Barriers to Clozapine Use for Competency Restoration and the Value of Further Study

Cheryl D. Wills, MD

Hospital-based restoration of adjudicative competence can be challenging, especially for patients who have treatment-resistant psychosis. Clozapine, which has helped many such individuals in the community, has not been well-studied in individuals who are incapable of proceeding with trial. In their small study, Ghossoub and colleagues have brought attention to the potential for this protocol and advocate for further study. This commentary examines potential barriers to conducting larger studies, including Institutional Review Board requirements for research with individuals who are under court supervision. Also, factors that can result in patients relapsing and being readmitted to the hospital for competency restoration due to poor treatment adherence are described. This adverse outcome burdens the judicial and health care systems and prolongs the time between the patient's arrest and trial. Clozapine may be a promising treatment for competency restoration as long as we are cognizant of barriers to further study and treatment adherence.

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In this issue of The Journal, Ghossoub and colleagues[1] have presented research and a thoughtful discussion regarding an option for competency restoration for hospitalized defendants who have treatment-resistant psychosis that, by definition, has either not resolved or not improved sufficiently despite two documented trials of antipsychotic therapy.[2] Although clozapine may reduce, and sometimes resolve, psychosis and related impairment in these patients, it is underutilized. This commentary addresses obstacles to clozapine therapy management in patients in the community and those who are legally confined in hospitals for competency restoration or jails after being adjudicated competent to proceed with trial.

Clozapine's complex prescribing protocol includes monitoring patients for disabling side effects that can be fatal, including agranulocytosis, granulocytopenia, seizures, myocarditis, gastrointestinal hypomotility, etc.[2] Unresolved psychosis causes deficits in cognition that can result in social, occupational, or educational impairment. Psychosis can impede a patient's ability to have meaningful relationships and be a barrier to accessing equitable housing, employment, and health care. These problems can derail proper treatment and monitoring. Functional impairment, compounded by health disparities, can increase the likelihood of patients being legally confined for minor and serious offenses.[3] Consequently, for some patients, the potential benefits of clozapine therapy may outweigh the risks.

Psychiatrists' failures to offer clozapine to qualifying patients deprive some patients of a better quality of life while potentially increasing the use of more costly health services, including hospital beds. Clozapine therapy also can be derailed by health disparities that can restrict access to resources, including affordable health care that covers serial lab tests, transportation to and from the prescriber's office, and a support team that will facilitate the patient's engagement in psychiatric care and promote treatment adherence.[4]

Relative to treatment with many psychiatric medications, clozapine therapy requires greater utilization

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Dr. Wills is Associate Professor, Department of Psychiatry, Case Western Reserve University, Cleveland, OH. Address correspondence to: Cheryl D. Wills, MD, Associate Professor of Psychiatry, Case Western Reserve University, 5247 Wilson Mills Rd, #452, Cleveland, OH 44143. E-mail: cwforensic@earthlink.net.

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of health care resources, including laboratory services. Clozapine may, however, reduce the emotional burden and impairment of some patients when other options have failed. Despite this knowledge, many psychiatrists remain reluctant to initiate clozapine therapy due to the severity of the side effects and the challenge of ensuring compliance with monitoring protocols, especially since a significant proportion of patients do not take medication as prescribed.[5]

Researchers who study medication treatment responses strive to use the best available research design. They also select study participants who have a high likelihood of completing the study protocol. These patients tend to have fewer comorbidities and barriers to participation. Study exclusion criteria often bar patients who have complicated psychosocial concerns from participation. While the selection bias may improve the quality of the study, its conclusions may not be directly transferrable to the average patient in the community, especially when the patient lacks health equity. Many patients with treatment-resistant psychosis may fit into this group, and correctional and community psychiatrists routinely work with many of them. These psychiatrists, who may have a "come as you are" treatment philosophy, do not select for patients who have few or no obstacles to care.

Perhaps a subset of studies, especially those involving medications intended for people who have serious mental disorders, should factor in concerns that are prevalent in real-world clinical settings, especially under-resourced settings. Although the approximation of real-life situations in research may delay the completion of studies and obfuscate conclusions, we may learn more about how barriers to care can affect clinical outcomes and identify thoughtful ways to reduce these obstacles.

