychiatric pharmacists in particular may include recommending and interpreting pharmacogenomics testing.⁷⁴ The increasing availability of pharmacogenomic testing tools has led to

the misconception that these tools provide simple answers. Instead, the psychiatric pharmacist may assist in providing a more nuanced approach to their use.⁷⁵

Beyond clozapine treatment, psychiatric pharmacists play important roles that improve broader medication therapy management.⁷⁶ Furthermore, in all areas of pharmacy, the roles of advanced practice pharmacists are expanding as the number of residency programs increase. Most states permit collaborative practice agreements and pharmacists in the VA frequently have prescriptive authority. Policy makers, payers, and other collaborative mental health team members can help address critical health care needs by advocating for the expansion of the scope of practice for appropriately credentialed psychiatric pharmacists and developing new reimbursement models that include them.⁷⁷

In conclusion, clozapine remains one of the most underutilized evidence-based treatments in psychiatry. We challenge all psychiatric pharmacists as well as other clinically trained pharmacists with psychiatric experience to examine their role in health care teams and systems and strive to participate in and develop innovative models for the delivery and management of clozapine. We also challenge the health care system to recognize important roles psychiatric pharmacists can provide to expand access to clozapine monitoring, education, and treatment and provide medication therapy management in many practice settings. Pharmacists have a long history of managing treatment with high-risk agents, such as warfarin, in a cost-effective manner.⁷⁸⁻⁸⁰ Just as appropriately trained pharmacists can safely monitor, resolve medication-related problems, and adjust doses of patients receiving anticoagulation, psychiatric pharmacists can manage patients receiving clozapine. The high-quality services they provide and the superior outcomes achieved with clozapine may help offset the costs of using psychiatric pharmacists. Advocating for payment for these services is a critical need to help address this discrepancy in care. If access to clozapine is improved, scores of patients potentially could benefit. In turn, their improved care could result in substantial cost savings to the entire health care system.

References

1. Howes OD, McCutcheon R, Agid O, de Bartolomeis A, van Beveren NJM, Birnbaum ML, et al. Treatment-resistant schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. *Am J Psychiatry*. 2017;174(3):216-29. DOI: [10.1176/appi.ajp.2016.16050503](https://doi.org/10.1176/appi.ajp.2016.16050503). PubMed PMID: [27919182](https://pubmed.ncbi.nlm.nih.gov/27919182/).
2. 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](https://pubmed.ncbi.nlm.nih.gov/3046553/).

3. 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](https://doi.org/10.1186/1471-244X-14-102). PubMed PMID: [24708834](https://pubmed.ncbi.nlm.nih.gov/24708834/); PubMed Central PMCID: [PMC3999500](https://pubmed.ncbi.nlm.nih.gov/PMC3999500/).
4. Wahlbeck K, Cheine M, Essali A, Adams C. Evidence of clozapine's effectiveness in schizophrenia: a systematic review and meta-analysis of randomized trials. *Am J Psychiatry*. 1999; 156(7):990-9. DOI: [10.1176/ajp.156.7.990](https://doi.org/10.1176/ajp.156.7.990). PubMed PMID: [10401441](https://pubmed.ncbi.nlm.nih.gov/10401441/).
5. Chakos M, Lieberman J, Hoffman E, Bradford D, Sheitman B. Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. *Am J Psychiatry*. 2001;158(4):518-26. DOI: [10.1176/appi.ajp.158.4.518](https://doi.org/10.1176/appi.ajp.158.4.518). PubMed PMID: [11282684](https://pubmed.ncbi.nlm.nih.gov/11282684/).
6. Tuunainen A, Wahlbeck K, Gilbody S. Newer atypical antipsychotic medication in comparison to clozapine: a systematic review of randomized trials. *Schizophr Res*. 2002;56(1-2):1-10. DOI: [10.1016/S0920-9964\(01\)00212-2](https://doi.org/10.1016/S0920-9964(01)00212-2). PubMed PMID: [12084413](https://pubmed.ncbi.nlm.nih.gov/12084413/).
