Published in final edited form as:

Psychiatr Q. 2018 March ; 89(1): 157–168. doi:10.1007/s11126-017-9521-z.

Clozapine in Reducing Aggression and Violence in Forensic Populations

Kathleen Patchan¹, Gopal Vyas², Ann L. Hackman¹, Marie Mackowick³, Charles M. Richardson², Raymond C. Love⁴, Ikwunga Wonodi⁵, MacKenzie A. Sayer⁵, Matthew Glassman⁵, Stephanie Feldman⁵, and Deanna L. Kelly⁵

¹Department of Psychiatry, University of Maryland School of Medicine, 630 W Fayette St, Baltimore, MD 21201, USA

²Spring Grove Hospital and Maryland Psychiatric Research Center, University of Maryland School of Medicine, PO Box 21247, Baltimore, MD 21228, USA

³Clifton T. Perkins Hospital Center, 8450 Dorsey Run Rd, Jessup, MD 20794, USA

⁴School of Pharmacy, University of Maryland, 20 N Pine St, Baltimore, MD 21201, USA

⁵Maryland Psychiatric Research Center, University of Maryland School of Medicine, PO Box 21247, Baltimore, MD 21228, USA

Abstract

Correspondence to: Kathleen Patchan.

Kathleen M. Patchan is an Assistant Professor of Psychiatry at the University of Maryland School of Medicine.

Gopal Vyas is an Assistant Clinical Professor at the University of Maryland School of Medicine and staff psychiatrist at the Treatment Research Unit, Spring Grove Hospital Center

Ann L. Hackman is an Associate Professor of Psychiatry at the University of Maryland School of Medicine and Director of the Division of Community Psychiatry

Marie Mackowick is Director of Pharmacy at Clifton T Perkins Hospital in Jessup Maryland and the Associate Director of the Mental Health Program, University of Maryland School of Pharmacy.

Charles M. Richardson is a staff psychiatrist and Clinical Unit Director of the Treatment Research Unit at Spring Grove Hospital Center and Assistant Clinical Professor with the Department of Psychiatry at the University of Maryland School of Medicine

Raymond C. Love is Professor at the School of Pharmacy and Department of Psychiatry at the University of Maryland Baltimore. He also directs the School of Pharmacy Mental Health Program

Ikwunga Wonodi is Associate Professor of Psychiatry at the Maryland Psychiatric Research Center, University of Maryland School of Medicine

MacKenzie A. Sayer is a Research Coordinator at the Maryland Psychiatric Research Center, University of Maryland School of Medicine

Matthew Glassman is a Clinical Research Specialist at the Maryland Psychiatric Research Center, University of Maryland School of Medicine

Stephanie Feldman is Director of Research Operations, Treatment Research Program at the Maryland Psychiatric Research Center, University of Maryland School of Medicine

Deanna L. Kelly is Professor of Psychiatry at the University of Maryland School of Medicine and Director of the Treatment Research Program at the Maryland Psychiatric Research Center

Research Involving Human Participants and/or Animals

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with human participants or animals performed by any of the authors.

Compliance with Ethical Standards

This work was supported in part by grants NIMH R01 MH102215 (Kelly PI) and R01 MH105571–01 (Kelly PI). **Disclosure of**

Potential Conflicts of Interest

Dr. Raymond Love owns stock in GlaxoSmithKline. All other authors declare that they have no conflict of interest.

Popular media often portray people with a mental illness as being aggressive, violent, and incarcerated as a result of their behavior. Despite exaggeration in the media, risks for some aggressive behaviors are in fact higher in individuals with schizophrenia. This is often the case with influence of comorbid substance use disorders. It is essential that mental health professionals are aware of treatments that may help with attenuating and treating behaviors that contribute to violence, aggression and incarceration. This paper reviews violence and incarceration in individuals with schizophrenia as well as recommendations, guidelines and benefits for the use of clozapine in this population. Clozapine remains one of the most underutilized evidence-based medications available in the psychiatric arena in the United States. It is a viable and recommended option in the forensic population and it may be helpful on the path to recovery as well as bring substantial savings to the criminal justice system.

Keywords

Clozapine; Forensic; Violence; Aggression; Criminal justice

Introduction

Schizophrenia is a chronic illness characterized by “positive symptoms,” including hallucinations and delusions, and “negative symptoms,” such as apathy and anhedonia. The illness is also associated with decreased cognitive capacity and difficulty in social, work and school performance [1–4]. There is some controversy regarding the association of schizophrenia and violence. Popular media often portrays people with a mental illness as being aggressive, violent, and incarcerated as a result of their behavior; this portrayal perpetuates the stigma that all those with mental illness are dangerous.

