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Assessment #1

Clozapine Underutilization: Addressing the Barriers

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Clozapine Underutilization: Addressing the Barriers

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Executive Summary

Clozapine is a medication that exhibits unique efficacy and effectiveness for those with serious mental illness. However, its side effects present challenges to its use. These challenges have evolved into a set of barriers that discourage the use of clozapine. The barriers include a lack of prescriber knowledge and confidence, negative prescriber attitudes, special monitoring requirements, administrative factors, lack of preparation by health systems, and inadequate understanding or acknowledgement of clozapine's unique nature by policy makers, and payers.

Proven approaches using inter-professional models of care can help meet the needs of patients receiving clozapine. State and local government, federal agencies, academic medical centers, prescribers, researchers, and the pharmaceutical industry all have vital roles to play in increasing access to clozapine for those with serious mental illness.

Introduction: Importance of Clozapine

While clozapine has demonstrated unique efficacy for the treatment of serious mental illness, its real-world use presents challenges to clinicians in a variety of settings, leading to its under-utilization. These challenges can best be addressed by understanding the benefits and risks of clozapine, its place in treatment, and the barriers that impact clozapine treatment. In addition to identifying specific barriers, this paper offers a series of recommendations for a variety of stakeholders that, if implemented, would promote access to clozapine, address barriers to its use, and improve the management of patients receiving clozapine.

Background

Clozapine's Efficacy

Clozapine is the most effective antipsychotic for patients with schizophrenia who do not respond to treatment with first- or second-generation antipsychotics.^[1] Several meta-analyses of controlled trials and systematic reviews of clozapine provide evidence of its superiority.^[2-7] The most recent meta-analysis^[8] reported that clozapine (effect size relative to placebo= 0.88) was almost twice as efficacious as other available antipsychotics. Large effectiveness studies, such as the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) study (phase 2),^[9] demonstrated benefits such as longer treatment duration. The Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 2)^[10] found that clozapine was associated with greater symptom improvement and higher patient satisfaction ratings. Another large effectiveness study, the Schizophrenia Outpatient Health Outcomes (SOHO) study, also found clozapine to be superior to other antipsychotics on clinician and patient ratings after six months of treatment.^[11]

Broader Range Effectiveness of Clozapine

Clozapine is recognized as superior to other antipsychotics in several treatment guidelines and recommendations for treatment resistant schizophrenia. The Schizophrenia Patient Outcomes Research Team (PORT)^[12] summarizes the large evidence-based literature supporting clozapine as the gold standard and recommends that patients with persistent positive symptoms of schizophrenia receive an adequate trial of clozapine. More recent guidelines that recommend clozapine after two failed antipsychotic trials include the Harvard South Shore Program Algorithm^[13] and the British Association for Psychopharmacology Guidelines.^[14] The National Institute for Health, and Care Excellence (NICE) Clinical Guideline for Schizophrenia, which is evidence-based and updated regularly, acknowledges the value of clozapine for refractory psychosis and recommends that prescribers, “offer clozapine to people with schizophrenia whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least [two] different antipsychotic drugs.”^[15] The early use of clozapine is critical for young patients with schizophrenia who are treatment-refractory and for whom only clozapine offers a chance for improvement and course stabilization as the basis for recovery.^[16]

In addition to schizophrenia and schizoaffective disorder, accumulating evidence supports clozapine's utility for a variety of other disorders and conditions, such as the treatment of hostility and aggression,^[17] treatment-resistant bipolar disorder,^[18] psychogenic polydipsia/hyponatremia,^[19] Parkinson's disease psychosis^[20] and psychosis in Lewy body dementia,^[21] borderline personality disorder^[22], and tardive dyskinesia (TD).^[23] Growing evidence also suggests clozapine may be an option in youth with early onset schizophrenia.^[24] Importantly, clozapine is the only antipsychotic with a Food and Drug Administration approval for suicidality. Due in part to this unique action of clozapine, this medication has been shown in two large epidemiologic studies to have the lowest mortality rate among all antipsychotic treatments.^[25] Lastly, Velligan and colleagues have demonstrated that the use of clozapine was cost-effective in a Medicaid population.^[26] Thus, clozapine may actually result in substantial overall system costs in the long run. Given clozapine's efficacy, it should not be relegated to a third-line treatment used only after many years of poor symptom control and functioning.^[27]

Risk to Benefit Profile of Clozapine

Clozapine use is associated with a variety of side effects, some of which are potentially serious. Common side effects include hyper-salivation, tachycardia, enuresis, sweating, eosinophilia, metabolic syndrome, and constipation.^[28-30] Among the more serious side effects of clozapine are an approximately 3 percent risk of myocarditis^[31] and 0.02 percent to 0.1 percent risk of cardiomyopathy,^[32] 1 to 3 percent risk of seizures,^[33] and a 0.05 to 0.86 percent risk of severe neutropenia.^[34-38] It is this severe neutropenia risk that has led the Federal Food and Drug Administration (FDA) to mandate regular blood draws to monitor the absolute neutrophil count.

Constipation with clozapine may be severe and fatal, leading to complications such as ileus and bowel perforation.^[39] 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.^[40] Often ignored in risk-benefit discussions are the psychiatric and medical risks of not using clozapine. While clozapine might pose particular problems, other antipsychotics are not devoid of such medical risks (e.g., metabolic problems associated with antipsychotics), and the frequently employed practice of polypharmacy—with its potentially more serious risks—is not necessarily medically safer than clozapine monotherapy.^[41] In addition, poorly treated psychiatric illness can complicate medical treatment.

Underuse of Clozapine

Despite the overwhelming evidence of clozapine's superior efficacy and effectiveness, and its availability in generic form, clozapine is prescribed infrequently in the U.S., at a rate considerably lower than the estimated prevalence of treatment-resistant schizophrenia.^[42-46] The use of clozapine in the US has been steadily declining, from 11 percent of all antipsychotic prescriptions in 1999, to about 4 percent in 2008.^[25] In contrast, it is more frequently used in other countries (e.g., antipsychotic market share 36 to 38 percent in Australia, 26 percent in China, 20 to 30 percent in Taiwan).^[43, 47] Despite

the lack of evidence to support antipsychotic polypharmacy for treatment resistant schizophrenia, multiple antipsychotics are more frequently prescribed than clozapine monotherapy, suggesting that many clinicians choose unproven strategies over clozapine.^[48, 49] Medicaid and pharmacy prescription data from all 50 states found that only 6 states (Washington, Colorado, South Dakota, Connecticut, Vermont, and Maine) used clozapine at the “bare minimum” rate of 10 percent or higher, while states using the least amount employed it in less than 3 percent of cases (these states included Oregon, Nevada, Arizona, Mississippi, Kentucky, North Carolina, Georgia, Alabama, and Louisiana).^[50]

In addition to underuse, prescribers may frequently delay starting clozapine. For example, the mean wait time for clozapine initiation of those patients with two adequate failed antipsychotic trials was found to be about 48 months with patients receiving five prior antipsychotic trials. Over two-thirds of schizophrenia patients have at least three trials and wait years prior to clozapine initiation.^[51, 52]

Finally, clozapine may be underused when the trial is inadequate. For instance, poor adherence, smoking and drug interactions (primarily from cytochrome P450 1A2 inducing agents) may all reduce clozapine levels.^[53-56] Use of clozapine blood levels can help assure that the patient is receiving an adequate amount of clozapine before a trial is discontinued.

Overcoming Barriers to Clozapine Use

Clinically and administratively, a wide variety of barriers to the use of clozapine exist, but few large scale studies examine this issue.^[42, 57-59] Many variables contribute to low clozapine use, including patient, prescriber, health system, payer, and administrative issues.^[44, 59-62] In order to overcome barriers and provide more effective care for patients with severe mental illness, every healthcare system needs to provide ready access to clozapine, provide appropriate safety monitoring of patients receiving it, encourage prescribers to consider its use when appropriate, and support prescribers in learning how to use it.

Prescriber Knowledge and Comfort

Prescriber knowledge and comfort around the decision to use clozapine remains a significant barrier to care. Prescribers overestimate patients’ unhappiness with many side effects of clozapine, including the frequency of blood draws and sedation, while patients report less concern about these disadvantages.^[62] Studies comparing consumer and prescriber attitudes have found that people with schizophrenia have more favorable attitudes toward clozapine treatment than prescribers expect.^[61, 62] In fact, the published literature demonstrates that as many as 86 percent of patients report feeling better on clozapine, and 89 percent prefer it to other antipsychotics. As many as 87 percent of patients think the advantages outweigh the disadvantages of clozapine, with only 28 percent rating frequent blood draws as a disadvantage.^[61] With regards to severe neutropenia, one study reports that about one-quarter of physicians think the risk is

greater than 1 percent, when it is actually estimated to occur less than 0.8 percent of the time. Furthermore, approximately two-thirds of prescribers do not realize that the greatest risk for severe neutropenia occurs in the first 6 months of clozapine treatment.^[59]

