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Monitoring Clozapine Adverse Effects Calls for the Integration of Protocol and Good Clinical Practice

M. Bak, MD, PhD

Clozapine is viewed as a last-resort treatment for patients with a diagnosis of schizophrenia. Evidence has shown, however, that switching to clozapine after an unsuccessful intervention with olanzapine or risperidone is far more efficient than switching to either risperidone or olanzapine first.[1] It has even been argued that clozapine should be considered the first-choice treatment of a first-episode psychosis.[2] In addition, clozapine appears to be more beneficial than other antipsychotics in the treatment of negative and cognitive symptoms.[3,4] Finally, clozapine has clearly been shown to be the most effective pharmacologic treatment currently available for positive symptoms in psychotic patients.[5] In terms of treatment efficacy, therefore, it seems worthwhile to prescribe clozapine in an early phase of the treatment process, as recommended by Cohen and colleagues,[6] whose article this commentary addresses. Yet, despite this compelling evidence, clinicians are reluctant to prescribe clozapine to their psychotic patients, and the question is *why*.

The most obvious reason is, as Cohen et al[6] rightfully indicate, the adverse side effects profile of clozapine, especially the increased incidence of agranulocytosis.[7] Agranulocytosis is a life-threatening and well known adverse side effect of clozapine. It is most prevalent within the first 4–5 months after initiating treatment. The insidious clinical presentation of agranulocytosis calls for a mandatory monitoring system to detect in time a decline in the number of leukocytes and granulocytes so as to avoid a life-threatening illness or death. Therefore, in many countries, initiating clozapine is allowed only if a clinician uses a monitoring system that helps to detect early, important life-threatening adverse effects. Cohen et al[6] argue that the standard monitoring system used to detect agranulocytosis needs to be expanded to detect early signs and symptoms of myocarditis, gastrointestinal hypomotility, and diabetic ketoacidosis.

MYOCARDITIS

In the case of myocarditis, the signs and symptoms are generally flu-like, mild, and, for the most part, unnoticeable and self-limiting. A more serious complaint is chest pain. Tachycardia, hypotension, dizziness, palpitations, and dyspnea may also be present. An even more serious symptom of myocarditis is weakening of the heart muscle that may cause heart rhythm irregularities or heart failure. Myocarditis is thought to be caused by an inflammatory process or by an immune disease. Electrocardiogram and elevated heart muscle enzymes (creatine phosphokinase levels) are the primary diagnostic tests and of importance for monitoring.[8] The negative impact of clozapine on the immune system may explain the slightly elevated incidence of myocarditis in patients who use clozapine. The negative impact of myocarditis is serious. About 50% of patients receiving clozapine treatment recover from myocarditis, whereas around 10% suffer from long-term complications that need additional treatment.[9] This finding might suggest that about 40% continue to have some complications that do not need treatment, however. Cohen et al[6] found an incidence of myocarditis of 0.7%, with the exception of some Australian studies. Another problem with diagnosing myocarditis is the increase in body temperature. After starting with clozapine treatment, a substantial number of patients develop an increase in body temperature during the first 3–6 weeks, although the clinical significance remains obscure.[10] Diagnosing myocarditis can be problematic not only because the inflammation is a relatively rare condition but also because the flu-like symptoms that may accompany myocarditis are not very indicative.

Therefore, monitoring for myocarditis seems to be a good strategy for detecting as soon as possible this potentially serious condition. One needs to consider that the symptomatology is nonspecific, the incidence is very low, and the tests are not very specific for myocarditis. Clinicians should be aware that clozapine might be associated with an increased incidence of myocarditis. Because of the severe consequences of myocarditis, the subclinical or flu-like presentation of symptoms and the rise in body temperature, although often clinically insignificant, within the first weeks after starting with clozapine call above all for performing good clinical practice.

GASTROINTESTINAL HYPOMOTILITY

Gastrointestinal hypomotility may lead to discomforting constipation and abdominal pain. Although the data as presented by Cohen et al[6] are inconclusive regarding incidence rates, gastrointestinal hypomotility is a serious and relatively prevalent problem that is probably undervalued. Noteworthy is that constipation is related not only to clozapine but to almost all antipsychotics.[11] The condition of gastrointestinal hypomotility, therefore, deserves serious attention of the clinician, because most patients might think the problem is not worth mentioning.