What is discussed much less often is the fact that people diagnosed with mental illness, including schizophrenia, are more likely to be victims of violence than to be perpetrators [5] and that most people living with schizophrenia are not violent. A recent systematic review reported one year prevalence of violent victimization and found that between 7 and 56% of patients had been a victim of assault or violence [6]. Although exaggerated in the media, several studies have found increased risk for some aggressive behaviors in individuals with schizophrenia compared with the general population. A meta analysis of over 18,000 people in 20 epidemiologic studies that compared violence rates in schizophrenia to the general population, reported that approximately 9.9% of individuals with schizophrenia (compared to 1.6% of general population) exhibited violent behaviors [7]. The review also found that comorbid substance use contributes significantly to the risk of violence and suggested that the excess risk of violence in this population may be mediated largely by the use of alcohol and illicit drugs. This is important to note as drug and alcohol use disorders are common in people with schizophrenia [8] and contribute a fourfold higher risk of violence than having schizophrenia alone [7]. Regardless of underlying risk factors, when violent behaviors occur, these issues often lead to incarceration. Therefore, the high rate of involvement of individuals with schizophrenia in the criminal justice system, particularly in the United States (US), is an important public health issue. It is essential that mental health

professionals discuss treatments that may help with attenuating and treating behaviors that contribute to violence, aggression and incarceration.

Prevalence of Criminal and Legal Charges in People with Schizophrenia

An increasing number of individuals with schizophrenia are involved with the criminal justice system. Despite promising advances in early intervention [9] and increasing focus on jail diversion, more than one million individuals with a serious mental illness are in county jails. Such individuals are imprisoned eight times more frequently than they are admitted to state psychiatric hospitals [10, 11]. Furthermore, many of these individuals with severe mental illness entering the county jails would have been previously sent to state-operated psychiatric facilities. Instead, they are now being displaced by larger numbers of forensic patients entering state systems because of their legal entanglements. Contributing factors include closure of state-funded psychiatric institutions that had historically provided a safety net, inadequate community mental health resources, poverty, and transient lifestyles that lead to increasing encounters between those with mental illness and the criminal justice system. Once in the correctional setting, people with serious mental illness are likely to have longer sentences. One report found that individuals with schizophrenia were more likely to remain in prison and complete their entire sentence, less likely to be paroled or placed on probation, more likely to incur violent infractions, and were moved more often for medical or disciplinary reasons [9].

The National Commission on Correctional Health Care published a report in 1994 estimating that, on any given day, 1% of the population in US jails may have a psychotic disorder. Data from 1999 suggest that as many as 5% of prison inmates may have schizophrenia, five times higher than rates in the general population [12]. In 2005, the Bureau of Justice Statistics (BJS) estimated that 705,600 adults with mental illness were incarcerated in state prisons, 78,800 in federal prisons and 479,900 in local jails. These estimates account for up to 50% of the entire correctional population. The estimates exceed 75% when one includes individuals with substance abuse problems [13].

Soyka et al. [14] reviewed the national crime register for records of criminal offenses committed by 1662 patients with schizophrenia in a German inpatient psychiatric hospital and found that 10% of these patients had been convicted 7–12 years after discharge. The rate of violent crimes was especially high, with 3.7% of patients convicted for physical injury offenses, including manslaughter or murder. Another cross-sectional study by Ghoreishi et al. [15] found that more than 59% of people with schizophrenia were offenders with criminal status in an Iranian study. In the US, one study found that 46% of schizophrenia patients were involved with the legal system [16]. Greenberg et al. [17] examined variables of schizophrenia patients that were correlated with 12-month involvement in the criminal justice system. Data were taken from subjects enrolled in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) from 2001 to 2004. A history of childhood conduct disorder, being young, male, African American, a history of akathisia, and substance use increased the risk for involvement in the criminal justice system. In fact, many states report a high prevalence of schizophrenia within criminal justice systems [18–21]. For example, of almost 35,000 prisoners in the State of Florida, 15% had schizophrenia [22]. Substance

abuse also contributes to the risk of incarceration in this group [23]. In another large study of over 79,000 inmates, those with major psychiatric disorders such as schizophrenia were found to be at a substantially higher risk of multiple incarcerations [18]. This group represents a population that is very difficult to treat and costly to the system.

Costs of Mental Illness and Forensic Issues

The cost of providing care for individuals in the correctional system in the US is considerable. Robertson et al. [24] examined data from 25,133 adults involved in Connecticut's public behavioral health system. Nearly 27% of the sample, 37% of whom had schizophrenia, was involved in the legal system during the two year study period. After controlling for gender, age, and race-ethnicity, treatment costs were nearly 27% higher for those involved in the legal system compared with those who were not (\$31,166 versus \$24,602). Total predicted treatment costs for justice-involved adults with schizophrenia (\$61,824) were nearly 70% higher than the costs for adults with schizophrenia and no justice involvement (\$36,408).