In recent surveys, physicians note that a significant barrier to more widespread use of clozapine is the lack of experience during residency training and an overall discomfort with prescribing clozapine. This is critical, as physicians who have never prescribed clozapine are more likely to overestimate the significance of these challenges than current prescribers.^[63] Incorporating clozapine education in residency training to increase the knowledge of clozapine and comfort level of future prescribers would create a generation of future psychiatrists who have at least had some exposure to real-world clozapine prescribing. In the Massachusetts General Hospital-McLean Adult Residency Program, second-year psychiatry residents rotate for six weeks in a clozapine clinic and are taught an accompanying curriculum about the clinical use of clozapine, which has been shown to increase their knowledge about the therapy.^[64] In this way, no resident graduates without some basic knowledge of clozapine prescribing.

Another study^[65] found that providing exercises for psychiatric trainees, using case vignettes with clinical and patient perspective information, improved understanding of the complex decision-making required. The authors recommended that practice-based learning education be included in training. Thus, a more comprehensive review of continuing education is needed, including the possible role of public and community fellowships for workforce development.

Patient and Family Knowledge and Comfort

Patient-centered care was introduced by the Institute of Medicine's *Crossing the Quality Chasm* report, with shared decision-making intrinsically linked to patient-centered care.^[66] Shared decision-making is now unequivocally recognized as a cornerstone of medical care, and not as an option.^[67] The spirit of shared decision-making requires an honest attempt to convey information in a way that allows patients and their families to engage in a dialogue with their physician. For example, one study has shown that a pharmacist-created patient information leaflet was significantly more readable than a pharmaceutical manufacturer-produced educational leaflet.^[68] In the context of clozapine, patient education and shared decision-making around the use of clozapine is critical. There is a need for toolkits that clinicians, patients, and families can easily access. Moreover, clinicians may require training in how to perform and implement shared decision making.

Clozapine Clinics

Clozapine clinics or specialized clozapine programs are currently used in some health care systems in the U.S. and Europe. However, few resources are available to help plan these specialized programs. Successful clinics and programs tend to thrive in settings that are collaborative and interdisciplinary.^[69] Services that should be considered during planning for a clozapine clinic or specialized programs include: phlebotomy, pharmacy, nursing, psychiatry, patient/family education, case management, transportation, medical consultation for adverse effects/contraindications, on-call services, and clozapine

initiation. Many successful clinics also offer clozapine groups for patients and/or families. These groups provide education on the use and monitoring of clozapine, provide support for those considering taking clozapine, and help patients and their families deal with challenges that occur during treatment. Peer support groups have been reported to be useful interventions to address social network and adherence in patients with serious mental illness.^[70-72] Clozapine clinics may offer the opportunity to further implement this intervention.

Some clozapine clinics are administered by or utilize monitoring by non-psychiatrists in order to preserve the time of more highly trained clinicians for tasks congruent with their traditional roles. One Veterans Administration (VA) report describes a pharmacist-run clozapine clinic that led to cost savings, high clozapine continuation rates, patient and family satisfaction, and early intervention in cases of decompensation and suicidal ideation.^[73] Other studies have examined the effects of nurse-led clinics. For example, a study comparing sole nurse-led and doctor-led multidisciplinary teams found that management by community psychiatric nurse visits reduced the number of hospital psychiatrist appointments.^[74] Another study reported a reduced number of medical appointments and reduced mortality rates with nursing oversight in clinics and computer-based central monitoring.^[75]

Unfortunately, the resources necessary to run an interdisciplinary program are not always available. Reimbursable expenses vary from payer to payer, even among Medicaid programs in different states. Programs that are able to provide same day/same site laboratory and pharmacy dispensing services may help contain costs associated with patient transport and reduce factors that might interrupt treatment. The provision of weekly services, such as patient and/or family groups, paired with weekly dispensing and monitoring may offer opportunities to provide associated (and billable) services. Consultation with skilled health care administrators, Medicaid programs, and other payers can be invaluable in clarifying which costs of a clozapine clinic may be reimbursable and in developing models that maximize reimbursement.

Hospitals and Formularies

In order for a patient to be started on any medication, they must be able to access it. Unfortunately, not all hospitals stock clozapine. In some cases, it is treated as a non-formulary agent, and acquisition is delayed until there is delivery from a wholesaler. Hospitals that do not have clozapine on formulary may also lack protocols or procedures necessary to comply with clozapine risk evaluation and mitigation strategies (REMS) mandated by the FDA, adding another obstacle to use. In cases where clozapine is not on the formulary or prescribers are not confident in its use, patients may be removed from clozapine and placed on other medication when discharged from the hospital and back into the community.

