LETTERS

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Agranulocytosis in a Second Clozapine Trial

To the Editor: For patients on clozapine, the period of highest risk of agranulocytosis is during the first 12 to 18 weeks of treatment (1). The following case suggests that agranulocytosis may occur during a second clozapine trial despite a successful previous trial.

Mr. P was a 58-year-old man with a *DSM-IV* diagnosis of schizophrenia, undifferentiated type, who attended a continuing day treatment program. He had had multiple psychiatric hospitalizations in the past, beginning with a six-month hospitalization when he was in his early 20s.

In April 1996, Mr. P was hospitalized with an episode of neuroleptic malignant syndrome that was successfully treated with bromocriptine after haloperidol and lithium carbonate were discontinued. He remained in the hospital, where, on July 17, he was placed on clozapine for the first time. The dosage was titrated to 400 mg daily, with good results, and he was discharged about six weeks later, on August 30. At discharge, findings of a laboratory workup, which included a complete blood cell (CBC) count and differential count, thyroid studies, electrolytes, and liver function tests, were unremarkable. The patient's white blood cell (WBC) count was 6,500/mm^3.

Mr. P subsequently discontinued outpatient follow-up and his medication. His symptoms of severe disorganization and thought disorder recurred, and he was hospitalized again in June 1997. Clozapine was started for the second time on June 19, 1997, with 50 mg at bedtime, and was titrated to 400 mg daily. His symptoms of disorganization and thought disorder showed considerable improvement. However, between weeks two and five of clozapine treatment, his WBC count declined from 5,100/mm^3 to 3,900/mm^3. The next WBC count on July 25 dropped to 1,600/mm^3, with an absolute neutrophil count of 170. Agranulocytosis was diagnosed, the clozapine was discontinued, and Mr. P was transferred to the medical service.

On July 28 Mr. P was started on daily subcutaneous doses of 300 μg granulocyte-colony-stimulating factor. High fever of 102 degrees Farenheit occurred the next day, and broad-spectrum antibiotics were started, including piperacillin (4 grams intravenously every six hours) and gentamicin (500 mg daily). The fever remitted in 48 hours. No focal causes of sepsis were detected. On August 4 his WBC count began to increase to 2,400/mm^3, and the next day it rose to 6,300/mm^3, with 59 percent granulocytes and an absolute neutrophil count of 3,000. The patient's thought disorder and disorganization had reappeared.

In the patient's second clozapine trial, agranulocytosis occurred at week six, which points to the importance of doing weekly blood counts in the first 12 to 18 weeks. It might be important to monitor the WBC trend because the overall trend in this case was a declining one, from 5,100/mm^3 to 1,600/mm^3. Care should be taken in using clozapine with older patients and with women because the risk of agranulocytosis may be higher (2). A review of the 13 reported deaths due to agranulocytosis associated with clozapine since 1990 indicated that seven of these patients were age 60 or above (personal communication, Novartis Pharmaceuticals Corporation, August 6, 1997).

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Incarceration as "Therapy"

To the Editor: Lamb and Weinberger's April 1998 review (1) of the incarceration of those with severe psychiatric illness was of considerable interest. We would like to add to this discussion a phenomenon we have observed that may contribute to the increased numbers of psychiatric patients in our jails. Specifically, use of law enforcement sometimes takes the place of acute psychiatric intervention when involuntary commitment is not possible. Because of the stringency of our involuntary commitment laws, many families find themselves in the difficult position of having to call on police to intervene in physically volatile situations that result from an ill relative's failure to take medication properly.

A typical scenario is that of a male patient with paranoid schizophrenia who does not take antipsychotic medications properly, regularly, or at all. Psychosis impairs his judgment and insight and often leads him to irritable, hostile, and threatening behavior, yet he is not a sufficient threat to self or others to justify involuntary com-

mitment. At this point, relatives, desperate to obtain treatment but denied access to mental health services, may be forced to resort to police intervention. The ill relative's behavior justifies an arrest on the grounds of, for example, damage against property. In this situation, psychiatric treatment is, paradoxically, more accessible in jail than in the community.

It would be helpful to know how many such individuals are jailed in lieu of being involuntarily committed for treatment, how long such incarcerations last, and the process by which they eventually move from the legal to the mental health system. While we must guard against abusive involuntary commitment, we must also support the treatment of psychosis (2). Further study of this phenomenon is important if we are to provide individuals suffering from psychosis with treatment rather than punishment.

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Patients' Preferences About Medication Dosing Regimens

To the Editor: In the context of psychiatric treatment, compliance often means the extent to which patients take medication as prescribed (1). Cramer and Rosenheck (2) recently pointed out that with the growing fiscal pressure to reduce the intensity of outpatient and other treatments, contact between physicians and patients may become more restricted. As a result, encouraging patients to comply with their medication regimen may be more important than ever. Physicians must become more effective in encouraging compliance. To do so, they need information about factors that influence compliance.

Clinicians believe that patients' compliance worsens as the dosing frequency increases and as medication regimens become more complex (3). Therefore, they prefer once-a-day dosing or long-acting medication given weekly or monthly by injection or skin patch. However, little is known about patients' preferences regarding dosing schedules.

In 1997 we administered a 12-item questionnaire about compliance and preferred dosing schedules to 106 consecutive patients at two mental health clinics in southeastern Michigan. Patients' identities were unknown to the investigators; each patient's chart diagnosis was added to the questionnaire form by clerical personnel who were otherwise not involved in the study.

A total of 106 patients answered the questionnaire. Sixty-four percent were women, 66 percent were white, and 56 percent had a college education. Their mean±SD age was 43± 10.8 years. Major depression was the most frequent diagnosis, for 34 percent of the patients, and an antidepressant had been prescribed as primary medication for 64 percent of all patients. The majority of patients, 71 percent, reported being compliant with their medication regimen during the previous week and had not missed a single dose.

Fifty-one percent of patients preferred once-a-day dosing, 36 percent twice a day, 6 percent three times a day, and 2 percent four times a day. Interestingly, 4 percent preferred injections, and 1 percent preferred patches. Forty percent of patients on the four-times-a-day regimen would miss one of their daily doses, as would 21 percent of patients on a once-a-day regimen, 10 percent of patients on a twice-a-day regimen, and 25 percent of patients on a three-times-a-day regimen. In addition, 4 percent of patients receiving once-a-month injections would miss one dose.

Thirty-three percent of patients missed their medication during short-term use (up to four weeks), 33 percent during long-term use (four weeks to a year), and 35 percent during lifelong use. The majority of patients (67 percent) did not feel that having to take several different medications at a time would cause them to miss a dose.

Our sample was not large enough to perform separate analyses with different diagnoses and medications. However, the compliance rates between patients with different diagnoses and medications may not differ very much (2). Results of our study demonstrate that patients believe they may be more noncompliant with an increased number of daily doses, but generally they do not feel that polypharmacy affects their compliance. Thus the commonly held belief that a simpler dosing strategy leads to better compliance seems to be confirmed by patients' preferences. However, it is not clear how much the patients' preferences reflect the extent of their factual compliance. Further studies addressing this issue are needed.

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