Ascher-Svanum et al. [16] compared costs of 609 patients with schizophrenia with and without involvement in the criminal justice system. Overall, 278 (46%) of 609 participants reported at least one criminal justice system encounter. This group was also more likely to be substance users and noncompliant with antipsychotic treatment compared to participants without justice involvement. The mean annual per-patient cost of involvement was \$1429, translating to 6% of total annual direct health care costs for those with involvement (11% when excluding crime victims). Thus, not only is mental illness high within prison populations, the costs to society are enormous and maximizing effective treatments and medications is paramount to manage costs in our health care and criminal justice systems.

Medication Strategies in the Forensic Population

Given the prevalence of violence among individuals with schizophrenia, efforts should be made to consider ways to mitigate violent acts, especially in the forensic population. The antipsychotic clozapine may be a useful medication in this regard. There is emerging research that indicates that clozapine can reduce violence, in addition to demonstrating efficacy among those with treatment resistant schizophrenia. A recent White Paper from the National Association of State Mental Health Program Directors (NASMHPD) has recommended that all forensic facilities adopt clozapine procedures and have clozapine available [25].

Clozapine Background

Clozapine was formally marketed in the 1960s as a treatment for schizophrenia. Numerous clinical trials demonstrated its efficacy over traditional first-generation antipsychotics and its second-generation competitors. Kane et al. [26] in their landmark study found that 30% of treatment resistant schizophrenia subjects randomized to clozapine had significant improvement in positive and negative symptoms compared to 4% of subjects randomized to chlorpromazine. At least five meta-analyses have reported that clozapine is superior to both

first-generation and second-generation antipsychotics in treatment-resistant schizophrenia with moderate effect size [27–32]. It is, without doubt, a superior antipsychotic for the treatment of schizophrenia.

Clozapine is also the most effective antipsychotic for aggressive and violent behavior. Frogley et al. [33] performed a systematic literature review to investigate clozapine's anti-aggressive effects in a variety of mental disorders. The review identified six animal studies, four randomized controlled trials, 12 prospective non-controlled studies and 22 retrospective studies, with four case studies. The authors found considerable evidence in support of clozapine's ability to reduce violent and aggressive behavior, specifically in those with treatment-resistant schizophrenia. Citrome et al. [34] and Volavka et al. [35] found clozapine to be the only agent to reduce hostility on the Positive and Negative Syndrome Scale (PANSS) in a clinical trial (effect size = 0.25). Comparable effect sizes for olanzapine, risperidone, and haloperidol were 0.06, 0.05, and 0.03 respectively. Furthermore, clozapine was more effective than haloperidol at reducing the number and severity of aggressive once an adequate clozapine dose had been achieved (mean 465.2 mg/d). Krakowski et al. [36] found that clozapine was associated with statistically significant reductions in physical and verbal aggression scores compared to olanzapine and haloperidol in a large double blind 12 week clinical trial. Additionally, clozapine was associated with a statistically significant reduction in violence against property, compared to haloperidol, but not olanzapine.

Victoroff et al. [37] followed up with another systemic review to determine the effectiveness of antipsychotics in managing hostility and aggression in individuals with schizophrenia spectrum disorders. Based on this review, they concluded that clozapine is more effective than other antipsychotics for the management of hostility. Finally, it is noteworthy that clozapine is the only FDA approved medication for the treatment of suicidality, making it a unique medication that has the ability to reduce aggression towards self as well as others. Thus, the Schizophrenia Patient Outcomes Research Team (PORT) treatment guidelines specify that clozapine is the best choice for patients with suicidal behaviors but also recommends clozapine for those with persistent violent or aggressive behaviors [38].

Clozapine in the Forensic Setting

Due to this medication's superiority in schizophrenia and its ability to reduce violent and aggressive behaviors, clozapine is a unique and possibly ideal choice for treatment in the forensic population. A handful of studies in England, Australia, and Scotland have examined the effect of clozapine in forensic populations.

Practitioners working with the forensic population in Britain have extensive experience prescribing clozapine. Stone-Brown et al. [39] found that nearly 30% of seriously violent men with schizophrenia and/or personality disorders were prescribed clozapine. Qurashi et al. [40] assessed the impact of clozapine on patient's subjective well-being and effectiveness compared to other antipsychotics using a five-point scale. Subjects included 56 men at a British forensic hospital who had been treated with clozapine for a minimum of 90 days. An estimated 89% of respondents reported greater satisfaction with clozapine than with their previously prescribed antipsychotic medication. A majority of patients reported positive

effects in terms of an improvement in their quality of life (68%) and social abilities (52%) with clozapine in comparison with previously prescribed antipsychotics. Smith and White [41] found that among 32 forensic patients participating in a psychiatric day program, 19 were prescribed clozapine while the remaining 13 received long-acting injectable antipsychotic medications or oral formulations of olanzapine, quetiapine, or sulpride. Although not statistically significant in the small sample, patients prescribed clozapine were less likely to be hostile or destructive than those prescribed other antipsychotics.