Severe Neutropenia

The adverse effect of clozapine that most significantly limits its widespread use is the risk of severe neutropenia (formerly referred to as agranulocytosis, ANC (absolute neutrophil count) < 500 cells/mm³), which could result in life-threatening infections. Six large

epidemiologic studies, each containing over 5000 clozapine patients, have estimated the risk of severe neutropenia at 0.05 to 0.86 percent.^[34-38] The risk of severe neutropenia is low, and has been found to be similar across differing cultural and geographic areas. Two U.S. studies showed the risk of severe neutropenia to be 0.80 percent and 0.08 percent, respectively. Two studies in the United Kingdom demonstrated rates of 0.18 percent and 0.10 percent, while studies in Finland, Australia, and Argentina reported rates of 0.11 percent, 0.06 percent, and 0.05 percent, respectively.

Despite its low incidence, psychiatrists are five times more likely than patients to regard severe neutropenia as the most critical concern of clozapine treatment.^[59]

African American Patients and Benign Ethnic Neutropenia

Racial disparities are present in clozapine prescribing and use. The frequency of clozapine treatment has been found to be lower for African-American patients than for Caucasian patients.^[57, 76-78] African Americans are twice as likely to have their clozapine discontinued due to their white blood cell count or ANC falling below the FDA-mandated thresholds for monitoring.^[78, 79] Some researchers have found that the fear of neutropenia was the most frequently cited reason for discontinuing clozapine treatment of African-American patients.^[80] Benign Ethnic Neutropenia (BEN) may explain these high fluctuations and discontinuations in this racial group.

BEN occurs in people of African or Middle Eastern ancestry, identifies a group with low ANCs that does not have an increased risk of severe neutropenia or infection,^[81-83] and is not related to clozapine exposure. Recent evidence possibly implicates a genetic polymorphism in the pathophysiology of BEN.^[84-88] 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 populations, in individuals of other ethnic groups who are otherwise healthy and do not have repeated or severe infections.”^[81] BEN is diagnosed by repeated low measurements of ANC (usually < 1500 cells/mm³ without identifiable causes of neutropenia).^[89]

The new clozapine U.S. prescribing information and monitoring guidelines that went into effect on October 12, 2015 under the FDA’s Clozapine REMS program take into account ANC differences in patients with BEN. The guidelines provide separate algorithms for monitoring patients with and without BEN, and establish a lower threshold for discontinuation for those with BEN. The patient enrollment webpage for patients in the Clozapine REMS program allows the prescriber to indicate that the patient enrolling has BEN. Unlike similar guidelines in the United Kingdom, it is not mandatory to get a hematologist verify that a patient has BEN. The new guidelines are meant to facilitate access to clozapine and reduce unnecessary interruptions in treatment. However, not all prescribers understand BEN or how to manage patients who have it. Recommendations on identifying and managing BEN patients are beginning to emerge.^[90]

The Clozapine REMS

The federally-mandated process and paperwork for the initiation of clozapine has previously been considered a barrier to clozapine treatment, and the FDA's introduction of the Clozapine REMs in late 2015 was promoted as a way to reduce confusion and lack of clarity surrounding the existence of six separate clozapine registries.

However, the new program itself presented additional barriers to the use and initiation of clozapine. The central role of the pharmacist in clozapine monitoring was substantially reduced in the new program, imposing additional administrative burdens on prescribers. Furthermore, longstanding systems that included pharmacists playing a central role in monitoring were disrupted since pharmacists could no longer access historical or complete data on the Clozapine REMS website. Initial software and system issues requiring personal interaction with the Clozapine REMS vendor resulted in long wait times and delays for busy clinicians. Mandates for prescriber and health professional training and enrollment, as well as a system for requiring a pharmacy to secure a pre-dispensing authorization, were put on hold as a result of the initial difficulties in implementing the Clozapine REMS. However, as of August 2016, those mandates have not been permanently eliminated, and will further complicate initiation and maintenance of clozapine. Other issues complicated by the REMS include admissions of patients to acute care facilities and emergency rooms, transitions of care, transfers between wards, and communication between VA and non-VA systems.

