The Impact of Clozapine on 25 Forensic Patients

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Clozapine was approved by the Food and Drug Administration (FDA) in October of 1989 for use through the Clozaril Patient Management System (CPMS). Prior to that date clozapine was prescribed on a "compassionate use" basis at 16 study centers in the U.S. It was used primarily with patients with a diagnosis of schizophrenia and schizoaffective disorder whose symptoms were refractory to traditional neuroleptics, or patients who had serious side effects to traditional neuroleptics, like tardive dyskinesia.[1, 2] Because clozapine can cause agranulocytosis in one to two percent of patients, the FDA approved the release of the drug through a controlled program that ensured close monitoring of the WBC and differential. The CPMS became the first company to establish a national monitoring system for a new drug.[3-5]

A review of European[6] and American[7-10] studies on clozapine demonstrated that clozapine outperformed other neuroleptics. One-third to one-half of patients who did not respond to traditional neuroleptics, did respond to clozapine. Aside from a paper that described the use of clozapine with "psychopathic prisoners" in South Africa,[11] however, there have been no published reports of the use of clozapine with forensic patients. One study at a large state hospital specifically excluded them.[12] American studies that compared the use of clozapine to other neuroleptics were usually of a six to eight week duration.[13] This paper will report our experience with 25 forensic patients who were treatment resistant to traditional neuroleptics. It reports on the effectiveness of the medication for a minimum of 6 months and a maximum of 15 months.[14]

Description of Facility

The Forensic Program, part of Mendota Mental Health Institute, a JCAHO accredited facility, in Madison, Wisconsin, has 190 beds, divided in 10 units. There are four maximum security units (73 beds), four medium security units (87 beds), and two minimum security units (30 beds). The units are under a single clinical/administrative leadership. Programmatically the three security dimensions are integrated as a tier system. The system has been described in several publications.[15, 16]

Patient Selection and Initiation of Treatment

Patient Selection Criteria More than 75 percent of the patients admitted

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to the Forensic Program have a DSM-III-R diagnosis of a major mental disorder on Axis I (see Table 1). Eighty-five percent of these have a type of schizophrenia. Traditional neuroleptics have been the principal pharmacologic treatment of choice for these patients. When clozapine became available, we identified 35 of 170 patients who manifested significant psychotic symptoms while on other neuroleptics and who met criteria 1, 2 and 3, and criteria 4 as appropriate, as described below:

1. A DSM-III-R diagnosis of schizophrenia or schizoaffective disorder.

2. Treatment refractory, as evidenced by a completed trial on high doses of at least two neuroleptics, for at least three months without complete remission of symptoms.

3. That clozapine was likely to result in release from hospital within one year, or improve patient safety while confined in hospital.

4. Presence of serious side effects from traditional neuroleptics, tardive dyskinesia or intractable EPS.

Criteria 3 was suggested by the administration as a practical gauge of improvement and to help clinicians select patients who were either aggressive or likely to be considered for release if symptoms could be removed. These were later called the Forensic Criteria.

Table 1
Demographic Information

Sex	Male	
Age at Start of Trial	Range 26–50 years	
	Average 36	
Race	White 18	72%
	Black 6	24%
	Indian 1	4%
	Total	100%*
Principal Crime	1st degree murder	8
	Attempted murder	4
	Sexual assault	3
	Battery	1
	Conduct regardless of life	1
	Arson	1
	Other	3
	Assaultive behavior	4
Wisconsin Statute	Treat to competency	1
	Civil commitment	2
	Guardianship	3
	NGRI	19
DSM-III-R Diagnosis	Schizophrenia paranoid	18
	Schizophrenia undifferentiated	5
	Schizoaffective	1
	Organic mood	1**
Length of Treatment	Shortest 6 months	
	Longest 15 months	

* The racial distribution, by chance, fit the average racial distribution of our program on a per year basis.
** The principal diagnosis, Organic Mood Disorder, did not fit our criteria. The patient had had a previous diagnosis of Psychosis NOS, and was accepted because of this.

