Jefferson Journal of Psychiatry

Volume 14 | Issue 1 Article 7

January 1998

[In Response to "The neuroleptic treatment of schizophrenia: dosing strategies, depot preparations and novel medications" by Alexander S. Young, M.D. (volume 13, 18-26)]

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Letter to the Editor

We feel that Alexander S. Young's recent article, "The neuroleptic treatment of schizophrenia: dosing strategies, depot preparations and novel medications" (*Journal*, 13, 18–26), may overstate the risks and complications associated with the use of clozapine. While pre-marketing data (as cited in the package insert)[1] did suggest that clozapine had a relatively high incidence of serious adverse effects, post-marketing surveillance by the Clozaril Patient Monitoring Service (CPMS) does not confirm this. It would be unfortunate if your readers were left with the impression that the use of clozapine were more difficult or dangerous than it truly is.

Young describes the risk of agranulocytosis as 1%, with a death rate of 0.05%. Based on data collected by the CPMS on 99,502 patients to the end of 1994, a more up-to-date figure would be 0.38%, with a total of 12 agranulocytosis-related deaths (or 0.01%) in the United States[2]; this compares favorably to the agranulocytosis rates of up to 0.7% which have been observed with phenothiazines[3] and, given the required weekly hematological monitoring, may well result in a *lower* death rate from blood dyscrasias than is seen with typical neuroleptics.

The risk of clozapine-associated seizures also appears now to be significantly less than suggested by the Stage III studies. Again, post-marketing surveillance via the CPMS suggests a seizure rate of 1.3% in the United States;[4] of these patients, half were concurrently receiving medications known to lower the seizure threshold and a third had a prior history of seizures. Only 0.4% of patients had recurrent seizures—the others were isolated single events during initial dose titration—and three-quarters of those patients were able to continue taking clozapine with the addition of an anti-convulsant. In addition, seizure rates appear to be considerably lower in Europe, with only one seizure reported in 765 patients treated by the Munich group,[5,6] and similar data from other centers;[7,8] this may reflect the lower (but seemingly equally efficacious) dosages of clozapine used there.[8,9] These figures again compare favorably with the 0.5-1% incidence of seizures associated with typical neuroleptics.[10]

While we agree that respiratory arrest is an extremely rare, but recognized, adverse effect associated with clozapine use, we would disagree with the recommendation that "patients should not be on benzodiazepines when starting clozapine." It is certainly true that this combination can cause extreme sedation (to the point of obtundation), particularly in the early stages of clozapine dose titration.[11] However, of the six reported cases of respiratory arrest associated with the combination, four patients were on extremely high doses of oral benzodiazepines (up to 32 mg/day lorazepam equivalents) and were started on considerably higher doses of clozapine than recommended by the manufacturer,[12] while the other cases[13,14] reported patients on long-standing clozapine therapy who were administered *intravenous* benzodiazepines, a route which is well-recognized as producing an idiosyncratic, non-dose-dependent respiratory arrest in susceptible persons.[15] Although the manufacturer's data sheet[1] urges caution in the concomitant prescription of clozapine and benzodiazepines, this regimen is not contra-indicated.

The use of clozapine does require special precautions and increased vigilance, but it would be unfortunate if patients suffering from a painful, terrifying and devastating disease were

denied a safe, cost-effective, well-tolerated and uniquely efficacious treatment because of excessive concern about possible adverse effects on the part of psychiatrists.

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