Blood Draws

The most widely cited barrier in every survey assessing barriers to clozapine treatment is concern about anticipated nonadherence to or refusal of blood draws by patients prescribed clozapine.^[63, 91, 92] The coordination of frequent blood draws is a barrier that can be difficult to overcome. U.S. prescribing information requires weekly ANC monitoring during the first six months of treatment, followed by monitoring every two weeks during the following six months. The frequency of required blood draws is reduced to once monthly after the first year provided that the ANC has not fallen below threshold levels. Other countries have less stringent blood draw maintenance, with Denmark recently moving to once monthly blood drawing after the first 18 weeks of treatment.^[93]

Assuring that patients have their blood drawn in a timely manner may require coordination among families, laboratories, clinics, and transportation systems. Patients with impairments in executive function may have difficulty planning, remembering, or participating in such coordinated arrangements.

Improving the feasibility of blood draw coordination could help eliminate or lessen this barrier. Home visits through Assertive Community Treatment teams or use of publicly available or free transportation assistance through some state Medicaid programs can be effective strategies for addressing this barrier. The risk of missed blood draws remains significant without case management or oversight from community treatment providers to help organize this endeavor.

Point-of-Care Monitoring

Researchers in the State of Maryland surveyed psychiatrists to determine strategies for addressing barriers that arise when using clozapine. Point-of-care monitoring for clozapine was rated as the most preferred solution by these prescribers.^[63] There has been continued interest in using point-of-care monitoring devices to reduce the time spent coordinating blood draws and eliminate concerns about nonadherence to these mandated tests.

Bogers et al.^[94] tested a capillary blood sampling point-of-care system and compared subjective experiences of patients and practitioners in comparison to standard blood draws. Patients and practitioners strongly preferred the point-of-care device over routine blood draws. Others have also reported patient preferences for the point-of-care system over standard laboratory measures.^[95] The biggest barrier to routine implementation has been the lack of specificity for neutrophils (five-part differential) with most devices only demonstrating the ability to report granulocytes (three-part differential). The FDA has not recommended using point-of-care devices in the new guidelines for monitoring. Also, point-of-care devices must obtain the Clinical Laboratory Improvement Amendments (CLIA) waiver in order to be implemented in routine practice settings instead of centralized laboratories. CLIA waivers must also comply with state laws and Center for Medicare and Medicaid Services (CMS) rules in order to meet criteria for reimbursement.

Pharmacogenomics Testing for Severe Neutropenia

Many research groups have been working to develop pharmacogenomics testing for clozapine-induced severe neutropenia. A test that could predict which patients are at high risk could be used to determine which patients might require laboratory monitoring or for whom clozapine might be contraindicated. If such a test could identify patients at very low risk, hematological monitoring could be relaxed or even eliminated.^[96] The majority of findings in the studies to date have been on the human leukocyte antigen (HLA) region and amino acid changes in HLA alleles, but the sensitivity of the testing has not yet been high enough to suggest clinical application for routine screening.

Clozapine Initiation

The initiation of clozapine involves a thoughtful consideration of risks and benefits, shared decision-making with the patient and sometimes the patient's family, and close monitoring of side effects, particularly in the first weeks. Clozapine must be slowly titrated due to the risk of severe hypotension. Sedation and fatigue may be problematic when the drug is first started. Depending on the nature of the patient receiving clozapine, consideration must be given to cross-titration from other antipsychotics. When prescribers harbor concerns that patients will not tolerate side effects, the medication is often not considered.^[91]

Hospitals and facilities with full-time staff to monitor and encourage patients and deal with administrative and safety issues certainly facilitate the initiation of clozapine. However, surveys show that clinicians may overestimate patient resistance to phlebotomy and adverse effects.^[62] In contrast, Gee et al.^[91] found that pharmacists tend to be more

confident in the use of clozapine and contribute successfully to multidisciplinary decision-making.

The New York State Office of Mental Health has successfully utilized a multi-faceted approach to promote the evidence-based use of clozapine, increasing use of clozapine in a Medicaid population from 1.5 percent to 2.1 percent, and increasing inpatient starts to 3.7 percent.^[97] The Clozapine Authorization and Monitoring Program of the Maryland Behavioral Health Administration (BHA), operated by the University of Maryland School of Pharmacy, helps facilitate clozapine use statewide with more than 15 percent of inpatients in Maryland BHA facilities receiving clozapine.^[43]

The administrative complexities of patient registries and, now, Clozapine REMS present additional obstacles to the initiation of clozapine. The combination of these clinical and patient concerns with administrative obstacles has caused some clinicians to avoid using clozapine or to assume that clozapine can only be started in an inpatient setting. A large survey study in the U.K., polling 2771 consultant psychiatrists, found that one third of the reporting psychiatrists thought it was not safe to start clozapine in a community setting.^[92] However, clozapine can be safely initiated in the outpatient setting. The issue of outpatient initiation of clozapine is critical as many acute care hospitals will opt to merely stabilize patients rather than initiating clozapine treatment.

