Adjunctive Medication Effects May Increase Risk for Neutropenia

TO THE EDITOR: In the July 2008 issue of the *Journal*, the Clinical Case Conference by Sharmin Ghaznavi, M.D., Ph.D., et al. (1) provided a good example of a treatment plan and discussed three major clozapine-related issues pertaining to 1) the risk of neutropenia/agranulocytosis and seizures, 2) drug-drug interaction, and 3) the use of anticonvulsants in the prophylaxis of seizures.

For many years, the authors' patient was treated with clozapine, 750–800 mg/day, and valproic acid, 1500 mg/day, was added later. During these regimens, the patient's white blood cell and neutrophil counts remained normal. At some stage, donepezil was added, and the patient, for the first time, presented with decreased white blood cell and neutrophil counts. In addition, the patient showed a marked decrease in his white blood cell and neutrophil counts when clozapine, 500 mg/day, was added to a regimen of valproic acid, 1500 mg/day, and risperidone, 6 mg/day. Before the addition of clozapine and following the discontinuation of the drug, the patient's white blood cell and neutrophil counts were normal.

Dr. Ghaznavi et al. concluded that the occurrence of neutropenia/agranulocytosis in both instances was not actually clozapine-induced. However, we feel that an alternative interpretation is more likely. In the first instance, the development of neutropenia/agranulocytosis is difficult to explain completely. Donepezil, as acknowledged by the authors, has not been shown to cause neutropenia. In addition, the drug does not activate/inhibit enzymes that influence clozapine or valproic acid metabolism (1A2, 2D6, 3A4). Assuming that the patient did not alter his smoking habit or did not take any other drug that may increase clozapine levels, it is possible that valproic acid may have increased clozapine concentration, which has been reported previously (2). In the second instance, before and after clozapine treatment, the patient's white blood cell and neutrophil counts were normal. It is unlikely that risperidone was the primary offender as suggested by the authors. However, risperidone could be a second-degree offender, since it significantly increases clozapine plasma concentration (3) and, hence, increases the risk of neutropenia/agranulocytosis. The patient had a relatively high clozapine plasma concentration level (520 ng/ml) while taking clozapine, 325 mg/day, and lithium, 300 mg/day, alone. Since lithium does not influence clozapine pharmacokinetics, it is reasonable to suggest that when the patient was taking the combination of clozapine, 500 mg/day, and risperidone, 6 mg/day, clozapine plasma concentration reached toxic levels and caused neutropenia/agranulocytosis and the adjunctive therapies did not have a direct effect on hematopoiesis.

In conclusion, we agree that the use of anticonvulsants for the treatment of seizures among patients taking clozapine is a secondary prophylaxis. However, lamotrigine should be avoided because it causes a threefold increase in clozapine blood concentration (4, 5) and, hence, the risk of toxic effects.

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Drs. Ghaznavi and Bhagwagar Reply

TO THE EDITOR: We thank Dr. Caetano for expressing interest in our article. To summarize, we reported on a patient who was treated with clozapine, 750 mg/day, and valproic acid, 1500 mg/day, for several years without incident. The first episode of clozapine-induced neutropenia occurred 1 month following the addition of donepezil to our patient's treatment regimen. Dr. Caetano raises two related points regarding this initial episode of neutropenia. First, donepezil does not activate/inhibit enzymes that influence clozapine or valproic acid (1A2, 2D6, 3A4). Second, it is possible that valproic acid was responsible for increased clozapine concentration, leading to neutropenia. We agree that valproic acid can lead to increased concentrations of clozapine (1), which we noted in our article. In fact, we raised the possibility that the combination of clozapine and valproic acid *may* confer a greater risk of later onset neutropenia in some patients. However, the fact that our patient was treated for years with the combination of clozapine and valproic acid without incident suggests that we cannot dismiss the setting in which our patient developed neutropenia, namely the addition of donepezil. To further address this point as well as the comment by Dr. Caetano pertaining to donepezil's effect on the P450 isoenzymes 2D6 and 3A4, donepezil, to the best of our knowledge, is metabolized by the isoenzymes 2D6 and 3A4 (2), which are also responsible for the metabolism of clozapine. Thus, it is possible that donepezil may have led to increased serum levels of clozapine and placed our patient at greater risk for developing neutropenia.