Patient Selection Process Initiating a new treatment in a confined system is a little like starting practice in obstetrics in a small town; the first delivery should be a healthy baby. Because we hoped to give clozapine a "live birth" we decided to initiate the treatment simultaneously with a number of cooperative patients on maximum, medium, and minimum security units. Eleven patients were identified, four in maximum, three in medium, and four in minimum, who consciously voiced a desire to be rid of hallucinations, paranoid thinking, and/or side effects of other neuroleptics and who were willing to accept the potential risk of seizures, agranulocytosis, and a needle stick per week, because of the promise of improvement.

Once identified, the nurse manager of the unit and the author met with each patient individually and explained the risks and benefits of clozapine. Once the consent forms were signed, the applications for use of clozapine for each patient were then sent to the Institute Pharmacy and Therapeutics Committee, where they were approved. Each patient was then enrolled in the CPMS. Once enrolled, each patient was reapproached individually and given another review of the risks and benefits of clozapine. Practical questions like the phase-out of traditional neuroleptics and phase-in of the clozapine were discussed. Because of the possibility of the reemergence of aggressive behavior or unwanted psychotic symptoms, traditional neuroleptics were continued during the two-week standard titration of clozapine to 300 mg. They were then discontinued. All benzodiazepines, however, were stopped before clozapine was started. Security and release criteria were used to establish the therapeutic impact of the drug. In particular, transfer to a less secure unit in our system, transfer to another less secure hospital, or release by the courts were the three forensic criteria that were used to judge the practical impact of clozapine.

The Standard Titration Process On May 9, 1990, 11 patients were started on the standard titration protocol. They were, therefore, titrated from 25 mg on day one to 300 mg by day 14. All of them were then left to stabilize for a period of two weeks on 300 mg as we became acquainted with the effects of the drug. After this period of assessment the dose was decreased to minimize side effects like sedation, or increased to reduce psychotic symptoms. The highest dose level used on any patient for the first year was 600 mg/day because the incidence of seizures increases with doses over 600 mg. The average dose was about 450 mg/day. The guidelines for leukopenia were those suggested by CPMS. We followed their monitoring protocol to the letter.

When the CPMS was discontinued on April 1, 1991, the Institute took on the responsibility of monitoring the WBC and differential. We set our standards of leukopenia slightly higher than those described in the clozapine packaging insert, a conservative measure to ensure safe monitoring. We also set the Quantity Regulation (QR) dose at 700 mg/day even though the package insert listed the therapeutic range from 25 to 900 mg/day.

Response

Of the first 11 patients started on the standard titration of clozapine, nine had a diagnosis of schizophrenia, paranoid type, and two of schizophrenia, undifferentiated type. Two patients (patient A and patient B) responded positively in the first two to three weeks. The rapid change was greeted positively by staff and other patients who could not help but notice the positive changes. At the same time, two patients developed significant side effects that eventually resulted in the discontinuation of clozapine. These cases are briefly described in the section below on adverse effects.

Of the remaining seven patients, one had two grand mal seizures. The clozapine was stopped. Staff were disappointed that the clozapine had to be stopped because the patient was responding positively. His case is described below. The other six patients all appeared in the early months to benefit from clozapine but were described as slow responders. They continued to show incremental positive change. Delusional thinking decreased. They appeared more emotionally stable. They gained a positive sense of self-esteem. Clozapine appeared to have an impact on both the positive and negative symptoms of schizophrenia.