Correctional System and Forensic Settings

People with schizophrenia are at increased risk of violent behavior with about 20 to 25 percent of patients exhibiting some degree of hostility or violence.^[98-100] One large study^[101] reviewed the national crime register for records of criminal offences committed by 1662 patients with schizophrenia treated between 1990 and 1995 in the inpatient psychiatric hospital at the University of Munich. An estimated 10 percent of patients had been convicted of crimes in the 7 to 12 years after discharge.^[101] Clozapine may be a useful medication in this regard^[17], and has been recommended in the Schizophrenia PORT guidelines for use with patients exhibiting hostile and violent behaviors.^[12]

Clozapine has been shown to be effective in the forensic population in a handful of studies.^[102-105] However, the special protections and federal approvals needed to conduct research related to clozapine effectiveness in this population complicate research and the dissemination of findings. Nonetheless, algorithms have been proposed that would permit prescribing clozapine in the forensic setting.^[106]

Many correctional systems are independent of mental health systems, and routine psychiatric care is often marginalized. The complexities of using clozapine and the scarcity of psychiatric services lead to clozapine being an overlooked and rarely used treatment in forensic settings. With more frequent use of clozapine in an integrated mental health-forensic services system,^[107] clozapine could provide positive outcomes such as reduced recidivism.

Managing Side Effects

Knowledge of clozapine's side effects and strategies to manage them are important to prescribing clozapine safely, both in the short run and in the long run.^[108] Moreover, patients may discontinue clozapine unless side effects are addressed or strategies to minimize them are implemented. Many side effects are not unique to clozapine, and clinicians are already familiar with their management. Examples include sexual side effects, weight gain from second-generation antipsychotics, or antipsychotic-related sedation.

Clozapine's side effects can be grouped into early side effects which are most problematic during initiation and late side effects which pose problems for maintenance treatment. Early and potentially life-threatening side effects include severe neutropenia (see above) and myocarditis. The main long-term concern is weight gain and associated metabolic issues.^[109]

Clozapine-induced myocarditis usually occurs during the initiation phase and requires particular vigilance during the first several weeks of treatment, peaking around Week 4.^[110] While no agreed-upon monitoring schedule exists, a high index of suspicion for non-specific symptoms of myocarditis (e.g., malaise, chest pain, palpitation), combined with electrocardiograms (ECGs) at baseline and in symptomatic patients, as well as markers of cardiac damage and inflammation (e.g., troponin and C-reactive protein) weekly for four weeks, should raise concerns.^[111] Electrocardiogram monitoring should be available in settings where clozapine is used. Some side effects (i.e., seizures, excessive sedation, cardiovascular collapse) are avoided by slow titration when patients are first given clozapine.

The main long-term, medical concern with clozapine is weight gain and the associated risk of the metabolic syndrome. In one naturalistic cohort study, one-third of patients were diagnosed with diabetes during the study's five-year observation period.^[109] To prescribe clozapine safely, clinicians need to be proactive with regards to guideline-concordant monitoring and appropriate referrals when problems are detected.

Unfortunately, many psychiatric settings do not provide evidence-based interventions to address metabolic effects and promote wellness.^[112] Without a comprehensive, long-term prevention and treatment approach tailored towards those with serious mental illness and aimed at preventing obesity and metabolic problems, medical morbidity and mortality will remain excessive.^[113] Individual clinicians who do not have access to referral resources for addressing metabolic issues, may still be able to work with families to access community resources where they exist. The use of metformin as an adjunct to blunt clozapine-associated weight gain is a strategy that has some support in clinical trials.^[114]

For a detailed description and management recommendations of the many other side effects during clozapine treatment (e.g., sialorrhea; constipation), clinicians can consult the literature.^[1, 12, 25, 40, 115-117] However, clinicians with limited clozapine experience who consider using clozapine should have access to a colleague with expertise in prescribing clozapine and to primary care consultation should medical complications arise.

Transitions of Care

The risk of clozapine discontinuation in the transition of care is a significant concern, and has resulted in abrupt discontinuations that have led to serious outcomes such as suicide.^[118] This may happen in a variety of care setting transitions such as hospital to outpatient, outpatient to inpatient setting, and even from public health to private psychiatrist or general practitioner. An Australian study of 215 clinicians prescribing clozapine reported that the most significant transition barriers are the cost of private care and the need for ongoing care coordination.^[119] Transition involves not only changes in the identity of the treating clinician but also changes in the dispensing pharmacy and the coordination of blood draws.