Barriers to accessing care can occur in unexpected ways. In early 2020, during the first months of the COVID-19 pandemic, several patients changed their preferred pharmacies as a result of a change in their daily routines. Three patients who are prescribed clozapine told me that the pharmacists, who work for the same chain of pharmacies, would not fill clozapine prescriptions unless they reviewed the lab reports. The data had been entered into the clozapine Risk Management Evaluation System (REMS) registry, and I confirmed with the clozapine REMS staff that clozapine was approved to be released to each patient.[6]

I interviewed six pharmacists from the chain of pharmacies with the alleged restrictive policy. Five of them reported that they are not permitted to release clozapine prescriptions until they personally examine the lab report and enter the data. They said that they do not check the clozapine REMS registry until after they enter the data. I informed the pharmacists that the clozapine registry staff had verified receipt of the labs and had authorized the release of the patients' prescriptions. The pharmacists said that they were following the company protocol that requires the pharmacist to review and enter the test results into the registry.

The sixth pharmacist told me that there is no such protocol. He and his colleagues prefer not to log in to the clozapine REMS database because the pharmacy database, which is linked directly to the clozapine registry database, permits direct lab entry and saves the pharmacist one step in the process. I reviewed this with each affected patient along with the salient parts of The Health Insurance Portability and Accountability Act (HIPAA). Each patient chose autonomy over coercion, requested prescriptions be sent to a different chain of pharmacies, and has been satisfied with the outcome.

Prescribing clozapine in outpatient settings can be challenging. Ghossoub and colleagues[1] discuss using clozapine in a different setting for a different purpose: hospital-based restoration for adjudicative competency in adults. Competency restoration frees up hospital beds, can result in speedier trials, and can decrease the overall cost of psychiatric care for patients who are legally confined. These outcomes are laudable goals, especially in a country that has psychiatric hospital bed shortages and overcrowded jails and prisons.

The patient who cannot be restored to competence should be released from the legal system but can be eligible for hospitalization under civil proceedings.[7] The same patient, if adjudicated competent to proceed, may have one of several possible outcomes, including being found not guilty, being found guilty of the original charge, accepting a plea agreement that reduces the sentence relative to the original charge(s), or having the charge(s) dropped.

The authors correctly conclude that it will be challenging, at best, to conduct a multicenter double-blind placebo-controlled trial of clozapine in pretrial hospitalized patients. First, multi-center trials are more arduous to conduct than those involving one hospital. Second, the population of patients who have treatment-resistant psychosis and require competency restoration is relatively small. The study will need to last for several years. Also, it will require a patient to

take clozapine when treatment options that may involve prescribing more than one medication can be less intrusive and potentially effective, may have fewer debilitating side effects, and can be safer to study. This requirement may result in problems with obtaining approval for a clozapine research project.

Institutional review boards (IRB), which approve research projects, use more stringent criteria for studies involving prisoners because they are not on equal footing with those who supervise them.[8] Prisoners lack autonomy that would permit them to seek care with a different prescribing physician or in a different facility. This dynamic makes it difficult for a research team to obtain informed consent from the prisoner and approval from the IRB for the study.

Consent for medical care cannot be wholly voluntary for prisoners because they are in an unequal relationship with those who supervise them and are at risk for coercion. Also, patients who lack adjudicative competence may not be capable of comprehending and weighing treatment options appropriately, including the risk for serious medication side effects, the need for lab work and other potentially intrusive forms of monitoring, and the constraints of being involved in a research protocol. These concerns also extend to consenting to the research protocol. Additionally, there is a concern about prescribing a placebo to patients who are confined and cognitively impaired. Doing so can prolong their emotional suffering, hospitalization, and time to trial.

Research with patients awaiting competency restoration requires approval from a prison IRB.[8] The panel must include a prisoner or prisoner representative and uses criteria that exceed those used by IRBs that review projects involving non-court-involved people or animals.[8] Approval of the authors' retrospective research protocol[1] was easier to obtain than the multi-center trial that they recommend because it did not interfere with the patients' mental state and liberty interests and did not require the researchers to prescribe medication.

The U.S. Supreme Court addressed psychiatric treatment over objection for adjudicative competence in *Sell v. United States*.[9] The Court, in the *Sell* case, ruled that prescribing forced medication for competency restoration requires a case by case determination. The treatment regimen must have a substantial probability of restoring the defendant's adjudicative competence while not causing side effects that can prevent the defendant from having a fair trial. Also, less intrusive treatments must be considered.

