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Adding and Switching Antipsychotics

To the Editor: The article by Kreyenbuhl and colleagues (1) in the July issue illustrates an important topic in the treatment of patients with schizophrenia, because we know that 10% to 30% of our patients do not respond to standard treatment. The literature on the efficacy of clozapine for these patients is abundant. Therefore, the results of this study—that neither adding another antipsychotic nor switching to some other antipsychotic is an effective way of treating resistant schizophrenia—are hardly surprising. Moreover, Kreyenbuhl and colleagues did not follow the patients for whom the antipsychotic was stopped. Perhaps these patients did as well as those whose medication was switched. Moreover, it is shocking that only one patient for whom a medication was added (1%) and only 11 (8%) whose medication was switched received clozapine.

Unfortunately, data on the adherence of the patients were also not reported. The Clinical Antipsychotic

Trials in Intervention Effectiveness study (2) showed that approximately 25% to 30% of patients did not remain on their medication (2). Even for patients who persist in the use of medication, at least 20% do not take the medication as prescribed (3). Lack of adherence may reflect lack of efficacy (4).

In Kreyenbuhl and colleagues' study 14% of the patients for whom a medication was added and 10% of those patients whose medication was switched used a long-acting injection. It is our clinical impression that especially in this group, in which the adherence question does not arise, adding clozapine has a substantial beneficial effect. Currently, we ask all our patients whether they prefer oral medication or a long-acting injection (5).

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In Reply: Dr. Hovens and Dr. Loonen raise several important points regarding the methods and results of our study of adding or switching antipsychotic medications for treatment-resistant positive psychotic symptoms. As they correctly note, the design of our study did not permit us to follow patients for whom antipsychotic treatment was discontinued. We specifically asked psychiatrists to report on the response to a medication change (defined as either a switch to or an addition of another medication, and not a change in dosage) of one of their patients who was exhibiting treatment-refractory psychotic symptoms. Although we cannot know for certain, it is unlikely that discontinuing antipsychotic treatment would have led to clinical outcomes similar to those observed in the chronically ill, treatment-resistant sample of patients who switched antipsychotic medications in our study, as suggested by Hovens and Loonen. A clinical trial of antipsychotic discontinuation may be warranted in a limited number of cases—for example, after sustained symptom remission following a single psychotic episode. However, clinical experience suggests and guidelines for the treatment of schizophrenia (1) recommend continuous antipsychotic therapy to prevent symptom relapse among persons who have experienced multiple episodes of psychotic symptoms.

Hovens and Loonen correctly point out that we did not query psychiatrists in detail about the extent to which their patients adhered to the change in antipsychotic treatment. Because more complicated treatment regimens, such as antipsychotic polypharmacy, have been shown to increase the likelihood of medication nonadherence (2), it is possible, as suggested by Hovens and Loonen, that the lack of effectiveness of antipsychotic polypharmacy reported by psychiatrists in our study may have been a result of patients' nonadherence to the treatment rather than to its inherent lack of efficacy. However, several randomized con-

trolled trials of antipsychotic combinations have not produced favorable results (3). Second, although we did not report it in our paper, 28% of psychiatrists in the study who added an antipsychotic and 34% who switched agents agreed that patients' refusal to accept optimal medication management was a barrier to effective treatment. As such, medication nonadherence may have been a complicating factor in both groups of patients, and as suggested by Hovens and Loonen, improving the therapeutic alliance by asking patients about their treatment preferences is one possible strategy for providers to enhance patients' acceptance of evidence-based treatments and improve outcomes.

With respect to evidence-based treatments, we echo the sentiment of Hovens and Loonen regarding the exceedingly low use of clozapine in the sample of treatment-resistant patients in our study. Despite strong evidence for its efficacy, clozapine remains underused in the United States, probably because of administrative barriers (4) and concerns about agranulocytosis and other admittedly troublesome potential metabolic side effects (5). However, serious discussion is warranted among clinicians, researchers, and patients affected by medication management decisions to determine whether these concerns about clozapine justify the use of treatment strategies, such as antipsychotic polypharmacy, with little evidence of efficacy and demonstrated safety concerns of their own.

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Seeking Safety Protocol for Men and Women

To the Editor: The report by Weaver and colleagues (1) in the July issue on the use of the manualized treatment protocol, Seeking Safety, with men is excellent. It is a wonderful example of a thoughtful analysis blended with a solid empirical evaluation. However, one correction should be noted: the published manual (2) was actually designed for both genders. Although the first empirical paper on the model, published in 1998 (3), focused on its development for women, in subsequent years the draft manual was rewritten, and the final published version was designed for both genders. Also, two studies describing its successful use with men have been published (4,5).

Both men and women are subject

to the tragic combination of posttraumatic stress disorder and substance abuse. The work of Weaver and colleagues and others is important because it offers empirical support to help guide treatment. It is also helpful in correcting the misperception that the model is for women only.

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