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Clozapine: More Side Effects but Still the Best Antipsychotic

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Clozapine, the gold-standard antipsychotic, has had a fascinating history. Hippius[1] documented this history well, but, in essence, at a time when everyone believed that antipsychotic activity and extrapyramidal symptoms (EPS) were inseparable. Wander AG laboratories, Basel, Switzerland, developed clozapine, which does not produce EPS.

In our initial 1974 study,[2] the most memorable effect appeared to be on the nurses, who marveled at patients' improvement in the absence of EPS while being treated with clozapine. Routine treatment at that time was to increase the dose until improvement took place or EPS were noted. For someone like Haase,[3] this meant subclinical EPS, ie, changes in handwriting, which he claimed correlated with the therapeutic dose. We were able to confirm Haase's findings and also showed that clozapine did not produce cramping of handwriting.[1,2]

In our small-sample study,[2] clozapine was shown to be active and to produce sedation and salivation, but no EPS. Tardive dyskinesia that was present in 2 patients improved. We also saw changes in heart rate and blood pressure as well as significant weight gain. Withdrawal symptoms, including confusion, were noted when clozapine was abruptly withdrawn.[2] Soon after this study came the report of deaths in Finland from agranulocytosis, which meant that in our next study[4] of clozapine to treat tardive dyskinesia, we carried out twice-weekly white blood cell counts. Side effects noted included neutropenia, seizures, hypotensive collapse, tachycardia, and QT flattening, but no EPS. There was improvement in tardive dyskinesia, and 3 of the 12 treated patients elected to continue on clozapine treatment after the study was over. Nonetheless, the side effect burden was large considering the small sample size of the study.[4] The experience in Finland brought about curtailment of the use of clozapine in some countries. However, because of the almost universal view of the superior efficacy of clozapine, its availability in other countries kept it afloat and ultimately resulted in Study 30, for which much credit goes to Gilbert Honigfeld, Sandoz Labs, John Kane, and Herbert Meltzer (see reference 5). This large study convincingly showed the superiority of clozapine in treatment-resistant schizophrenia and confirmed the absence of EPS.[5] This study ultimately resulted in the availability of clozapine for treatment in the United States with necessary blood monitoring. The superiority and efficacy of clozapine have stood the test of time, but additional side effects continue to be reported. They have ranged from the ones listed above to a long list in the *Physicians' Desk Reference*, including deep-vein thrombosis and myocarditis. This latter side effect is well documented in this issue of the *Journal*.[6] Also included in the article by Ronaldson et al[6] are strategies that can lessen or prevent this potentially serious or fatal side effect. This study of well-defined cases of clozapine-induced myocarditis also looked for predictors. Patients who receive clozapine in Australia are usually hospitalized for 3 weeks while treatment is initiated. Days 14 to 22 of treatment are a high-risk period for myocarditis, and there is a suggestion that special attention be given to the third week.[6] While such care is unlikely to take place in other countries, special attention should be given during this time period, ie, the first 4 weeks. This close attention should cut down on the risk of developing severe myocarditis. This length of time for special attention might seem cumbersome, but so too was the blood monitoring system for clozapine, which works well.

It is troubling that, despite all of the positive data about the benefits of clozapine, the prescriptions remain flat over the years. Many mental health clinics do not offer clozapine. In these days of evidence-based psychiatry and concerns about costs, it is difficult to understand why clozapine's market share did not reach 3.5 percent in any one of the last 12 months,[7] while aripiprazole, risperidone, olanzapine, and quetiapine each reached double digits (10%–30%), and sometimes 2 or 3 of these agents are combined, with no data to support this use and with no apparent concern for costs.

A recent study[8] from Finland confirms that clozapine is associated with less suicide than any other antipsychotic, typical or atypical, and is associated with the lowest all-cause mortality rate compared to all other antipsychotics. The authors suggest that the restrictions on the use of clozapine might have caused thousands of premature deaths worldwide "in patients who have been exposed to other antipsychotic drugs."[8(p7)]

It would seem reasonable when initiating clozapine treatment to pay special attention during the first 4 weeks. A pulse above 100 bpm or the presence of an elevated temperature should result in close monitoring. Chest pain or an elevated C-reactive protein should result in cessation of clozapine treatment and should trigger an intensive work-up for myocarditis.

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Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), olanzapine ((Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others).

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