To submit questions for this regular feature, please send them to the Journal of Psychiatry & Neuroscience / Revue de psychiatrie & de neuroscience, *Canadian Medical Association, 1867 Alta Vista Dr., Ottawa ON K1G 3Y6, Canada; fax 613 729-9545; jpn.office@sympatico.ca Please include details of any relevant case and your name, address, telephone and fax numbers as well as your email address.*

Is there a way to overcome oversedation in a patient being treated with clozapine?

The pharmacologic management of schizophrenia has changed over the past decade through the introduction of new medications with generally fewer side effects than the older antipsychotics. Unfortunately, some patients do not respond to the second-generation antipsychotics. In this situation, a trial of clozapine may be undertaken. However, although schizophrenic symptoms may be alleviated, the patients often continue to suffer psychologically and socially because of the side effects of clozapine. One of these so-called "nuisance" side effects is sedation, and one result of oversedation is an inability to participate in rehabilitation programs aimed at improving social skills, social integration and interpersonal relationships.

Coincidentally, there has been an increase in our understanding of the role of cytochrome P450 (CYP) enzymes in the mechanisms of the side effects related to concomitant use of medications. For example, an increase in the serum concentration of clozapine is a well-known result of concomitant use of fluvoxamine. This effect is believed to result from inhibition of the activity of CYP1A2 by fluvoxamine and can lead to concentration-dependent clozapine-related side effects such as sedation, orthostatic hypotension and seizures.

Although interactions between medications at the level of the CYPs are viewed primarily in the context of negative treatment outcomes, it may be possible to exploit such interactions for the benefit of patients. Two recent reports have described such potential benefits, observed in clinical studies of low doses of clozapine and fluvoxamine.

Lammers et al (*Pharmacopsychiatry* 1999;32:76-7) reported an open clinical trial in which 18 patients were treated with fluvoxamine (50 mg) and a titrating dose of clozapine. The patients required relatively low doses of clozapine (mean 96.9 [standard deviation, SD, 37.2] mg), but therapeutic serum levels of the drug were still achieved. The patients experienced clinically significant reductions in the symptoms of their illness while avoiding the sedative side effects associated with the usual doses of clozapine.

In a similar study, Lu et al (*J Clin Psychiatry* 2000;61:594-9) gave clozapine (100 mg daily) to 18 patients with treatment-resistant schizophrenia. After 14 days, treatment with fluvoxamine (50 mg daily) was initiated. The authors reported a significant increase in serum clozapine levels (to a mean of 432.4 [SD 190.9] ng/mL) after initiation of fluvoxamine, which coincided with clinical relief in two-thirds of the patients. Again, the patients did not suffer significant side effects.

Both of these studies were short and involved a limited number of patients. Nonetheless, the results indicate that it may be possible to achieve therapeutic serum levels of clozapine with corresponding improvements in clinical symptoms with lower doses of the drug. Interestingly, no increase in side effects was reported, and the side effects that did occur were described as minor. The study samples did not involve people known to suffer from clozapine-induced sedation, and it may be that such patients would still experience excess sedation if this approach were used. Use of combination therapy should be considered only after standard manipulations such as reducing the clozapine dose have been attempted. Careful monitoring is important; such monitoring should include serum levels of clozapine so as to avoid elevated concentrations that might lead to serious complications.

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The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided.