Aggressive and delusional about his alien origins, but refusing treatment

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Mr. C, age 23, has persistent hallucinations and delusions, despite 4 trials of antipsychotic medication. He refuses clozapine because of the required weekly blood draws. What would you do next?

CASE Alien thoughts

Mr. C, age 23, is admitted to an intermediate-security facility because of unmanageable aggression. He is not charged with a crime and his legal status is admission by guardian. He is taking haloperidol decanoate, 300 mg IM every 28 days, and divalproex sodium, 1500 mg/d, but he continues to experience auditory hallucinations and the delusion that he is an alien.

Mr. C is given a primary diagnosis of chronic undifferentiated schizophrenia. He is started on risperidone tablets, 3 mg/d, and then switched to risperidone orally disintegrating tablets, titrated to 8 mg/d, to ensure compliance. Later, he receives separate trials of high-dose quetiapine (up to 1200 mg/d) and olanzapine orally disintegrating tablets (up to 30 mg/d). Lithium, 1200 mg/d, sertraline, 100 mg/d, and long-acting propranolol, 120 mg/d, were added at various periods of his treatment.

He continues to experience hallucinations and delusions, is intermittently aggressive, is not engaged in the treatment program, and needs prompting for basic hygiene. Several times, we discuss with Mr. C using clozapine, but he refuses, mainly because of weekly blood draws.

How would you proceed with Mr. C's care?

a) consider electroconvulsive therapy
b) order aripiprazole and an omega-3 fish oil supplement
c) consider involuntary clozapine therapy and lab testing

The authors' observations

Schizophrenia remains a chronic and often refractory illness. Patients suffer from intrusive hallucinations; social and self-care deficits; cognitive impairment; and increased risk of violence, suicide, and premature death from medical causes. Pharmacotherapy is the mainstay of treatment, supplemented by individual and group therapies, psychosocial rehabilitation, housing assistance, and income support. Antipsychotics are fundamental and clozapine has been established as the most effective antipsychotic in the Clinical Antipsychotic Trials for Intervention Effectiveness (CATIE) study,[1] but it remains underutilized.[2]

In 2008, clozapine accounted for only 4.4% of antipsychotic prescriptions in the United States.[3] In our state forensic facility, only 10% of patients on an antipsychotic received clozapine in 2011. Despite the CATIE trial,

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How would you handle this case?

Answer the challenge questions throughout this article

Table 1

Barriers to clozapine therapy

Patient factors
Frequent lab testing
Dangerous adverse reactions
Disagreeable adverse reactions
Divided doses
Physician factors
Dangerous adverse reactions
Labor intensive (informed consent, paperwork)
Slow titration
Lack of IM formulation

there were no significant increases in clozapine prescribing after the results were published[4] and patients often experience a substantial delay before clozapine is initiated.[5] In the last several years, we have looked at methods to increase clozapine use in our hospital and have described some of our experiences.

Despite enthusiasm for, and good experience with, clozapine, barriers limit the use of this medication (***Table 1***). One significant barrier is patient acceptance. Although most of our patients taking an atypical antipsychotic will accept a blood draws every 6 months for metabolic monitoring, many will reject clozapine because of the initial weekly blood draw. Other patients will reject a trial of clozapine because of fears of serious adverse reactions.

Clinicians may be reluctant to initiate clozapine treatment because of increased time demands to obtain and document informed consent, complete initial paperwork, initiate a clozapine titration protocol, and order laboratory work. Clinicians also may fear more serious adverse reactions with clozapine such as agranulocytosis, acute diabetes, severe constipation, and myocarditis. With close monitoring, however, these outcomes can be avoided, and clozapine therapy can decrease mortality.[6] With the increasing availability and decreasing cost of genetic analysis, in the near future we may be able to better predict clozapine responders and the risk of agranulocytosis before initiating clozapine.[7,8]

Overcoming barriers

When initiating clozapine, it is helpful to reduce barriers to treatment. One strategy to improve patient acceptance of blood testing is to use fingerstick hematology profiles rather than the typical venipuncture technique. The Micros 60 analyzer can provide a complete blood count and granulocyte count from a blood specimen collected in a mini capillary tube.