Furthermore, Buscema et al. [42] proposed an algorithm for treating individuals with schizophrenia in the correctional setting. The Forensic Algorithm Project proposed four tracks of intervention, one of which includes the use of clozapine when other antipsychotics had not been effective [39–41, 43]. However, literature on clozapine in the forensic setting is limited due to the restriction of studying medication prospectively in a forensic setting with special federal Institutional Review Board approvals needed.

Barriers to Clozapine

Clozapine use is often associated with a variety of adverse effects including hyper-salivation, tachycardia, enuresis, sweating, metabolic syndrome and constipation. Among the more serious are the risks of myocarditis, [44] cardiomyopathy, [45] seizures, [46] and a 0.05–0.86% risk of severe neutropenia. [47–51] Constipation with clozapine has also been known to be serious with cases of ileus and bowel perforation [52]. However, it is the concern for severe neutropenia that has led to mandated regular monitoring of neutrophil counts by the Food and Drug Administration (FDA), representing one of the most difficult challenges to routine use and one of the biggest barriers to more widespread use [53–56].

With the risk of some potentially serious side effects, the decision to use clozapine requires a risk to benefit consideration through a patient centered approach—a system that facilitates safe and appropriate use [57]. Many correctional systems are independent of other public mental health systems and providing routine psychiatric care is a challenge given the violent nature of inmates; many of whom have psychiatric illness. The complexities of using clozapine, including routine blood draws and the scarcity of psychiatric services, leads to clozapine being an overlooked and rarely used treatment in forensic settings. In fact, the forensic setting is optimal for the initiation and use of clozapine in appropriate patients in that medication adherence can be closely monitored and regular laboratory assessment insured. Both more frequent use of clozapine and integration of mental health services [58] could lead to better outcomes such as less recidivism.

African American Patients and Benign Ethnic Neutropenia

Minorities may be over represented in the criminal justice system. Specifically, African Americans compose 37% of the total male population compared to 32% of non-Latino white males, and 22% Latino males. Conversely, white females compose 49% of the prison population compared to 22% of African American females. This is important to note as racial disparities are present in clozapine prescribing and use. The frequency of clozapine use has been found to be lower in African-American patients compared to White patients.

[59–62] African Americans are twice as likely to have their clozapine discontinued due to their white blood cell count (WBC) or absolute neutrophil count (ANC) falling below the FDA mandated thresholds for monitoring [62, 63]. Some have found that the fear of neutropenia was the most cited reason for discontinuation of clozapine in African-American patients [64]. Benign Ethnic Neutropenia (BEN) may explain these high fluctuations and discontinuations in this racial group. Thus, racial minorities may be systematically excluded from the most effective treatment available for treatment-resistant schizophrenia.

BEN occurs in people of African or Middle Eastern ancestry and identifies a group with low ANCs who do not have an increased risk of severe neutropenia or infection [65–67]. These low ANC's are not related to clozapine exposure, but occur as a baseline finding. Recent evidence possibly implicates a genetic polymorphism in the pathophysiology of BEN. [68–72] While there is no universally accepted definition of BEN, it has been defined as “the occurrence of neutropenia, defined by normative data in European Ancestry (EA) populations, in individuals of other ethnic groups who are otherwise healthy and do not have repeated or severe infections” [65]. BEN is diagnosed by repeated low measurements of ANC (usually <1500 cells/mm³ without identifiable causes of neutropenia) [73].

New U.S. clozapine prescribing information and monitoring guidelines went into effect in 2015 offering separate algorithms for monitoring patients with and without BEN and establishing a lower ANC threshold for discontinuation for those with BEN. The patient enrollment webpage for patients in the new Clozapine REMS allows the prescriber to indicate that the patient enrolling has BEN. Unlike similar guidelines in the UK, there is no mandate for a hematology consult to establish that a patient has BEN. The new guidelines are meant to facilitate access to clozapine and reduce unnecessary interruptions in treatment. This new guideline may facilitate greater use of clozapine, particularly in those of African descent whose access may have been limited by low baseline ANCs.

Summary

Evidence-based guidelines recommend clozapine in the treatment of violent and aggressive behaviors. These recommendations are especially important to the forensic population. Clozapine is the one agent that has demonstrated superiority in the treatment of schizophrenia, with evidence of its efficacy in violent and aggressive behavior. New clozapine labeling should also facilitate use in patients of African descent.