Monitoring might help bring the problem to the attention of the clinician and patient and identify whether an intervention is necessary. But is a monitoring system really

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Corresponding author: *M. Bak, MD, PhD, Department of Psychiatry and Psychology, Maastricht University, PO Box 616, 6200 MD Maastricht, The Netherlands (m.bak@maastrichtuniversity.nl).*

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necessary for identifying the problem of gastrointestinal hypomotility? Should a good patient-doctor contact not be more appropriate?

DIABETIC KETOACIDOSIS

The condition of diabetic ketoacidosis refers to an acute exacerbation of diabetes mellitus that is caused by cessation of insulin availability. The first signs are anorexia, nausea, vomiting, and polyuria. Sometimes people have abdominal pain. If untreated, ketoacidosis results in diabetic coma. Laboratory examination shows abnormalities in glucose metabolism and hemoglobin A_{1c} (HbA_{1c}). Patients in stressful conditions like trauma, surgery, infections, or stress because of psychosis are more prone to develop diabetic ketoacidosis, suggesting a decrease in the immune defense capacity.

Diabetic ketoacidosis is a sudden glycogenic disturbance that is associated not only with clozapine but with almost all antipsychotics. The association with clozapine is most likely the strongest, as clozapine is most strongly associated with metabolic changes compared to other antipsychotics.[12,13] The question is whether monitoring is sufficient. The answer is yes only if the monitoring time interval is small enough and the tests are sensitive enough.[14] The problem with diabetic ketoacidosis is that this complication might develop within a couple of days, or sooner. Therefore, diagnosing diabetic ketoacidosis poses some serious problems from a monitoring perspective, as monitoring alone is insufficient.

In general, monitoring of metabolic side effects is mandatory for all types of antipsychotic treatments. It is known that almost all antipsychotics, including clozapine, are associated with weight gain and an increased risk for metabolic syndrome and type 2 diabetes. Because of the gradual development of these side effects, monitoring is a method for early detection and offers opportunities for interventions.

MONITORING

The essence of monitoring is that clinicians implement safety measures for adverse symptoms recognition and treatment. Also, a good monitoring system provides clinicians with adequate information to avoid the most hazardous pitfalls. A good monitoring system might lead to the safer use of clozapine. Despite the mild symptomatology of myocarditis, it seems wise to monitor for myocarditis in case of serious problems that would otherwise remain undetected and untreated. Considering the clinical presentation, physical examination, and clinical diagnostic tests that are not very specific for myocarditis, one needs to remain aware of identifying false-positive cases, especially given the possibility that a natural rise in body temperature might be misinterpreted as a problem.

Although many patients complain about constipation, it is doubtful that clinicians will interpret it as gastric hypomotility. If a monitoring system is helpful in identifying the problem for clinicians, installing a monitoring system is worthwhile.

The problem with diabetic ketoacidosis is its insidious onset, with often no clear clinical preceding features. A monitoring system at least every week might fail to notice diabetic ketoacidosis. It is therefore dependent on the sampling rate of the monitoring process as to whether the onset of ketoacidosis is detected. But monitoring for metabolic parameters, especially glucose (and HbA_{1c}) and lipids, is mandatory not only for clozapine but for all antipsychotics.

CONCLUSION

A good monitoring system is essential for patients who use clozapine. This system must focus on serious adverse effects that are difficult to detect otherwise and provide follow-up signs or test results that help to identify serious problems and offer information for adequately timed intervention or prevention strategies. However, it is essential that clinicians be aware that they have to interpret the monitoring results based on their contact with patients and the data from the monitoring system.

Drug names: clozapine (FazaClo, Clozaril, and others), olanzapine (Zyprexa and others), risperidone (Risperdal and others).
Author affiliation: Department of Psychiatry and Psychology, Maastricht University, Maastricht, The Netherlands.
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