Case Examples

Case 1 Patient A, a 50-year-old white male, was found not guilty by reason of mental disease for attempted murder.[17] The patient had marked paranoid ideation that was unresponsive to high doses of traditional neuroleptics. Over the years, fluphenazine decanoate was found to be the most effective neuroleptic, but the patient's paranoid ideation would still not remit even with high doses. Further, this patient suffered severe akathisia. The fluphenazine was discontinued and clozapine was started. Within weeks of starting clozapine, the patient began to undergo a personality change. Not only was there relief from the side effects of fluphenazine, but the patient's paranoia receded, he developed positive self-esteem, and his relationship with staff and peers improved. News of his response to clozapine had a positive impact on staff and patients.

The judge was also impressed with his improvement and conditionally released him at a hearing four months after he started clozapine. Because the patient had a past history of noncompliance with other medications, the county officials who were responsible for providing aftercare required baseline and then ongoing monitoring of the serum level of clozapine.[18,19] This was done on a three-month basis. Once the clozapine funding issue was worked out the patient was released.

Case 2 Patient B had a longstanding diagnosis of schizophrenia. Because of his inability to care for himself when actively psychotic, the court appointed a guardian in 1985. In fact, years before that he had left a civil commitment unit in the middle of a wintery night and froze the fingers on both hands so that they required amputation. The patient on another occasion claimed that he was possessed by the devil. Medication could not remove this delusion. During delu-

sional periods he would pound his head with his fist. This pounding was so severe that he detached the retina of his left eye, which became legally defined as blind.

During the current admission the devil demanded that he receive an exorcism. Caught in his devilish delusion, he began to pound his other eye. He was sent to the orthotics clinic and fitted for a special helmet, complete with face guard. The chin strap was so structured that he could not remove the helmet. He was required to sleep with this helmet.

He was started on clozapine and after a period of one week he was discovered reading the newspaper. Then he spontaneously called his mother, something he had never done. His response to clozapine was so remarkable that not only did the delusional idea of possession leave him, he was no longer a danger to himself. His helmet was retired. He was transferred from a maximum security unit to a medium security unit and then to a group home. News of his improvement had a similar positive effect on staff and patients.

Case 3 Patient C suffered from paranoid schizophrenia. He had a longstanding, unsatisfactory response to neuroleptics. He was stuck in the belief that everything he did, he had done before. He said he was stuck in "deja vu." At the same time, his thought processes were vague. It was impossible to form a meaningful relationship with him. At times he became aggressive. On one occasion he impulsively took the budgie birds on the unit, put them in his pockets, and thumped them to death. The patient was started on clozapine, and within three weeks his demeanor changed, his thoughts cleared, and the problem of "deja vu" receded. More important, the patient became interested in his Native American identity. He began to talk about feeling abandoned by his mother. Personal and family issues that had been known but never discussed in any meaningful way became the topic of therapy. He developed insight into his problem with alcoholism. This change was so remarkable that within four months the court conditionally released him to his home community.

Case 4 For more than two years, patient D was on the most secure hospital unit in the state of Wisconsin.[20] He was diagnosed with schizoaffective disorder. Even on high doses of two neuroleptics he had frequent aggressive temper tantrums. Over the three-month period prior to starting clozapine, he had 77 aggressive temper tantrums requiring 54 seclusions. After six months on clozapine, his temper tantrums reduced to one every three weeks and seclusions stopped. He began a six-month period of emotional maturation. His preoccupation with death and fear of dying seemed to resolve. He was transferred to a medium security unit. He was then transferred to an open civil unit where he currently resides. Clozapine acted as both an antipsychotic and antiaggression drug for this patient.

Case 5 Patient E had a longstanding history of paranoid schizophrenia with aggressive outbursts. At the same time he suffered from a psychogenic polydyp-

sia. Traditional neuroleptics and Tegretol made some impact on his paranoid behavior, but the only way he could keep from gorging himself was to manage his water intake for him. While the patient's current diagnosis was organic personality syndrome, the reports that clozapine may help manage psychogenia polydipsia qualified him for a trial on clozapine.[21,22] Tegretol was stopped. The traditional neuroleptics were discontinued as the clozapine increased. After four to five weeks his thinking improved. He developed impulse control. A sense of humor appeared. He attended to his personal appearance. Given this progress he was given a trial of water self-management. The trial failed miserably. Within 24 hours of free access to water, the patient gorged himself and had a water-induced seizure. Given his lack of ability to control his water intake but the improvement of psychotic symptoms, he was transferred to an outpatient setting where his water could be monitored carefully.

Case 6 Patient F had a diagnosis of paranoid schizophrenia. He had a very poor response to traditional neuroleptics during his 10 admissions to hospital over the past 15 years. The patient was facing a burglary charge. He suffered from a fixed delusion that he was being poisoned. He had great difficulty eating, which resulted in a marked weight loss. Clozapine was started with the consent of both him and his attorney. Two weeks after he started on clozapine a report was sent to the court indicating that he was not competent to proceed. By the time the court responded, the patient had had such a remarkable response to clozapine that the earlier opinion was no longer valid. Because of the rapid response there had not been time to arrange for continued funding for clozapine. Accordingly, the court delayed the competency hearing so that arrangements could be made so clozapine would continue to be funded once he was beyond the legal process and conditionally released. The court agreed. The arrangements for the continued funding of clozapine were made. The court dropped the charges and the patient voluntarily admitted himself to the local hospital. At the time of writing he is an outpatient.

Adverse Events

Side Effects In general the patients tolerated clozapine well. More than half experienced a transient period of sedation. While bothersome, the patients were not concerned. About 40 percent of the patients experienced persistent nighttime drooling. Initially these patients were given a towel to keep themselves dry. They were also given a second pillow case. The drooling stopped after three to six months for all but three patients for which it lessened and who therefore accommodated to it. No treatment was considered.

Patients on two of our units all gained up to 20 pounds in the first three months of use. While other patients gained up to five pounds, it was difficult to attribute this to the clozapine. We did not know how to explain the excessive weight gain experienced by the patients on these two units. Other minor side

effects like feeling faint, transient hypotension, constipation, and difficulty sleeping were noted, but of no significance.

Adverse Drug Reactions Four patients experienced an adverse drug reaction that resulted in the discontinuation of clozapine: Patient G experienced tachycardia, hypertension, and dizziness. At the same time he appeared sedated and depressed. Propranolol, 20 mg po b.i.d. was prescribed, but with little impact. Clozapine was stopped at a dose of 300 mg/day after five weeks. Patient H became excessively sedated, and since clozapine did not seem to have any impact on his paranoid delusions, clozapine was stopped at a dose of 500 mg/day, after nine weeks. Patient I had reversible tardive dyskinesia as a result of longstanding treatment with traditional neuroleptics for paranoid schizophrenia. He developed unstable hypotension. Clozapine was stopped at a dose of 400 mg/day after 10 weeks. Finally, patient J became sedated, depressed, and confused. Clozapine was stopped at a dose of 300 mg/day after three and a half weeks.

Seizures The literature suggests that clozapine may induce seizures.[23-25] One to two percent of patients have a seizure on doses up to 300 mg/day; three to four percent seizure on doses from 300 to 600 mg/day. Approximately five to six percent of patients have a seizure on doses over 600 mg. The following case examples describe our experience with seizures.

Case Examples

Case 7 Patient K was diagnosed as paranoid schizophrenia. He suffered from intense persecutory auditory hallucinations. He reported with great anguish that voices screamed in his head calling him names. He would often be seen in his room holding his head and yelling back at the voices. Traditional neuroleptics reduced the symptoms, but they did not bring him significant relief. The patient was started on the standard titration of clozapine. It became clear to the staff within weeks that the patient no longer manifested self-tortured behavior. He reported that the voices were receding. Because he still complained of auditory hallucinations, we increased clozapine to 400 mg. Approximately two weeks later, the patient had two grand mal seizures in about six hours. Clozapine was discontinued per policy and the patient was worked up for a seizure disorder. No organic cause was found to account for the seizures. Klonopin, 1 mg q.i.d., was prescribed and clozapine was restarted. The patient's clinical condition responded as before but without further seizures. He was transferred from a maximum security unit and is in the process of being returned to his regional hospital. While clozapine-induced seizures may be managed by reducing the dose of clozapine, we had decided prior to the use of clozapine to allay anxiety that might arise from uncertainty as to the etiology of seizures, to stop the clozapine and complete a formal workup before resuming clozapine.