Given its ability to reduce psychotic symptoms and violence, clozapine may have obvious stabilizing effects on those with severe mental illness. However, the stability of those receiving clozapine is jeopardized if the correctional facility to which they are admitted does not have a system for administering and monitoring the drug. Discontinuation can result from failing to include clozapine on a formulary or failure to prescribe due to fear of side effects. Failure to continue clozapine can result in the risk of a florid psychotic relapse, rebound side effects and an elevated risk for both aggression and suicidal behavior [74–77]. Thus, this paper not only advocates for increased utilization of clozapine in forensic and correctional settings, but development of appropriate monitoring systems and safeguards to reduce inappropriate discontinuation.

Finally, clozapine offers benefits beyond its clinical efficacy. When compared to brand name antipsychotics, generically available clozapine may be considerably less expensive. The reduction in aggressive behaviors may also lead to reduced resource utilization. Both of these factors yield financial dividends for systems providing access to this superior drug.

In conclusion, clozapine is one of the most underutilized evidence based medications available in the psychiatric arena. It is a viable and recommended option in the forensic population and is more effective than other agents for treatment-resistant schizophrenia and reducing violence. For these reasons, clozapine offers the possibility of shorter incarcerations, less recidivism, and better quality of life. Furthermore, it may be helpful on the path to recovery as well as bringing substantial savings to the criminal justice system.

Acknowledgments

This work was supported in part by grants NIMH R01 MH102215 (Kelly PI) and R01 MH105571-01 (Kelly PI).

References

1. Bortolato B, Miskowiak KW, Kohler CA, et al. Cognitive dysfunction in bipolar disorder and schizophrenia: a systematic review of meta-analyses. *Neuropsychiatr Dis Treat*. 2015; 11:3111–3125. [PubMed: 26719696]
2. Carbon M, Correll CU. Thinking and acting beyond the positive: the role of the cognitive and negative symptoms in schizophrenia. *CNS Spectr*. 2014; 19(Suppl 1):38–52. quiz 35–37, 53. [PubMed: 25403863]
3. Lysaker PH, Vohs J, Minor KS, et al. Metacognitive Deficits in Schizophrenia: Presence and Associations With Psychosocial Outcomes. *J Nerv Ment Dis*. 2015; 203:530–536. [PubMed: 26121151]
4. Bouwmans C, de Sonnevile C, Mulder CL, et al. Employment and the associated impact on quality of life in people diagnosed with schizophrenia. *Neuropsychiatr Dis Treat*. 2015; 11:2125–2142. [PubMed: 26316759]
5. Brekke JS, Prindle C, Bae SW, et al. Risks for individuals with schizophrenia who are living in the community. *Psychiatr Serv*. 2001; 52:1358–1366. [PubMed: 11585953]
6. Latalova K, Kamaradova D, Prasko J. Violent victimization of adult patients with severe mental illness: a systematic review. *Neuropsychiatr Dis Treat*. 2014; 10:1925–1939. [PubMed: 25336958]
7. Fazel S, Gulati G, Linsell L, et al. Schizophrenia and violence: systematic review and meta-analysis. *PLoS Med*. 2009; 6:e1000120. [PubMed: 19668362]
8. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. *JAMA*. 1990; 264:2511–2518. [PubMed: 2232018]
9. Mueser KT, Penn DL, Addington J, et al. The NAVIGATE Program for First-Episode Psychosis: Rationale, Overview, and Description of Psychosocial Components. *Psychiatr Serv*. 2015; 66:680–690. [PubMed: 25772766]
10. Dixon LB, Goldman HH, Bennett ME, et al. Implementing Coordinated Specialty Care for Early Psychosis: The RAISE Connection Program. *Psychiatr Serv*. 2015; 66:691–698. [PubMed: 25772764]
11. Miami-Dade County Criminal Mental Health Project. [cited 2016 9/7]; Available from: <http://www.jud11.flcourts.org/Criminal-Mental-Health-Project>
12. Weinstein H, Kim D, Mack A, et al. Prevalence and assessment of mental disorders in correctional settings. *Handbook of correctional mental health*. 2005:43–68.
13. James, D., Glaze, L. Mental health problems of prison and jail inmates (Bureau of Justice Statistics Special Report, NCJ 213600). Washington, DC: Department of Justice; 2006.