7. Sinclair D, Adams CE. Treatment resistant schizophrenia: a comprehensive survey of randomised controlled trials. *BMC Psychiatry*. 2014;14:253. DOI: [10.1186/s12888-014-0253-4](https://doi.org/10.1186/s12888-014-0253-4). PubMed PMID: [25227719](https://pubmed.ncbi.nlm.nih.gov/25227719/); PubMed Central PMCID: [PMC4177431](https://pubmed.ncbi.nlm.nih.gov/PMC4177431/).
8. Citrome L. A systematic review of meta-analyses of the efficacy of oral atypical antipsychotics for the treatment of adult patients with schizophrenia. *Expert Opin Pharmacother*. 2012; 13(11):1545-73. DOI: [10.1517/14656566.2011.626769](https://doi.org/10.1517/14656566.2011.626769). PubMed PMID: [21999805](https://pubmed.ncbi.nlm.nih.gov/21999805/).
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](https://doi.org/10.1176/appi.ajp.163.4.600). PubMed PMID: [16585434](https://pubmed.ncbi.nlm.nih.gov/16585434/).
10. Moncrieff J. Clozapine v. conventional antipsychotic drugs for treatment-resistant schizophrenia: a re-examination. *Br J Psychiatry*. 2003;183:161-6. PubMed PMID: [12893670](https://pubmed.ncbi.nlm.nih.gov/12893670/).
11. Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013;382(9896):951-62. DOI: [10.1016/S0140-6736\(13\)60733-3](https://doi.org/10.1016/S0140-6736(13)60733-3). PubMed PMID: [23810019](https://pubmed.ncbi.nlm.nih.gov/23810019/).
12. Lehman AF, Lieberman J, Dixon LB, McGlashan TH, Miller AL, Perkins D, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry*. 2004;161(2 Suppl):1-56. PubMed PMID: [15000267](https://pubmed.ncbi.nlm.nih.gov/15000267/).
13. Moore TA, Buchanan RW, Buckley PF, Chiles JA, Conley RR, Crismon ML. The Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia: 2006 update. *J Clin Psychiatry*. 2007;68(11):1751-62. DOI: [10.4088/JCP.v68n1115](https://doi.org/10.4088/JCP.v68n1115). PubMed PMID: [18052569](https://pubmed.ncbi.nlm.nih.gov/18052569/).
14. Argo T, Crismon M, Miller A, Moore T, Bendele S, Suehs B. Texas Medication Algorithm Project procedural manual: schizophrenia algorithm. Austin: Texas Department of State Health Services; 2008.
15. 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](https://doi.org/10.1093/schbul/sbp116). PubMed PMID: [19955390](https://pubmed.ncbi.nlm.nih.gov/19955390/).
16. Osser DN, Roudsari MJ, Manschreck T. The psychopharmacology algorithm project at the Harvard South Shore Program. *Harv Rev Psychiatry*. 2013;21(1):18-40. DOI: [10.1097/HRP.0b013e31827fd915](https://doi.org/10.1097/HRP.0b013e31827fd915). PubMed PMID: [23656760](https://pubmed.ncbi.nlm.nih.gov/23656760/).
17. Barnes TRE. Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol*. 2011; 25(5):567-620. DOI: [10.1177/0269881110391123](https://doi.org/10.1177/0269881110391123). PubMed PMID: [21292923](https://pubmed.ncbi.nlm.nih.gov/21292923/).
18. NICE Guidelines [Internet]. Psychosis and schizophrenia in adults: prevention and management [updated 2014 Feb; cited 2018 Dec 5]. Available from: <https://www.nice.org.uk/Guidance/CG178>
19. Remington G, Addington D, Honer W, Ismail Z, Raedler T, Teehan M. Guidelines for the pharmacotherapy of schizophrenia in adults. *Can J Psychiatry*. 2017;62(9):604-16. DOI: [10.1177/0706743717720448](https://doi.org/10.1177/0706743717720448). PubMed PMID: [28703015](https://pubmed.ncbi.nlm.nih.gov/28703015/); PubMed Central PMCID: [PMC5593252](https://pubmed.ncbi.nlm.nih.gov/PMC5593252/).