Case 8 Patient L had a longstanding diagnosis of schizophrenia undifferentiated type. He had never satisfactorily responded to neuroleptics. He was started on clozapine. There were signs

of improvement at a dose of 300 mg when he appeared to have a seizure in his room. On two separate occasions, about a week apart, he came out of his room with a dazed look. On the first occasion he had a chipped tooth. It became impossible not to believe that he was having seizures. The clozapine therefore was discontinued. The patient was to be examined for a seizure disorder at the clinic when his mother called and told us that her son had said that he had been hoarding his medication. A room search did not yield any clozapine but weeks later the patient did show us where he had hid it. He admitted that he had saved the clozapine. He took five or six 100-mg clozapine pills at a time, which obviously was a seizure inducing dosage for him.

Leukopenia/Agranulocytosis We did not experience a case of severe leukopenia or agranulocytosis. One patient had a WBC count at the low end of an age adjusted scale. His values were in the 3.5 to 4.0 (1,000 cells/microliter) range on three measurements of an 18-month period. Since clozapine has its greatest depressant effect on the bone marrow in the first 6 months, we were prepared to endure leukopenia up to 2.8 without stopping the medication. During the first 10 weeks clozapine was held eight times for one to two days until the WBC rebounded to 3.5 or above. After the third month the WBC stabilized in the middle range of the norm.

Another patient gave blood on a Tuesday and started the standard titration of clozapine on Wednesday. The WBC count of 2.5 was reported at noon on Wednesday. It was suggested that the clozapine be held. It did not take long to realize that the leukopenia could not be attributed to clozapine but was associated with thioridazine, which the patient had been on for about two years. Traditional neuroleptics have a 1/10,000 rate of agranulocytosis.

Outcome Summary

Of the 25 patients in this study, four patients had an adverse reaction to clozapine (see Table 2). One patient took an overdose of clozapine on at least two occasions, causing seizures and for that reason was considered unreliable. Finally, a sixth patient experienced tachycardia that persisted even with 40 mg of Inderal per day. Since he had no significant clinical response after one year, clozapine was stopped. Therefore, clozapine was discontinued for 24 percent of the patients, 16 percent[4] because of significant side effects, four percent because one patient was irresponsible and four percent because of lack of substantial response with another.

Of the remaining 19 patients, 20 percent[5] were discharged by the court because of their marked improvement.

Table 2
Outcome Summary

	Number of Patients	Percent
Released by courts	5	20
Released to civil unit	2	8
Advanced one security level	6	24
Total	13	52*
Clozapine intolerance	6	24
Regressed one security level	2	8
Total	8	32*

* Four patients (16%) remained on the same security level.

These patients either moved up a security level and then to the community or went directly from their medium or minimum security unit to the community. Movement from one security level to a less secure unit was not measured for these patients given the greater importance of release. Consequently, 20 percent of the patients improved enough that judges were willing to release them. Two further patients (8%) were transferred to less secure units in civil hospitals. One patient went to the civil unit at our own facility, and the other was transferred to the civil unit at our sister facility at Winnebago. Consequently, according to the "forensic criteria" used to determine practical improvement, 28 percent of the patients received either a discharge or a transfer to a less secure civil hospital as a direct result of the clozapine.

Of the remaining 12 patients, six (24%) advanced at least one security level in the system. They moved from maximum to medium or medium to minimum. Two patients on medium security units (8%) returned to maximum security.