14. Soyka M, Morhart-Klute V, Schoech H. Delinquency and criminal offenses in former schizophrenic inpatients 7–12 years following discharge. *Eur Arch Psychiatry Clin Neurosci*. 2004; 254:289–294. [PubMed: 15365703]
15. Ghoreishi A, Kabootvand S, Zangani E, et al. Prevalence and attributes of criminality in patients with schizophrenia. *J Inj Violence Res*. 2015; 7:7–12. [PubMed: 24879076]
16. Ascher-Svanum H, Nyhuis AW, Faries DE, et al. Involvement in the US criminal justice system and cost implications for persons treated for schizophrenia. *BMC Psychiatry*. 2010; 10:11. [PubMed: 20109170]
17. Greenberg G, Rosenheck RA, Erickson SK, et al. Criminal justice system involvement among people with schizophrenia. *Community Ment Health J*. 2011; 47:727–736. [PubMed: 21113799]
18. Baillargeon J, Binswanger IA, Penn JV, et al. Psychiatric disorders and repeat incarcerations: the revolving prison door. *Am J Psychiatry*. 2009; 166:103–109. [PubMed: 19047321]
19. Steadman HJ, Osher FC, Robbins PC, et al. Prevalence of serious mental illness among jail inmates. *Psychiatr Serv*. 2009; 60:761–765. [PubMed: 19487344]
20. Fazel S, Danesh J. Serious mental disorder in 23000 prisoners: a systematic review of 62 surveys. *Lancet*. 2002; 359:545–550. [PubMed: 11867106]
21. Hawthorne WB, Folsom DP, Sommerfeld DH, et al. Incarceration among adults who are in the public mental health system: rates, risk factors, and short-term outcomes. *Psychiatr Serv*. 2012; 63:26–32. [PubMed: 22227756]
22. Lin I, Muser E, Munsell M, et al. Economic impact of psychiatric relapse and recidivism among adults with schizophrenia recently released from incarceration: a Markov model analysis. *J Med Econ*. 2015; 18:219–229. [PubMed: 25266814]
23. Robertson AG, Swanson JW, Frisman LK, et al. Patterns of justice involvement among adults with schizophrenia and bipolar disorder: key risk factors. *Psychiatr Serv*. 2014; 65:931–938. [PubMed: 24633645]
24. Robertson AG, Swanson JW, Lin H, et al. Influence of Criminal Justice Involvement and Psychiatric Diagnoses on Treatment Costs Among Adults With Serious Mental Illness. *Psychiatr Serv*. 2015; 66:907–909. [PubMed: 25975893]
25. Love, RC., Kelly, DL., Freudenreich, O., et al. Clozapine underutilization: Addressing the barriers. National Association of State Mental Health Program Directors; 2016. [cited 2016 October 4]; Available from: http://www.nasmhpd.org/sites/default/files/Assessment%20_Clozapine%20Underutilization.pdf
26. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry*. 1988; 45:789–796. [PubMed: 3046553]
27. Wahlbeck K, Cheine M, Essali A, et al. Evidence of clozapine's effectiveness in schizophrenia: a systematic review and meta-analysis of randomized trials. *Am J Psychiatry*. 1999; 156:990–999. [PubMed: 10401441]
28. Chakos M, Lieberman J, Hoffman E, et al. Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. *Am J Psychiatry*. 2001; 158:518–526. [PubMed: 11282684]
29. Tuunainen A, Wahlbeck K, Gilbody S. Newer atypical antipsychotic medication in comparison to clozapine: a systematic review of randomized trials. *Schizophr Res*. 2002; 56:1–10. [PubMed: 12084413]
30. Sinclair D, Adams CE. Treatment resistant schizophrenia: a comprehensive survey of randomised controlled trials. *BMC Psychiatry*. 2014; 14:253. [PubMed: 25227719]
31. 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; 13:1545–1573. [PubMed: 21999805]
32. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013; 382:951–962. [PubMed: 23810019]
33. Frogley C, Taylor D, Dickens G, et al. A systematic review of the evidence of clozapine's anti-aggressive effects. *Int J Neuropsychopharmacol*. 2012; 15:1351–1371. [PubMed: 22339930]