20. Agid O, Arenovich T, Sajeev G, Zipursky RB, Kapur S, Foussias G, et al. An algorithm-based approach to first-episode schizophrenia. *J Clin Psychiatry*. 2011;72(11):1439-44. DOI: [10.4088/JCP.09mo5785yel](https://doi.org/10.4088/JCP.09mo5785yel). PubMed PMID: [21457676](https://pubmed.ncbi.nlm.nih.gov/21457676/).
21. Victoroff J, Coburn K, Reeve A, Sampson S, Shillcutt S. Pharmacological management of persistent hostility and aggression in persons with schizophrenia spectrum disorders: a systematic review. *J Neuropsychiatry Clin Neurosci*. 2014;26(4): 283-312. DOI: [10.1176/appi.neuropsych.13110335](https://doi.org/10.1176/appi.neuropsych.13110335). PubMed PMID: [26037853](https://pubmed.ncbi.nlm.nih.gov/26037853/).
22. Li X-B, Tang Y-L, Wang C-Y, de Leon J. Clozapine for treatment-resistant bipolar disorder: a systematic review. *Bipolar Disord*. 2015;17(3):235-47. DOI: [10.1111/bdi.12272](https://doi.org/10.1111/bdi.12272). PubMed PMID: [25346322](https://pubmed.ncbi.nlm.nih.gov/25346322/).
23. Goldman M. The assessment and treatment of water imbalance in patients with psychosis. *Clin Schizophr Relat Psychoses*. 2010; 4(2):115-23. DOI: [10.3371/CSRP.4.2.3](https://doi.org/10.3371/CSRP.4.2.3). PubMed PMID: [20643634](https://pubmed.ncbi.nlm.nih.gov/20643634/).
24. Borek LL, Friedman JH. Treating psychosis in movement disorder patients: a review. *Expert Opin Pharmacother*. 2014; 15(11):1553-64. DOI: [10.1517/14656566.2014.918955](https://doi.org/10.1517/14656566.2014.918955). PubMed PMID: [24846479](https://pubmed.ncbi.nlm.nih.gov/24846479/).
25. Stinton C, McKeith I, Taylor J-P, Lafortune L, Mioshi E, Mak E, et al. Pharmacological management of Lewy body dementia: a systematic review and meta-analysis. *Am J Psychiatry*. 2015; 172(8):731-42. DOI: [10.1176/appi.ajp.2015.14121582](https://doi.org/10.1176/appi.ajp.2015.14121582). PubMed PMID: [26085043](https://pubmed.ncbi.nlm.nih.gov/26085043/).
26. Beri A, Boydell J. Clozapine in borderline personality disorder: a review of the evidence. *Ann Clin Psychiatry*. 2014;26(2):139-44. PubMed PMID: [24812651](https://pubmed.ncbi.nlm.nih.gov/24812651/).
27. Hazari N, Kate N, Grover S. Clozapine and tardive movement disorders: a review. *Asian J Psychiatr*. 2013;6(6):439-51. DOI: [10.1016/j.ajp.2013.08.067](https://doi.org/10.1016/j.ajp.2013.08.067). PubMed PMID: [24309853](https://pubmed.ncbi.nlm.nih.gov/24309853/).
28. Schneider C, Corrigan R, Hayes D, Kyriakopoulos M, Frangou S. Systematic review of the efficacy and tolerability of clozapine in the treatment of youth with early onset schizophrenia. *Eur Psychiatry*. 2014;29(1):1-10. DOI: [10.1016/j.eurpsy.2013.08.001](https://doi.org/10.1016/j.eurpsy.2013.08.001). PubMed PMID: [24119631](https://pubmed.ncbi.nlm.nih.gov/24119631/).
29. Meltzer HY. Clozapine: balancing safety with superior antipsychotic efficacy. *Clin Schizophr Relat Psychoses*. 2012;6(3):134-44. DOI: [10.3371/CSRP.6.3.5](https://doi.org/10.3371/CSRP.6.3.5). PubMed PMID: [23006238](https://pubmed.ncbi.nlm.nih.gov/23006238/).