As a total outcome then, 28 percent of the patients were discharged or moved to a less secure civil unit and 24 percent of the patients were advanced at least one security level. Therefore, 52 percent of the patients experienced clinical improvement that resulted in release by the courts or administrative authorities, or advance in our security system. Conversely, six patients (24%) either could not tolerate clozapine, misused it, or did not receive any benefit from it. Two patients (8%) moved back a security level in the system. Thus, 32% of the patients showed no positive response to clozapine. The two patients who returned to maximum security were not aggressive. One became hypomanic. Lithium was initiated and the dose of clozapine increased to 700 mg. He is ready for medium security again. The second patient's dose of clozapine is being increased to 900 mg at the time of writing. Finally, four patients (16%) did not change security levels. Clinical indicators show improvement, but not enough to impress release authorities.

Discussion

Many mentally disordered patients become immersed in the criminal justice system because of aggressive behavior. It is easy to speculate that many of them would not have received a full response to traditional neuroleptics and therefore it may not be surprising that a number of these patients now in forensic hospitals would be good candidates for long-term management on clozapine. This may account for our significantly positive response. Long-term hospitalized forensic patients may include an inordinately high number of patients who have not responded fully to traditional neuroleptics. Those schizophrenic patients that do respond are less likely to show up in the forensic system.

In reviewing the general impact of the use of clozapine in our program, the method we used to introduce the medication, that is to introduce it to a large number of patients in all security levels at the same time, was well received. We

had no significant noncompliance with the use of the medication. The fact that individual patients who were rapid responders moved quickly to discharge was a great encouragement to some of our long-term patients who had not felt hope for discharge in years.

As a consequence, the morale of patients and staff improved. Patients whom staff have given up on because of the chronicity of symptoms and the lack of response to traditional neuroleptics have been given renewed hope that a trial on clozapine may prove rewarding. Furthermore, seizure behavior was well tolerated by the patient communities and by the staff. The monitoring system of clozapine by the CPMS and then by the Institute appears to have been sound enough that all levels of staff felt confident in continuing clozapine even when it was reported that the white count had dropped and that a special blood sample would be required.

Finally, clozapine clearly had a significant impact on the negative symptoms of schizophrenia with some patients. When the symptoms of the Axis I diagnosis were resolved, some patients had an Axis II diagnosis emerge. At least two patients who had been aggressive when psychotic remained immature, impulsive, and threatening once the psychotic symptoms remitted. In both cases, however, the patients seemed to "grow up" in the succeeding six months. While two cases does not prove anything, it is interesting to speculate that clozapine somehow facilitated personal growth not just because it is a good antipsychotic medication, but because the sense of well-being that is a definitive characteristic of its therapeutic impact may allow patients to approach with optimism unresolved personality issues that are embedded in the personality but hidden from view by the psychotic/nonpsychotic cycle. While traditional neuroleptics may reduce the positive symptoms in some patients with schizophrenia, the residual symptoms often continue to prevent personality growth. One might say that the multiaxial system was adopted to account for maladaptive residual personalities of patients with major mental disorders. Clozapine may have a specific role in facilitating the growth of the immature personality of symptom-free schizophrenics. For those of us who work in an institutional setting, this could be a very exciting possibility.[26]

References

1. Claghorn J, Honigfeld G, Abuzzahab FS, et al: The risks and benefits of clozapine versus chlorpromazine. J Clin Psychopharmacol 7:377–84, 1987
2. Liberman JA, Saltz BL, Johns CA, et al: The effects of clozapine on tardive dyskinesia. Br J of Psychiatry 158:503–10, 1991
3. Professionals' Guide to the Clozaril Patient Management System. Sandoz Pharmaceutical Company, 1989
4. Reid WH: Access to care: clozapine in the public sector. Hosp Community Psychiatry 41:870–6, 1990
5. Peck CC: FDA's position on the clozarile patient management system. Hosp Community Psychiatry 41:876–7, 1990
6. Naber D, Hippius H: The European experience with use of clozapine. Hosp Community Psychiatry 41:886, 1990
7. Kane J, Honigfeld G, Singer J, et al: Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry 45:789–96, 1988
8. Ereshefsky L, Watanabe MD, Tran-Johnson