The *Sell C*ourt does not address competency restoration research projects like the one that the authors completed or now propose. The relatively small number of defendants who require and fail to achieve adjudicative competence in psychiatric hospitals comports with the small sample size in the authors' study.[1] The researchers reviewed the medical records of 250 patients who were hospitalized for competency restoration. The fact that 25 (10%) of the patients had treatment-resistant psychosis, and eight of the 25 (32%) regained adjudicative competence with clozapine, may not seem promising at first glance, especially given the potential for serious side effects. Still, eight people were able to leave the hospital with the flexibility to proceed with their legal cases and their lives. Restoring legal autonomy is important, especially when an individual is charged with serious offenses. Yet the expense of prescribing clozapine to patients when 68 percent will not achieve adjudicative competence, especially with patients who are facing less severe offenses, must also be considered. There is the chance that larger studies may suggest otherwise.

Perhaps electronic health records may reduce the expense of prescribing clozapine therapy for competency restoration. Access to electronic data may facilitate documentation of previous antipsychotic medication trials that failed, which has the potential to reduce the median length of hospitalization of 343 days that was reported by the authors[1] and might reduce rehabilitation costs.

Successful treatment with clozapine can improve a patient's adjudicative competency, capacity for self-advocacy, and internal locus of control. The court can return the patient to the detention facility or release the defendant to the community pending the trial. Either setting lacks the support and structure of a psychiatric hospital, so the patient may be at higher risk for psychiatric decompensation due to poor treatment adherence. Yet, following competency restoration, there may be no clinical or legal justification for continued hospitalization.

There are many ways to be noncompliant with clozapine therapy, including refusing to take the medication because of side effects, denial about the need for treatment, or denial of access to clozapine by the pharmacy if the patient does not comply with mandatory blood monitoring. Even when the patient is compliant, the side effects

mentioned above increase the risk for morbidity and mortality.

Some detention centers have better medical staffing and health care services for detainees than others. Facilities that have more reasonable staff-to-detainee ratios and train staff to work with detainees who have serious mental disorders have the potential for better patient outcomes. Some detention facility administrators, who run facilities that are understaffed and under-resourced, may decide to exclude clozapine from their formularies because there are less costly options available and it is prescribed infrequently.

Weekly blood tests can be labor-intensive or cost-prohibitive in a jail or detention center that is in budgetary crisis. The facility's floor plan may require a detention officer to escort the patient to and from the infirmary for the procedure and for a health care team member to obtain the blood specimen. Point of care tests (POCTs), which require a drop of blood rather than a venous sample, may be safer, faster, and more convenient for the patient and staff and may increase the likelihood of adherence to the treatment protocol for those reasons. Despite the obvious benefits of the newer technology, POCTs may be cost-prohibitive for many reasons. Competing budgetary and safety interests, for example, may place the needs of the many over the psychiatric care and competency of a few detainees.

Familiarity with clinical practices in detention facilities can help the inpatient hospital psychiatrist determine whether clozapine is a suitable medication for competency restoration, especially if petitioning the court for the patient to be transferred to a more suitable, mental health-friendly facility is not an option. Despite its potential benefits, clozapine's relatively demanding monitoring protocol can put a patient who is in an under-resourced detention center at risk for needing competency restoration again because of a change in the medication regimen by the prescriber or the patient's medication, or lab work refusal that results in psychiatric decompensation. I have had this happen with two patients, including twice in one patient, and it is not a pleasant experience for the patient, the judicial system, or the hospital system.

Clozapine may help a subgroup of patients who have treatment-resistant psychosis achieve adjudicative competency, but the barriers to timely initiation of the treatment regimen (including the requirement for the patient to fail two different antipsychotic trials) and potentially costly, though mandatory, physiological monitoring of the patient can be deterrents. Yet the clarity of thought that accompanies a reduction in hallucinations, delusions, and other debilitating symptoms of psychosis and the ability for the patient to receive a speedy trial may justify the risk.

Future studies involving pharmacological management of patients who have treatment-resistant psychosis for competency restoration include augmentation involving oral and long-acting injectable antipsychotic medications. Both options can be less externally intrusive than clozapine, although long-acting injectable medications are more pharmacokinetically intrusive due to their long half-life. Of course, individuals who have serious mental disorders are best served by community-based psychiatric treatment and avoiding legal involvement, since the penal system is not equipped to provide comprehensive mental health treatment.

Investing resources into improving access to quality community-based psychiatric services is conducive to reducing incarceration and recidivism of many people who have serious mental illness. This approach is probably the most effective treatment of all.

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