30. Velligan DI, Carroll C, Lage MJ, Fairman K. Outcomes of Medicaid beneficiaries with schizophrenia receiving clozapine only or antipsychotic combinations. *Psychiatr Serv*. 2015;66(2): 127-33. DOI: [10.1176/appi.ps.201300085](https://doi.org/10.1176/appi.ps.201300085). PubMed PMID: [25321616](https://pubmed.ncbi.nlm.nih.gov/25321616/).
31. Sagy R, Weizman A, Katz N. Pharmacological and behavioral management of some often-overlooked clozapine-induced side effects. *Int Clin Psychopharmacol*. 2014;29(6):313-7. DOI: [10.1097/YIC.000000000000044](https://doi.org/10.1097/YIC.000000000000044). PubMed PMID: [24932886](https://pubmed.ncbi.nlm.nih.gov/24932886/).
32. Mitchell AJ, Vancampfort D, Sweers K, van Winkel R, Yu W, De Hert M. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders—a systematic review and meta-analysis. *Schizophr Bull*. 2011;39(2):306-18. DOI: [10.1093/schbul/sbr148](https://doi.org/10.1093/schbul/sbr148). PubMed PMID: [22207632](https://pubmed.ncbi.nlm.nih.gov/22207632/); PubMed Central PMCID: [PMC3576174](https://pubmed.ncbi.nlm.nih.gov/PMC3576174/).
33. Raja M. Clozapine safety, 35 years later. *Curr Drug Saf*. 2011;6(3): 164-84. DOI: [10.2174/157488611797579230](https://doi.org/10.2174/157488611797579230). PubMed PMID: [22122392](https://pubmed.ncbi.nlm.nih.gov/22122392/).

34. Ronaldson KJ, Fitzgerald PB, McNeil JJ. Clozapine-induced myocarditis, a widely overlooked adverse reaction. *Acta Psychiatr Scand.* 2015;132(4):231-40. DOI: [10.1111/acps.12416](https://doi.org/10.1111/acps.12416). PubMed PMID: [25865238](https://pubmed.ncbi.nlm.nih.gov/25865238/).
35. Layland JJ, Liew D, Prior DL. Clozapine-induced cardiotoxicity: a clinical update. *Med J Aust.* 2009;190(4):190-2. PubMed PMID: [19220183](https://pubmed.ncbi.nlm.nih.gov/19220183/).
36. Williams AM, Park SH. Seizure associated with clozapine: incidence, etiology, and management. *CNS Drugs.* 2015;29(2):101-11. DOI: [10.1007/s40263-014-0222-y](https://doi.org/10.1007/s40263-014-0222-y). PubMed PMID: [25537107](https://pubmed.ncbi.nlm.nih.gov/25537107/).
37. Honigfeld G, Arellano F, Sethi J, Bianchini A, Schein J. Reducing clozapine-related morbidity and mortality: 5 years of experience with the Clozaril National Registry. *J Clin Psychiatry.* 1998;59(Suppl 3):3-7. PubMed PMID: [9541331](https://pubmed.ncbi.nlm.nih.gov/9541331/).
38. Munro J, O'Sullivan D, Andrews C, Arana A, Mortimer A, Kerwin R. Active monitoring of 12, 760 clozapine recipients in the UK and Ireland. Beyond pharmacovigilance. *Br J Psychiatry.* 1999;175:576-80. PubMed PMID: [10789357](https://pubmed.ncbi.nlm.nih.gov/10789357/).
39. Lahdelma L, Appelberg B. Clozapine-induced agranulocytosis in Finland, 1982-2007. *J Clin Psychiatry.* 2012;73(6):837-42. DOI: [10.4088/JCP.11m07244](https://doi.org/10.4088/JCP.11m07244). PubMed PMID: [22480452](https://pubmed.ncbi.nlm.nih.gov/22480452/).