34. Citrome L, Volavka J, Czobor P, et al. Effects of clozapine, olanzapine, risperidone, and haloperidol on hostility among patients with schizophrenia. *Psychiatr Serv.* 2001; 52:1510–1514. [PubMed: 11684748]
35. Volavka J, Czobor P, Sheitman B, et al. Clozapine, olanzapine, risperidone, and haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder. *Am J Psychiatry.* 2002; 159:255–262. [PubMed: 11823268]
36. Krakowski MI, Czobor P, Nolan KA. Atypical antipsychotics, neurocognitive deficits, and aggression in schizophrenic patients. *J Clin Psychopharmacol.* 2008; 28:485–493. [PubMed: 18794642]
37. Victoroff J, Coburn K, Reeve A, et al. Pharmacological management of persistent hostility and aggression in persons with schizophrenia spectrum disorders: a systematic review. *J Neuropsychiatry Clin Neurosci.* 2014; 26:283–312. [PubMed: 26037853]
38. Buchanan RW, Kreyenbuhl J, Kelly DL, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull.* 2010; 36:71–93. [PubMed: 19955390]
39. Stone-Brown K, Naji M, Francioni A, et al. Psychotropic prescribing in seriously violent men with schizophrenia or personality disorder in a UK high security hospital. *CNS Spectr.* 2016; 21:60–69. [PubMed: 26726766]
40. Qurashi I, Stephenson P, Chu S, et al. An evaluation of subjective experiences, effects and overall satisfaction with clozapine treatment in a UK forensic service. *Ther Adv Psychopharmacol.* 2015; 5:146–150. [PubMed: 26199716]
41. Smith H, White T. The effect of clozapine on the social behaviour schedule in patients attending a forensic psychiatry day hospital. *Med Sci Law.* 2004; 44:213–216. [PubMed: 15296244]
42. Buscema CA, Abbasi QA, Barry DJ, et al. An algorithm for the treatment of schizophrenia in the correctional setting: the Forensic Algorithm Project. *J Clin Psychiatry.* 2000; 61:767–783. [PubMed: 11078038]
43. Martin A, O'Driscoll C, Samuels A. Clozapine use in a forensic population in a New South Wales prison hospital. *Aust N Z J Psychiatry.* 2008; 42:141–146. [PubMed: 18197509]
44. Ronaldson KJ, Fitzgerald PB, McNeil JJ. Clozapine-induced myocarditis, a widely overlooked adverse reaction. *Acta Psychiatr Scand.* 2015; 132:231–240. [PubMed: 25865238]
45. Alawami M, Wasywich C, Cicovic A, et al. A systematic review of clozapine induced cardiomyopathy. *Int J Cardiol.* 2014; 176:315–320. [PubMed: 25131906]
46. Williams AM, Park SH. Seizure associated with clozapine: incidence, etiology, and management. *CNS Drugs.* 2015; 29:101–111. [PubMed: 25537107]
47. Honigfeld G, Arellano F, Sethi J, et al. Reducing clozapine-related morbidity and mortality: 5 years of experience with the Clozaril National Registry. *J Clin Psychiatry.* 1998; 59(Suppl 3):3–7.
48. Munro J, O'Sullivan D, Andrews C, et al. Active monitoring of 12,760 clozapine recipients in the UK and Ireland. Beyond pharmacovigilance. *The British Journal of Psychiatry.* 1999; 175:576–580. [PubMed: 10789357]
49. Lahdelma L, Appelberg B. Clozapine-induced agranulocytosis in Finland, 1982–2007: long-term monitoring of patients is still warranted. *J Clin Psychiatry.* 2012; 73:837–842. [PubMed: 22480452]
50. Drew L. Clozapine and agranulocytosis: re-assessing the risks. *Australas Psychiatry.* 2013; 21:335–337. [PubMed: 23804114]
51. Balda MV, Garay OU, Papale RM, et al. Clozapine-associated neutropenia and agranulocytosis in Argentina (2007–2012). *Int Clin Psychopharmacol.* 2015; 30:109–114. [PubMed: 25486383]
52. Ikai S, Suzuki T, Uchida H, et al. Reintroduction of clozapine after perforation of the large intestine—a case report and review of the literature. *Ann Pharmacother.* 2013; 47:e31. [PubMed: 23757383]
53. Kelly DL, Ben-Yoav H, Payne GF, et al. Blood Draw Barriers for Treatment with Clozapine and Development of Point-of-Care Monitoring Device. *Clin Schizophr Relat Psychoses.* 2015
54. Gee S, Vergunst F, Howes O, et al. Practitioner attitudes to clozapine initiation. *Acta Psychiatr Scand.* 2014; 130:16–24. [PubMed: 24004162]

