Increasing Psychosis in a Patient Switched From Clozaril to Generic Clozapine

To the Editor: Since Clozaril's patent expired in 1998, three generic products have entered the market (Zenith Goldline Pharmaceuticals, Geneva Pharmaceuticals, and Mylan Pharmaceuticals). These products have been deemed by the U.S. Food and Drug Administration (FDA) as therapeutically equivalent to the branded product. However, bioequivalency was based on pharmacokinetic studies utilizing a significantly subtherapeutic clozapine dose of 12.5 mg/day in healthy male volunteers (1). In the few studies performed in the target population, clinical differences between products have been detected.

Mr. A was a 79-year-old man with a history of paranoid schizophrenia who was treated as an outpatient with Clozaril (Novartis Pharmaceuticals), 200 mg in the morning and 300 mg at bedtime. Mr. A's psychosis had been stable with this dose for more than 4 years. During one visit, Clozaril was switched inadvertently to generic clozapine (Mylan Pharmaceuticals). One month later, Mr. A was admitted to the hospital with increasing paranoid delusions of being poisoned as well as failure to thrive after refusing to take anything by mouth for several days. Other causes for his altered mental status were ruled out, and it was concluded that Mr. A's symptoms were due to an exacerbation of his schizophrenia. Mr. A was discharged 3 days later with the same dose of generic clozapine. He was readmitted the following month for similar symptoms and hospitalized for 10 days. During this admission, Mr. A was switched back to name-brand Clozaril. Two months after his, his psychosis was stable without a need for further intervention.

A pharmacokinetic study comparing the Zenith Goldline Pharmaceuticals product and Clozaril in schizophrenic patients found a significant difference between the mean log-transformed $C_{max,ss}$ and that the 90% confidence interval ratio for the $C_{max,ss}$ of the two products fell outside the FDA's established range for bioequivalence (2). In a randomized crossover study of 45 schizophrenic patients, mean Brief Psychiatric Rating Scale and Clinical Global Impression scores were significantly improved with Clozaril compared to the Zenith Goldline Pharmaceuticals generic (3). Five patients in this study experienced a relapse after switching from Clozaril to a generic, but there were no instances when the switching was in the opposite direction. Several cases of exacerbation of psychosis have been reported with the Zenith Goldline Pharmaceuticals product (3, 4), but this is the first report of worsening psychosis with the Mylan Pharmaceuticals brand, to our knowledge. This case demonstrates the need for careful consideration before switching to a generic product in fragile patients stabilized with Clozaril.

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Classification of Somatoform Disorders

To the Editor: Richard Mayou, M.A., M.Sc., M.Phil., F.R.C.P., F.R.C.Psych., and others (1) presented a comprehensive description of the problems of the classification of somatoform disorders according to DSM-V. Their main suggestion was to abolish the classification of patients with unexplained physical symptoms as a psychiatric disorder and to include a new axis III category for patients with "functional somatic symptoms and syndromes." We argue that improving rather than abolishing the classification would be the preferred route for DSM-V and ICD-11. Expectations that anything would improve if the category of somatoform disorders is abolished are unwarranted. Our major comments are the following:

1. Patients with these complaints represent one of the major groups of patients with abnormal health care use, increased sick leave days, and early retirement. Therefore, a clear diagnosis is needed.
2. Former diagnoses (e.g., hysteria, neurasthenia, functional syndromes, and psychosomatic complaints) were stigmatizing, unreliable, and rarely used even in psychiatry. The category of somatoform disorders improved the description of syndromes and the reliability of classification and was the basis of an overwhelming development in psychiatry.
3. We do not need more axis III categories (as suggested by Dr. Mayou et al.) but fewer. ICD-10 already includes a long list of syndromes describing patients with unclear somatic complaints (e.g., dyspepsia, functional stomach disorder, irritable bowel syndrome, different headache types, back pain). There is strong evidence that these diagnoses frequently describe the same patient with multiple somatic complaints (2). One of the benefits of DSM-III was to offer *one* diagnosis for patients with multiple functional symptoms affecting multiple body sites.
4. The missing acceptance of the diagnosis of somatoform disorders is not a question of the term. Patients' acceptance of the diagnosis depends on the explanation of the term provided by their doctors. Doctors' acceptance of the category was not improved by any of the psychiatric or axis III diagnoses offered for patients with functional somatic complaints in the past. Doctors' acceptance of the category will improve with increased knowledge and guidelines of how to explain the diagnosis and how to manage these patients.
5. Most research and treatment suggestions of somatoform disorders came from mental health specialists. We should not risk stopping these activities by abolishing a DSM category. As we mentioned, there is no reason to hope that