40. Drew L. Clozapine and agranulocytosis: re-assessing the risks. *Australas Psychiatry.* 2013;21(4):335-7. DOI: [10.1177/1039856213491990](https://doi.org/10.1177/1039856213491990). PubMed PMID: [23804114](https://pubmed.ncbi.nlm.nih.gov/23804114/).
41. Balda MV, Garay OU, Papale RM, Bignone I, Bologna VG, Brandolini A, et al. Clozapine-associated neutropenia and agranulocytosis in Argentina (2007-2012). *Int Clin Psychopharmacol.* 2015;30(2):109-14. DOI: [10.1097/YIC.000000000000060](https://doi.org/10.1097/YIC.000000000000060). PubMed PMID: [25486383](https://pubmed.ncbi.nlm.nih.gov/25486383/).
42. Hill M, Freudenreich O. Clozapine: key discussion points for prescribers. *Clin Schizophr Relat Psychoses.* 2013;6(4):177-85. DOI: [10.3371/CSRP.HIFR.01062013](https://doi.org/10.3371/CSRP.HIFR.01062013). PubMed PMID: [23302447](https://pubmed.ncbi.nlm.nih.gov/23302447/).
43. Misawa F, Shimizu K, Fujii Y, Miyata R, Koshiishi F, Kobayashi M, et al. Is antipsychotic polypharmacy associated with metabolic syndrome even after adjustment for lifestyle effects? A cross-sectional study. *BMC Psychiatry.* 2011;11:118. DOI: [10.1186/1471-244X-11-118](https://doi.org/10.1186/1471-244X-11-118). PubMed PMID: [21791046](https://pubmed.ncbi.nlm.nih.gov/21791046/).
44. Fayek M, Flowers C, Signorelli D, Simpson G. Psychopharmacology: underuse of evidence-based treatments in psychiatry. *Psychiatr Serv.* 2003;54(11):1453-4, 1456. DOI: [10.1176/appi.ps.54.11.1453](https://doi.org/10.1176/appi.ps.54.11.1453). PubMed PMID: [14600298](https://pubmed.ncbi.nlm.nih.gov/14600298/).
45. Conley RR, Kelly DL, Lambert TJ, Love RC. Comparison of clozapine use in Maryland and in Victoria, Australia. *Psychiatr Serv.* 2005;56(3):320-3. DOI: [10.1176/appi.ps.56.3.320](https://doi.org/10.1176/appi.ps.56.3.320). PubMed PMID: [15746507](https://pubmed.ncbi.nlm.nih.gov/15746507/).
46. Lieberman JA. Maximizing clozapine therapy: managing side effects. *J Clin Psychiatry.* 1998;59 Suppl 3:38-43. PubMed PMID: [9541337](https://pubmed.ncbi.nlm.nih.gov/9541337/).
47. Taylor DM, Young C, Paton C. Prior antipsychotic prescribing in patients currently receiving clozapine. *J Clin Psychiatry.* 2003;64(1):30-4. DOI: [10.4088/JCP.v64n0107](https://doi.org/10.4088/JCP.v64n0107).
48. Weissman EM. Antipsychotic prescribing practices in the Veterans Healthcare Administration—New York metropolitan region. *Schizophr Bull.* 2002;28(1):31-42. PubMed PMID: [12047020](https://pubmed.ncbi.nlm.nih.gov/12047020/).
49. Xiang Y-T, Wang C-Y, Si T-M, Lee EHM, He Y-L, Ungvari GS, et al. Clozapine use in schizophrenia: findings of the Research on Asia Psychotropic Prescription (REAP) studies from 2001 to 2009. *Aust N Z J Psychiatry.* 2011;45(11):968-75. DOI: [10.3109/00048674.2011.607426](https://doi.org/10.3109/00048674.2011.607426). PubMed PMID: [21888603](https://pubmed.ncbi.nlm.nih.gov/21888603/).