National clozapine registries accept results derived from this method of blood analysis. Using preprinted medication and treatment orders can ease the paperwork burden for the psychiatrist. To help ensure safe use of clozapine, clinical pharmacists can help interface with the clozapine registry (see this article at CurrentPsychiatry.com for a list of clozapine registry Web sites), assist with monitoring laboratory and medication orders, and anticipate drug interactions and side effects. Staff members directly involved in the patient's care can try to improve the patient's insight of his (her) illness. Nursing staff can provide medication education.

Many efforts have been made to educate medical staff to reduce adverse effects and improve patients' experience with clozapine. Employing agents such as polyethylene glycol, desmopressin, terazosin, and topiramate can help to manage adverse effects of clozapine such as constipation, nocturnal enuresis, drooling, and weight gain, respectively. Lithium can help boost a low neutrophil count[9]; a lithium level >4.0 mEq/L may be needed to achieve this response. Although generally well tolerated, adding lithium can increase the risk of seizures with clozapine. A final hurdle has been the dilemma of an unwilling, but obviously ill and suffering, patient who has failed several medication trials and other therapeutic interventions.

Clinical Point

One strategy to improve patient acceptance of blood testing is to use fingerstick hematology profiles

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TREATMENT Involuntary clozapine

Mr. C continues to believe that he is an alien. He also thinks he is involved in a mission for God. He has physically assaulted staff on occasion. Overall, his mood shows no persistent abnormality and his sleep and appetite are normal. Family history reveals that Mr. C's brother has schizophrenia. Because of Mr. C's refractory illness, we seek the guardian's consent for a trial of clozapine and ask for permission to give backup medication and lab testing involuntarily if necessary. We obtain informed consent and orders are written. Mr. C refuses the first 2 doses of clozapine (12.5 mg at bedtime) and receives a backup order of IM olanzapine, 5 mg. He initially refuses baseline and 1-week hematology profiles, which then are obtained involuntarily by manual hold. Subsequently, Mr. C no longer refused medication or lab tests. His clozapine dosage is titrated to 400 mg/d, guided by clinical response and plasma level.

The authors' observations

We work in a public forensic psychiatry facility, where the average length of stay is 680 days. In a public psychiatry facility there may be pressure to reduce the length of stay by moving patients to a less restrictive setting and thereby reducing the overall census. Many patients at our facility likely would benefit from clozapine. In an effort to provide this important therapy to patients who refuse it despite refractory symptoms, chronic hospitalization, and dangerous behaviors, we have developed an option of involuntary clozapine administration. When efforts to convince the patient to agree to clozapine treatment fail, approval for the involuntary administration of medication and laboratory testing can be requested.

Involuntary clozapine treatment may be an important option for patients who have a guardian (as do approximately one-half of patients at our facility). It also might be an option for patients who have a court order or other legal document approving a trial of involuntary clozapine. When seeking approval from a guardian, explain the benefits and risks of treatment. Some guardians are public administrators, such as elected officials who serve as conservators and guardians, and may be familiar with clozapine and successes with other patients, and quickly support the request. In other cases, the guardian is a family member and might require more education and time to make a decision.

After obtaining approval from a guardian, inform the patient of the plan to initiate clozapine, with the goal of gradually reducing some or most of the other psychotropics. Describe to your patient why weekly hematology profiles are necessary. In collaboration with the treatment team, a convenient time is scheduled for the baseline lab draw. If lab results meet the baseline requirements, clozapine is initiated, usually using the orally disintegrating formulation. The patient is informed about the lab results, medication orders, and potential side effects. If the patient refuses medication, an IM backup of another atypical antipsychotic may be ordered in place of the missed clozapine dose, after obtaining the guardian's permission. Employing physical restraint such as a manual hold to obtain laboratory testing or to administer medication triggers restraint and seclusion policies.

continued

Table 2

Interventions when a patient refuses or avoids clozapine

Patient education
Fingerstick blood counts
Staff education
Streamlining administrative tasks
Involuntary laboratory testing
Involuntary IM atypical antipsychotic backup for refused clozapine doses

Clinical Point

When a patient does not agree to clozapine, approval for involuntary admission of medication and lab testing can be requested

See this article at CurrentPsychiatry.com for a list of clozapine registry Web sites

Clinical Point

Patients often do not resist the treatment plan once they see the medical team's commitment to their well-being

Related Resources

- Hill M, Freundenrich O. Clozapine: key discussion points for prescribers. Clin Schizophr Relat Psychoses. 2013;6(4):177-185.
- Nielsen J, Correll C, Manu P, et al. Termination of clozapine treatment due to medical reasons: when is it warranted and how can it be avoided? J Clin Psychiatry. 2013;74(6):603-613.