55. Tungaraza TE, Farooq S. Clozapine prescribing in the UK: views and experience of consultant psychiatrists. *Ther Adv Psychopharmacol*. 2015; 5:88–96. [PubMed: 26240748]
56. NC Division of Mental Health, Developmental Disabilities and Substance Abuse Services and the North Carolina Psychiatric Association. Clozapine (Clozaril): an underutilized evidence based treatment [PowerPoint Slides]. n.d. Retrieved from <http://naminc.org/nn/0910Conf/clozapineresearch.pdf>
57. Hill M, Freudenreich O. Clozapine: key discussion points for prescribers. *Clin Schizophr Relat Psychoses*. 2013; 6:177–185. [PubMed: 23302447]
58. Citrome L, Volavka J. Pharmacological management of acute and persistent aggression in forensic psychiatry settings. *CNS Drugs*. 2011; 25:1009–1021. [PubMed: 22133324]
59. Kelly DL, Dixon LB, Kreyenbuhl JA, et al. Clozapine utilization and outcomes by race in a public mental health system: 1994–2000. *J Clin Psychiatry*. 2006; 67:1404–1411. [PubMed: 17017827]
60. Mallinger JB, Fisher SG, Brown T, et al. Racial disparities in the use of second-generation antipsychotics for the treatment of schizophrenia. *Psychiatr Serv*. 2006; 57:133–136. [PubMed: 16399976]
61. Copeland LA, Zeber JE, Valenstein M, et al. Racial disparity in the use of atypical antipsychotic medications among veterans. *Am J Psychiatry*. 2003; 160:1817–1822. [PubMed: 14514496]
62. Kelly DL, Kreyenbuhl J, Dixon L, et al. Clozapine underutilization and discontinuation in African Americans due to leucopenia. *Schizophr Bull*. 2007; 33:1221–1224. [PubMed: 17170061]
63. Moeller FG, Chen YW, Steinberg JL, et al. Risk factors for clozapine discontinuation among 805 patients in the VA hospital system. *Ann Clin Psychiatry*. 1995; 7:167–173. [PubMed: 8721890]
64. Pai NB, Vella SC. Reason for clozapine cessation. *Acta Psychiatr Scand*. 2012; 125:39–44. [PubMed: 22017729]
65. Haddy TB, Rana SR, Castro O. Benign ethnic neutropenia: what is a normal absolute neutrophil count? *J Lab Clin Med*. 1999; 133:15–22. [PubMed: 10385477]
66. Denic S, Showqi S, Klein C, et al. Prevalence, phenotype and inheritance of benign neutropenia in Arabs. *BMC Blood Disord*. 2009; 9:3. [PubMed: 19323844]
67. Shoenfeld Y, Alkan ML, Asaly A, et al. Benign familial leukopenia and neutropenia in different ethnic groups. *Eur J Haematol*. 1988; 41:273–277. [PubMed: 3181399]
68. Crosslin DR, McDavid A, Weston N, et al. Genetic variants associated with the white blood cell count in 13,923 subjects in the eMERGE Network. *Hum Genet*. 2012; 131:639–652. [PubMed: 22037903]
69. Paz Z, Nails M, Ziv E. The genetics of benign neutropenia. *Isr Med Assoc J*. 2011; 13:625–629. [PubMed: 22097233]
70. Nalls MA, Wilson JG, Patterson NJ, et al. Admixture mapping of white cell count: genetic locus responsible for lower white blood cell count in the Health ABC and Jackson Heart studies. *Am J Hum Genet*. 2008; 82:81–87. [PubMed: 18179887]
71. Abecasis GR, Altshuler D, Auton A, et al. A map of human genome variation from population-scale sequencing. *Nature*. 2010; 467:1061–1073. [PubMed: 20981092]
72. Reich D, Nalls MA, Kao WH, et al. Reduced neutrophil count in people of African descent is due to a regulatory variant in the Duffy antigen receptor for chemokines gene. *PLoS Genet*. 2009; 5:e1000360. [PubMed: 19180233]
73. Thobakgale CF, Ndung'u T. Neutrophil counts in persons of African origin. *Curr Opin Hematol*. 2014; 21:50–57. [PubMed: 24257098]
74. Patchan KM, Richardson C, Vyas G, et al. The risk of suicide after clozapine discontinuation: Cause for concern. *Ann Clin Psychiatry*. 2015; 27:253–256. [PubMed: 26554366]
75. Buchanan RW. Clozapine: efficacy and safety. *Schizophr Bull*. 1995; 21:579–591. [PubMed: 8749886]
76. Borison RL, Diamond BI, Sinha D, et al. Clozapine withdrawal rebound psychosis. *Psychopharmacol Bull*. 1988; 24:260–263. [PubMed: 3212159]
77. Shiovitz TM, Welke TL, Tigel PD, et al. Cholinergic rebound and rapid onset psychosis following abrupt clozapine withdrawal. *Schizophr Bull*. 1996; 22:591–595. [PubMed: 8938913]

Biography

Vignette:

Mr. R. is a 54 year old African American man who is diagnosed with Schizophrenia. His symptoms began in childhood and included visual and auditory hallucinations that often commanded him to set fires and harm animals. Mr. R. believed that if he did not comply with these commands, he and his family would face dire consequences. He received little treatment and by his teenage years, he was using illicit drugs and getting in considerable trouble. Medications provided minimal relief. By age 40, Mr. R. had been in and out of jails, prisons, and psychiatric hospitals. Extensive legal charges included nuisance crimes, such as trespassing, rogue and vagabond, burglary, breaking and entering, and Controlled Dangerous Substances (CDS) possession. More serious charges included deadly weapon possession, assault and battery and arson (which destroyed a private residence). Mr. R.'s last incarceration, on these arson charges, resulted in four years of imprisonment, a significant portion of which was spent in solitary confinement because of problematic behaviors, such as fighting. Immediately upon release from incarceration, Mr. R. was psychiatrically hospitalized and started on clozapine. For the first time in his life, he experienced relief from his psychiatric symptoms. Subsequently he stopped using illicit drugs. He focused on maintaining sobriety and getting his life back together. He has now been in the community for nine years with no new legal charges or incarceration. He has avoided altercations and has not presented a danger to himself or others. He attends church every Sunday and has a part-time job. He attributes this success to clozapine, which he reports has transformed his life.