50. Gören JL, Meterko M, Williams S, Young GJ, Baker E, Chou C-H, et al. Antipsychotic prescribing pathways, polypharmacy, and clozapine use in treatment of schizophrenia. *Psychiatr Serv.* 2013;64(6):527-33. DOI: [10.1176/appi.ps.002022012](https://doi.org/10.1176/appi.ps.002022012). PubMed PMID: [23450334](https://pubmed.ncbi.nlm.nih.gov/23450334/).
51. Gallego JA, Bonetti J, Zhang J, Kane JM, Correll CU. Prevalence and correlates of antipsychotic polypharmacy: a systematic review and meta-regression of global and regional trends from the 1970s to 2009. *Schizophr Res.* 2012;138(1):18-28. DOI: [10.1016/j.schres.2012.03.018](https://doi.org/10.1016/j.schres.2012.03.018). PubMed PMID: [22534420](https://pubmed.ncbi.nlm.nih.gov/22534420/).
52. Torrey EF, Knable MB, Quanbeck C, Davis JM. Clozapine for treating schizophrenia: a comparison of the states [Internet]. A report of the Treatment Advocacy Center [updated 2015 Nov; cited 2018 Dec 5]. Available from: <http://www.tacreports.org/storage/documents/clozapine-for-treating-schizophrenia.pdf>
53. Howes OD, Vergunst F, Gee S, McGuire P, Kapur S, Taylor D. Adherence to treatment guidelines in clinical practice: study of antipsychotic treatment prior to clozapine initiation. *Br J Psychiatry.* 2012;201(6):481-5. DOI: [10.1192/bjp.bp.111.105833](https://doi.org/10.1192/bjp.bp.111.105833). PubMed PMID: [22955007](https://pubmed.ncbi.nlm.nih.gov/22955007/).
54. Alessi-Severini S, Le Dorze JA, Nguyen D, Honcharik P, Eleff M. Clozapine prescribing in a Canadian outpatient population. *PLoS One.* 2013;8(12):e83539. DOI: [10.1371/journal.pone.0083539](https://doi.org/10.1371/journal.pone.0083539). PubMed PMID: [24358290](https://pubmed.ncbi.nlm.nih.gov/24358290/).
55. Verdoux H, Quiles C, Bachmann CJ, Siskind D. Prescriber and institutional barriers and facilitators of clozapine use: a systematic review. *Schizophr Res.* 2018;201:101-9. DOI: [10.1016/j.schres.2018.05.046](https://doi.org/10.1016/j.schres.2018.05.046). PubMed PMID: [29880453](https://pubmed.ncbi.nlm.nih.gov/29880453/).
56. Love RC, Kelly DL, Freudenreich O, Sayer MA, et al. Clozapine underutilization: addressing the barriers [Internet]. NASHMPD White Paper [cited 2018 Oct 12]. Available from: https://www.nasmhp.org/sites/default/files/Assessment%201_Clozapine%20Underutilization.pdf
57. Kelly DL, Freudenreich O, Sayer MKA, Love RC. Addressing barriers to clozapine underutilization: a national effort. *Psychiatr Serv.* 2018;69(2):224-7. DOI: [10.1176/appi.ps.201700162](https://doi.org/10.1176/appi.ps.201700162). PubMed PMID: [29032704](https://pubmed.ncbi.nlm.nih.gov/29032704/).
58. Carruthers J, Radigan M, Erlich MD, Gu G, Wang R, Frimpong EY, et al. An initiative to improve clozapine prescribing in New York State. *Psychiatr Serv.* 2016;67(4):369-71. DOI: [10.1176/appi.ps.201500493](https://doi.org/10.1176/appi.ps.201500493). PubMed PMID: [26725299](https://pubmed.ncbi.nlm.nih.gov/26725299/).
59. Freudenreich O, Henderson DC, Sanders KM, Goff DC. Training in a clozapine clinic for psychiatry residents: a plea and suggestions for implementation. *Acad Psychiatry.* 2013;37(1):27-30. DOI: [10.1176/appi.ap.11090159](https://doi.org/10.1176/appi.ap.11090159). PubMed PMID: [23338869](https://pubmed.ncbi.nlm.nih.gov/23338869/).
60. 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](https://doi.org/10.1176/appi.ps.201500506). PubMed PMID: [27301765](https://pubmed.ncbi.nlm.nih.gov/27301765/).
61. Hack N, Fayad SM, Monari EH, Akbar U, Hardwick A, Rodriguez RL, et al. An eight-year clinic experience with clozapine use in a Parkinson's disease clinic setting. *PLoS One.* 2014;9(3):e91545. DOI: [10.1371/journal.pone.0091545](https://doi.org/10.1371/journal.pone.0091545). PubMed PMID: [24646688](https://pubmed.ncbi.nlm.nih.gov/24646688/).
62. Williams T, Purvis TL. Development of an outpatient pharmacist-managed clozapine clinic. *Am J Health Syst Pharm.* 2012;69(14):1192-5. DOI: [10.2146/ajhp110461](https://doi.org/10.2146/ajhp110461). PubMed PMID: [22761071](https://pubmed.ncbi.nlm.nih.gov/22761071/).
63. Bishop TF, Seirup JK, Pincus HA, Ross JS. Oopulation of US practicing psychiatrists declined, 2003-13, which may help explain poor access to mental health care. *Health Aff.* 2016;35(7):1271-7. DOI: [10.1377/hlthaff.2015.1643](https://doi.org/10.1377/hlthaff.2015.1643). PubMed PMID: [27385244](https://pubmed.ncbi.nlm.nih.gov/27385244/).
64. Institute NCMD. The psychiatric shortage: causes and solutions; 2017 [cited 2018 Oct 12]. Available from: https://www.thenationalcouncil.org/wp-content/uploads/2017/03/Psychiatric-Shortage_National-Council-.pdf
65. Dishman BR, Ellenor GL, Lacro JP, Lohr JB. Pharmacists' role in clozapine therapy at a Veterans Affairs medical center. *Am J Hosp Pharm.* 1994;51(7):899-901. PubMed PMID: [8017439](https://pubmed.ncbi.nlm.nih.gov/8017439/).
66. Fairview Pharmacy Clozapine Monitoring Program [Internet]. Services FH, ed; 2018 [cited 2018 Oct 12]. Available from: <https://www.fairview.org/~media/Fairview/PDFs/Pharmacy/Clozapine-Monitoring-Infographic.ashx?la=en>
67. VanderZwaag C, McGee M, McEvoy JP, Freudenreich O, Wilson WH, Cooper TB. Response of patients with treatment-refractory

- schizophrenia to clozapine within three serum level ranges. *Am J Psychiatry*. 1996;153(12):1579-84. DOI: [10.1176/ajp.153.12.1579](https://doi.org/10.1176/ajp.153.12.1579). PubMed PMID: [8942454](https://pubmed.ncbi.nlm.nih.gov/8942454/).
68. Tsuda Y, Saruwatari J, Yasui-Furukori N. Meta-analysis: the effects of smoking on the disposition of two commonly used antipsychotic agents, olanzapine and clozapine. *BMJ Open*. 2014;4(3):e004216. DOI: [10.1136/bmjopen-2013-004216](https://doi.org/10.1136/bmjopen-2013-004216). PubMed PMID: [24595134](https://pubmed.ncbi.nlm.nih.gov/24595134/); PubMed Central PMCID: [PMC3948577](https://pubmed.ncbi.nlm.nih.gov/PMC3948577/).
69. Ng W, Uchida H, Ismail Z, Mamo DC, Rajji TK, Remington G, et al. Clozapine exposure and the impact of smoking and gender: a population pharmacokinetic study. *Ther Drug Monit*. 2009;31(3):360-6. DOI: [10.1097/FTD.0b013e31819c7037](https://doi.org/10.1097/FTD.0b013e31819c7037). PubMed PMID: [19349931](https://pubmed.ncbi.nlm.nih.gov/19349931/).
70. Mauri MC, Paletta S, Maffini M, Colasanti A, Dragogna F, Di Pace C, et al. Clinical pharmacology of atypical antipsychotics: an update. *Excli J*. 2014;13:1163-91. PubMed PMID: [26417330](https://pubmed.ncbi.nlm.nih.gov/26417330/).