TK: Clozapine: an atypical antipsychotic agent. Clin Pharmacy 8:691–709, 1989
9. Barrett N, Ormiston S, Molyneux V: Clozapine: a new drug for schizophrenia. J Psychosoc Nursing 28:24–8, 1990
10. Marader SR, Van Putten T: Who should receive clozapine? Arch Gen Psychiatry 45:865–7, 1988
11. Van Wyk AJ, Robbertze JH: The effect of clozapine (HF-1854) on long-term psychopathic prisoners. In: 5th World Congr. of Psychiatry, Mexico, Nov. 28–Dec. 4, 1971. Abstr. Le Prensa Medica Mexicana, Mexico, 563–4, 1971
12. Conley RR, Schulz SC, Baker RW, Collins JF, Bell JA: Clozapine efficacy in schizophrenic nonresponders. Psychopharmacol Bull 24:269–74, 1988
13. McElroy SL, Dessain EC, Pope Jr. HG, et al: Clozapine in the treatment of psychotic mood disorders, schizoaffective disorder, and schizophrenia. J Clin Psychiatry 52:411–4, 1991
14. Honigfeld G, Patin J: A two-year clinician and economic follow-up of patients on clozapine. Hosp Community Psychiatry 41:882–5, 1990
15. Maier GJ: Relationship security: The dynamics of keepers and kept. J Forensic Sci 31:603–8, 1986
16. Miller RK, Maier GJ, Van Rybroek GJ, Weidemann J: Treating patients "doing time": a forensic perspective. Hosp Community Psychiatry 40:960–2, 1989
17. Maier GJ, Miller R, Roach L: The real cost of Clozaril: patient buys freedom. Hosp Community Psychiatry 43:177–8, 1992
18. Haring C, Fleischhacker WW, Schett P, Humpel C, Barnas C, Saria A: Influence of patient-related variables on clozapine plasma levels. Am J Psychiatry 147:1471–5, 1990
19. Perry PJ, Miller DD, Arndt SV, Cadoret RJ: Clozapine and norclozapine plasma concentrations and clinical response of treatment-refractory schizophrenic patients. Am J Psychiatry 148:231–5, 1991
20. Maier GJ, Van Rybroek GJ, Doren D, Musholt EA, Miller RD: A comprehensive model for understanding and managing aggressive inpatients. Am J Continuing Ed Nursing, Section C, pp 1–18, 1988
21. Vieweg WVR, Hundley PL, Godleski LS, Tisdelle DA, Pruzinsky T, Yank GR: Diurnal weight gain as a predictor of serum sodium concentration in patients with psychosis, intermittent hyponatremia, and polydipsia (PIP syndrome). Psychiatry Res 26:305–12, 1988
22. Lee HC, Alphs LD, Meltzer HY: Effect of clozapine on psychogenic polydipsia in chronic schizophrenia. J Clin Psychopharmacol 11:222, 1991
23. Haller E, Binder RL: Clozapine and seizures. Am J Psychiatry 147:1069–71, 1990
24. Clozapine and Seizures, Psychiatry Drug Alert. Millburn, NJ, M. J. Powers & Co. Publishers, July, 1991
25. Devinsky O, Honigfeld F, Patin J: Clozapine-related seizures. Neurology 41:369–71, 1991
26. Meltzer HY, Burnett S, Bastani B, Ramirez LF: Effects of six months of clozapine treatment on the quality of life of chronic schizophrenic patients. Hosp Community Psychiatry 41:892–7, 1990