Drug Brand Names

Aripiprazole • Abilify
Clozapine • Clozaril, FazaClo
Desmopressin • DDAVP
Divalproex sodium • Depakote
Haloperidol • Haldol
Lithium • Eskalith, Lithobid
Olanzapine • Zyprexa
Polyethylene glycol • MiraLax
Propranolol • Inderal LA
Quetiapine • Seroquel
Risperidone • Risperdal
Sertraline • Zoloft
Terazosin • Hytrin
Topiramate • Topamax

How do you ensure compliance with clozapine therapy in an unwilling patient?

a) mouth check
b) medication watch (sitting in a public area for 30 minutes after a dose)
c) dissolving clozapine tablets
d) monitoring therapy with clozapine/norclozapine plasma levels

The authors' observations

At times we have instituted all of the methods noted in ***Table 2*** (***page 63***). We have most often used dissolving tablets and plasma monitoring.

OUTCOME Improvement, transfer

Mr. C gradually improves over 6 months. The voices, delusions, and aggression resolve. He remains mildly disorganized and has poor insight, with unrealistic goals. Approximately 3 years after admission and 1 year after clozapine was initiated, Mr. C is transferred to a minimum-security facility.

The authors' observations

Overall, our experience has been successful with the approach we have described. Patients often do not resist the treatment plan once they see our commitment to their well-being. When they do resist, it has been only for 1 to 3 doses of medication, and 1 or 2 blood draws. Of 6 recent cases under this protocol, we have discharged 3; 1 is approaching discharge; 1 has had minimal improvement to date; and 1 required discontinuation because of neutropenia.

We recommend considering involuntary clozapine therapy for refractory patients who have a poor prognosis.

References

1. McEvoy JP, Lieberman JA, Stroup TS, et al; CATIE Investigators. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. Am J Psychiatry. 2006;163(4):600-610.
2. Stroup TS, Lieberman JA, McEvoy JP, et al; CATIE Investigators. Results of phase 3 of the CATIE schizophrenia trial. Schizophr Res. 2009;107(1):1-12.
3. Meltzer HY. Clozapine: balancing safety with superior antipsychotic efficacy. Clin Schizophr Relat Psychoses. 2012;6(3):134-144.
4. Berkowitz RL, Patel U, Ni Q, et al. The impact of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) on prescribing practices: an analysis of data from a large midwestern state. J Clin Psychiatry. 2012;73(4):498-503.
5. Howes OD, Vergunst F, Gee S, et al. Adherence to treatment guidelines in clinical practice: study of antipsychotic treatment prior to clozapine initiation. Br J Psychiatry. 2012;201(6):481-485.
6. Tiihonen J, Lönnqvist J, Wahlbeck K, et al. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). Lancet. 2009;374(9690):620-627.
7. Arranz MJ, Munro J, Birkett J, et al. Pharmacogenetic prediction of clozapine response. Lancet. 2000;355(9215):1615-1616.
8. Athanasiou MC, Dettling M, Cascorbi I, et al. Candidate gene analysis identifies a polymorphism on HLA-DQB1 associated with clozapine-induced agranulocytosis. J Clin Psychiatry. 2011;72(4):458-463.
9. Paton C, Esop R. Managing clozapine-induced neutropenia with lithium. Psychiatric Bulletin. 2005;29(5):186-188.

Bottom Line

Clozapine is an underutilized treatment for refractory schizophrenia, often because of patient refusal. In a case presentation format we review the barriers to clozapine therapy. We discuss clinical and legal issues for administering clozapine to an unwilling patient.

Table 2

Where to find clozapine registries on the Web

www.caracoclozapine.com
www.clozapineregistry.com
www.clozapineodtregistry.com
www.clozarilregistry.com
www.fazacloregistry.com/login.aspx
www.mylan-clozapine.com