Clozapine: Benefits and Risks

To the Editor:

The National Institute of Mental Health and Dr. David Shore are to be thanked and congratulated for the very complete and informative issue of the Schizophrenia Bulletin entitled "Special Report: Schizophrenia 1993."

Somehow the dangers of clozapine have been grossly exaggerated. Let us look at the facts. There are now over 60,000 patients being treated with clozapine in the United States. There have been seven deaths that arguably were due to agranulocytosis resulting from clozapine treatment. However, all of these deaths occurred in 1990 and 1991. There were no deaths in 1992 and so far there have been none in 1993. This is because of our greater experience with the medicine and the application of new drugs that cut the white blood cell count recovery time in half.

Also forgotten in evaluating the risks of clozapine is the known suicide rate of 10 percent for schizophrenia patients treated with standard neuroleptics. There have been no known suicides among those being treated with clozapine.

It might be rewarding to publish an entire issue of the Schizophrenia Bulletin examining the experiences of doctors, patients, and families in the use of clozapine and completely upgrading the statistics on its efficiency and risk. Such an issue might include some material from around the world on clozapine use; for example, the Chinese experience with making clozapine the medicine of choice in treating schizophrenia would be of great interest.

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Response to Fuchs

In his letter to the editor, Fuchs (1994, this issue) suggests that the dangers of clozapine are grossly exaggerated. We would agree with Mr. Fuchs that the current utilization levels of clozapine suggest that it is being markedly underutilized. Specifically, 60,000 patients have been exposed to the drug and 44,000 patients are currently receiving it (personal communication, Heidi Sykes-Gomez, Sandoz Pharmaceuticals, July 27, 1993); this number represents approximately 4 percent of patients with schizophrenia. Our experience, as well as estimates from the literature, regarding the prevalence of treatment-refractory or treatment-intolerant schizophrenia suggest that a trial of clozapine may be indicated in as many as 20 percent of the patients suffering from this illness. Clearly, utilization levels are far lower than one would expect.

We would not necessarily conclude, however, that the risks have been exaggerated. We now have a more precise estimate of the incidence of agranulocytosis (Alvir et al. 1993): 0.8 percent at 1 year, based on the first 11,555 patients treated in the United States between February 1990 and April 1991. Mr. Fuchs states that seven deaths have been attributed to clozapine-induced agranulocytosis, but that no deaths have occurred in 1992 or 1993. In fact, one of the seven deaths did occur in March 1992 and an eighth death occurred in July 1993 (personal communication, Heidi Sykes-Gomez, Sandoz Pharmaceuticals, July 27, 1993). Whether the risk of fatality has actually declined in recent years remains to be seen, since statistical analysis of the incidence of rare
events is difficult. However, it certainly does appear that strict weekly monitoring decreases the risk of fatality. Mr. Fuchs suggests that “our greater experience with the medicine and the application of new drugs that cut the white blood cell count recovery time in half” (p. 23) account for the apparent decline in mortality to which he refers. In reality, although the use of granulocyte colony-stimulating factor has become more widespread in the management of clozapine-induced agranulocytosis, there is no evidence as yet that this practice has reduced the actual morbidity or mortality associated with this condition.

Mr. Fuchs also alludes to the “known suicide rate of 10 percent for schizophrenia patients treated with standard neuroleptics” (p. 23). The estimates of suicide among schizophrenia patients range from 5 to 10 percent. In many of the reports providing such data, it is not clear to what extent patients were maintained on antipsychotic medications. It may be that clozapine is associated with a reduced risk of suicide; 15 definite suicides and 3 questionable cases have been reported to Sandoz as of December 31, 1992, of more than 43,000 patients exposed to clozapine during this time (personal communication, Felix Arellano, M.D., Sandoz Pharmaceuticals, July 27, 1993).

The extent to which clozapine might reduce the risk of suicide is an important question that requires further study, including assessment of the role that selection criteria (more extensive monitoring, higher rates of medication compliance, etc.) might play in any apparent effect.

In our view, the underutilization of clozapine is probably determined by multiple factors. In some health care systems cost may be a major factor. In other settings, anxiety about adverse effects, particularly agranulocytosis, may play a role. However, in our view, many mental health professionals have not been adequately convinced that clozapine does offer the possibility of real improvement to their persistently psychotic, treatment-refractory patients. In our view, the potential superior benefits have been clearly established, and we hope that more physicians will provide the opportunity for improvement to their patients. At the same time, the potential risks need to be clearly understood and appropriate safeguards maintained.

References


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