71. Leenhardt F, Perier D, Pinzani V, Giraud I, Villiet M, Castet-Nicolas A, et al. Pharmacist intervention to detect drug adverse events on admission to the emergency department: two case reports of neuroleptic malignant syndrome. *J Clin Pharm Ther*. 2017;42(4):502-5. DOI: [10.1111/jcpt.12531](https://doi.org/10.1111/jcpt.12531). PubMed PMID: [28488314](https://pubmed.ncbi.nlm.nih.gov/28488314/).
72. Crismon ML, Fankhauser MP, Hinkle GH, Jann MW, Juni H, Love RC, et al. Psychiatric pharmacy practice specialty certification process. *Am J Health Syst Pharm*. 1998;55(15):1594-8. PubMed PMID: [9706186](https://pubmed.ncbi.nlm.nih.gov/9706186/).
73. Love RC, Kelly DL, Freudenreich O, Sayer M, Sanders KM, McLean MF, et al. Clozapine underutilization: addressing the barriers. National Association of State Mental Health Program Directors [cited 2016 Oct 4]. Available from: http://www.nasmhpd.org/sites/default/files/Assessment%201_Clozapine%20Underutilization.pdf
74. ASHP statement on the pharmacist's role in clinical pharmacogenomics. *Am J Health Syst Pharm*. 2015;72(7):579-81. DOI: [10.2146/sp150003](https://doi.org/10.2146/sp150003). PubMed PMID: [25788513](https://pubmed.ncbi.nlm.nih.gov/25788513/).
75. Bishop JR, Ellingrod VL. Precision pharmacotherapy enables precision medicine. *Pharmacotherapy*. 2017;37(9):985-7. DOI: [10.1002/phar.1998](https://doi.org/10.1002/phar.1998). PubMed PMID: [28836287](https://pubmed.ncbi.nlm.nih.gov/28836287/).
76. Goldstone LW, DiPaula BA, Caballero J, Park SH, Price C, Slater MZ. Improving medication-related outcomes for patients with psychiatric and neurologic disorders: value of psychiatric pharmacists as part of the health care team. *Ment Health Clin [Internet]*. 2015;5(1):1-28. DOI: [10.9740/mhc.2015.01.001](https://doi.org/10.9740/mhc.2015.01.001).
77. Raymond JR Sr, Maurana CAP, Kerschner JE. Expanding the health-care pipeline through innovation: the MCW model. *Trans Am Clin Climatol Assoc*. 2017;128:90-107. PubMed PMID: [28790490](https://pubmed.ncbi.nlm.nih.gov/28790490/).
78. Saokaew S, Permsuwan U, Chaiyakunapruk N, Nathisuwan S, Sukonthasarn A, Jeanpeerapong N. Cost-effectiveness of pharmacist-participated warfarin therapy management in Thailand. *Thrombosis Res*. 2013;132(4):437-43. DOI: [10.1016/j.thromres.2013.08.019](https://doi.org/10.1016/j.thromres.2013.08.019). PubMed PMID: [24041634](https://pubmed.ncbi.nlm.nih.gov/24041634/).
79. Johnson SG. Improving cost-effectiveness of and outcomes from drug therapy in patients with atrial fibrillation in managed care: role of the pharmacist. *J Manag Care Pharm*. 2009;15(6 Suppl B):19-25. DOI: [10.18553/jmcp.2009.15.s6-b.19](https://doi.org/10.18553/jmcp.2009.15.s6-b.19). PubMed PMID: [19678723](https://pubmed.ncbi.nlm.nih.gov/19678723/).
80. Hou K, Yang H, Ye Z, Wang Y, Liu L, Cui X. Effectiveness of pharmacist-led anticoagulation management on clinical outcomes: a systematic review and meta-analysis. *J Pharm Pharm Sci*. 2017;20(1):378-96. DOI: [10.18433/J3SQoB](https://doi.org/10.18433/J3SQoB). PubMed PMID: [29145935](https://pubmed.ncbi.nlm.nih.gov/29145935/).