At the time of the second clozapine rechallenge, our patient was being treated with risperidone, and clozapine was added to the regimen. Given that risperidone is known to increase serum levels of clozapine (3), we concluded that the combination of clozapine and risperidone may have been responsible for neutropenia in our patient on that occasion. Thus, although we cite that risperidone alone carries a risk for neutropenia (4), we do not feel that the drug was the primary offender and agree with Dr. Caetano that risperidone likely increased clozapine serum levels that led to neutrope-

nia in our patient, and we appreciate the opportunity to clarify this point.

Finally, Dr. Caetano suggests that lamotrigine should be avoided because it increases clozapine serum concentration. Indeed, there has been a case report of a threefold increase in serum concentration with the addition of lamotrigine (5). However, Wong and Delva (6), in their review of treatment for clozapine-induced seizures, recommended lamotrigine for its relative lack of effect on serum clozapine levels. We would therefore advise caution when prescribing lamotrigine as a secondary prophylaxis for clozapine-induced seizures rather than avoiding one of two (gabapentin) agents that are effective for clozapine-induced seizures and which demonstrate a relative lack of interactions with clozapine compared with valproic acid (6).

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Delusional Parasitosis Facilitated by Web-Based Dissemination

TO THE EDITOR: Many scholars have anticipated and foreseen the positive effect of the Internet on medicine. Pallen (1) noted that "[the] Internet promises to bring enormous future benefits to medicine….Perhaps more importantly, the Internet culture will infect and transform the culture of medicine." However, one potential negative consequence is the dissemination of information with minimal or no supporting evidence that is incorrectly portrayed as factual. We report the case of an individual who experienced delusional ideation via the Internet.

"Mr. M" was a 57-year-old Caucasian man who presented at a detoxification center for crack cocaine dependence and schizophrenia marked by persistent auditory hallucinations and paranoid delusions. On assessment, the patient had patches of erythematous skin in his nose and on his right ear, forehead, and right leg. These erythematous patches had been present for 3 to 4 years. A dermatologist had diagnosed the lesions as a delusion of parasitosis. The patient strongly disagreed with this diagnosis and felt that the lesions were caused by a parasite. He stated that he had obtained information regarding his condition from the Internet and that the condition was called Morgellons. Our clinical team searched the Internet and found results under "Morgellons."

In 2002, the Morgellons Research Foundation was founded as a personal initiative by a family who claimed that their 2-year-old son had a dermatological condition that many physicians were unable to diagnose. The Morgellons Research Foundation named the unknown condition "Morgellons disease" and launched a concerted effort to achieve recognition of "Morgellons" as a dermatological entity of infectious cause, creating a website complete with written descriptions and images of skin as well as microscopy images. Over the course of the years, thousands of people have visited the Morgellons Research Foundation website, and mass media coverage has amplified its diffusion (2). Today, the website claims that more than 12,000 families affected by Morgellons are registered with the foundation, and self-accounts of affected individuals are overflowing (3). Furthermore, the foundation—through its website—has lobbied the Center for Disease Control to fund an epidemiological study of the condition, which is an unprecedented endeavor (4). The foundation's efforts and claims are in contrast to the most common clinical perception of the illness, since current medical opinion considers the phenomenon to be delusional parasitosis (2).

Aside from exemplifying that the Internet can be a misleading source of information, the situation we described demonstrates the challenge that some online communities represent to traditional diagnostic criteria, i.e., that a belief is not considered delusional if it is accepted by other members of an individual's culture or subculture. Although this may be appropriate in the context of spiritual or religious beliefs, the scenario in which a widely held belief is accepted as plausible simply because many people ascribe to it requires a revised conceptualization in our current era. That is, Internet technology may facilitate the dissemination of bizarre beliefs on a much wider scale than ever before. In the case of Morgellons, the potential facilitation of factitious cases creates yet another troubling concern. An awareness of the capacity of the Internet to make possible and spread shared delusional ideation is essential to current practice.

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