New approaches to transitions are needed to avoid interruptions in treatment, communicate challenges with previous clozapine treatment, and facilitate appropriate re-titration of clozapine. State health information exchanges can be helpful, but a more comprehensive system—such as registries that communicate more than just hematologic data—could be invaluable.

Suicide and Emergency Hotlines

In the United States, no hotline exists where clinicians can quickly receive clozapine-related guidance. An exemplary model for such a hotline exists in the form of the Neuroleptic Malignant Syndrome Information Service that was founded in 1997 by the Malignant Hyperthermia Association of the United States in collaboration with a group of prominent experts with extensive experience in treating neuroleptic malignant syndrome.^[120]

Working with Medicaid and Managed Care Companies

Medicaid Prescription Drug Plans do not always cover all dosage forms or may place some clozapine products on preferred drug list (PDL) tiers with high cost-sharing. Each state Medicaid Pharmacy program may treat clozapine or specific clozapine products differently on PDLs. Patients enrolled in managed care plans may also face obstacles in obtaining clozapine that are created by the prior authorization policies of the plan's pharmacy benefit manager and the placement of clozapine or specific products on the plan's PDL tier system. Negotiation of these barriers may be difficult for patients, family members, and staff attempting to offer assistance.

Recommendations

Prescribers

1. Prescribers of clozapine should establish links with primary care practices to assist in the management of side effects that may emerge during treatment with clozapine.
2. Prescribers should continually seek to improve their own knowledge base with lifelong learning on clozapine treatment.

3. Less experienced prescribers should establish links with more experienced prescribers who can assist them in addressing issues that arise during clozapine treatment.

Psychiatric Residency, Fellowship Programs, and Academic Health Centers

1. Psychiatric residency and training programs should consider including:
 - a. didactic instruction on the use of clozapine,
 - b. a requirement to become certified under the FDA Clozapine REMS Program,
 - c. clinical experience in treating and monitoring patients receiving clozapine,
 - d. clinical experience in initiating clozapine treatment in patients, and
 - e. participation in interdisciplinary teams that manage patients receiving clozapine.
2. Academic centers, in consultation with state or local mental health authorities, should encourage interdisciplinary consultation centers for community providers such as psychiatric pharmacists or nurse practitioners involved in the management of patients receiving clozapine.

Acute Care and Psychiatric Hospitals

1. All acute care and psychiatric hospitals should have clozapine on their formularies as an essential medication.
2. All acute care and psychiatric hospitals should have policies and procedures to facilitate the safe and appropriate use of clozapine.
3. All acute care hospitals should have access to appropriate staff or resources that allow continuation of clozapine on an inpatient basis when appropriate.
4. All acute care hospitals should establish a policy that discharges patients on clozapine if:
 - a. they were taking clozapine prior to admission,
 - b. they were exhibiting a therapeutic response to clozapine, and
 - c. there is no contraindication to the use of clozapine upon discharge.

Academic Scientists and Pharmaceutical Research Programs

1. Neuroscience and pharmacologic research should focus on the molecular underpinnings of clozapine's actions in order to facilitate the development of agents which share clozapine's efficacy while eliminating its worst side effects.
2. Research should also focus on improving the understanding of clozapine-induced blood dyscrasias, eliciting factors associated with a positive response to clozapine, and discovering biomarkers that could improve the risk-to-benefit ratio for treatment with clozapine.
3. Systems research should focus on demonstrating clozapine's cost-effectiveness in various systems of care including forensics, best practices for interdisciplinary teams

managing patients receiving clozapine, developing novel practice and service models, and establishing the effectiveness of prevention strategies for clozapine-associated weight gain and metabolic effects.

4. Technological support should include the development of point-of-care testing devices to perform hematologic monitoring for those receiving clozapine.
5. Research should be focused on aiding the FDA in modifying prescribing and monitoring guidelines for those receiving clozapine.

Local and State Health Authorities

1. Every public health system of care should have a system that provides ready access to clozapine, provides appropriate safety monitoring of patients receiving it, and encourages prescribers to consider its use when appropriate.
2. Mental health authorities should consider establishing model programs for the initiation and monitoring of clozapine patients, and consider offering evidence-based recommendations for addressing metabolic and other emergent side effects.
3. Mental health authorities should establish mechanisms for the initiation of clozapine in outpatient settings, such as for designated beds in respite care, sites offering 24-hour supervision, or clozapine clinics with capacity and expertise.
4. Academic centers, in consultation with state or local mental health authorities, should establish interdisciplinary consultation centers for community providers involved in the management of patients receiving clozapine.
5. Mental health authorities should develop community-specific systems for laboratory monitoring of patients receiving clozapine that may include the use of Assertive Community Treatment (ACT) teams, transportation systems, consultation with visiting phlebotomists, pharmacy-based phlebotomy, or other solutions.
6. Mental health authorities should develop population management tools to facilitate and monitor transitions of care and help assure continuation of treatment for patients receiving clozapine.

Payers

1. Payers should develop payment mechanisms that recognize the complexity of managing patients receiving clozapine including:
 - a. enhanced payment mechanisms for prescribers;
 - b. payment mechanisms for nurses, pharmacists, and social workers participating in interdisciplinary clozapine teams;
 - c. payment for telemedicine systems to provide consultation for community health professionals managing clozapine patients; and
 - d. payment for transportation for patients for laboratory monitoring and/or payments for home visits for phlebotomy.
2. Clozapine should be a preferred medication on the pharmacy drug lists of all state Medicaid programs and pharmacy benefit/managed care programs contracting with

state Medicaid programs, and on the formularies of Medicare prescription drug programs and other payers of pharmacy benefits.

3. Payers should encourage the development, adoption of, and reimbursement for Medication Therapy Management (MTM) services for patients receiving clozapine.

Correctional Systems

1. Every correctional health care system should have a system that provides ready access to clozapine or establishes mechanisms for referral for treatment of inmates who are appropriate for treatment with clozapine.
2. Every correctional health care system should have policies and procedures to facilitate the safe and appropriate use of clozapine.
3. Every correctional health care system should provide appropriate safety monitoring of patients receiving clozapine.

Providers of Continuing Education for Health Professionals

Health professional organizations and continuing education providers should develop and offer interdisciplinary continuing education programs on the use of clozapine to physicians, pharmacists, nurses, social workers, and other health care providers.

National Efforts

1. National efforts should coordinate the development and dissemination of the following types of toolkits and information related to clozapine:
 - a. Sample informed consent forms for clozapine;
 - b. Discussion papers on shared decision-making;
 - c. Forms for monitoring specific side effects;
 - d. Patient and family education materials;
 - e. Checklists for establishing a clozapine clinic, including materials on interdisciplinary roles in the management of patients receiving clozapine, establishing pharmacy linkages for patients receiving clozapine, options for hematologic testing, potential funding mechanisms or models for clozapine programs and models for a clozapine consultation service, including interdisciplinary telehealth models; and
 - f. Reference links to educational programs regarding the use of clozapine.
2. The Clozapine REMS Program should be routinely evaluated in order to assure that it facilitates clozapine use and does not present unintended barriers to use. This evaluation should consider scientific evidence and analyze data trends that might inform changes in clozapine monitoring guidelines, such as less frequent ANC monitoring, genetic testing that dictates less stringent hematologic monitoring, or elimination of ANC monitoring in patients that have minimal risk of developing severe neutropenia.

3. Relevant stakeholders should be sought out and brought together to explore the use of the Clozapine REMS Program as a population management tool that could be used by state systems to facilitate and monitor transitions of care, help assure continuation of treatment, and reduce interruptions in treatment in patients receiving clozapine.

Technology

1. Telehealth and call center technology should be used to provide access to professionals who can provide consultation on the complexities of clozapine use.
2. The technology of the Clozapine REMS registry should be harnessed to improve, facilitate, and monitor transitions of care, and reduce interruptions in treatment for those receiving clozapine.
3. Establishment of a dynamic, web-based source of educational programs providing information on delivery models, patient-monitoring, patient and family education, and provider education would assist all who might treat potential recipients of clozapine.
4. Point-of-care testing should be developed to assist in the monitoring of those receiving clozapine.
5. Biomarker testing should be developed to improve the predictability of response to clozapine and the risk of specific adverse effects.

Conclusion

Clozapine is a superior medication for the treatment of refractory schizophrenia, and it may be effective for a wide spectrum of other indications. However, clozapine is underused due to a variety of barriers related to the drug and its properties, the health care system, regulatory requirements, and reimbursement issues. This white paper provides the framework for addressing these barriers and recommending strategies for the entire health care system to consider.

If access to clozapine is improved, millions of patients could benefit. In turn, their improved care would result in substantial cost savings to the entire health care system.

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