

longer treatment period). Therefore, the assumption that the increase in adverse events and hospital time is associated with combination strategies may be incorrect and rather be a function of a different and more severe subtype of the illness in which patients are administered higher doses and multiple agents. For example, it has been suggested that tardive dyskinesia vulnerability may be a constitutional feature of a more severe schizophrenia phenotype that requires typical antipsychotic drug exposure for its expression and also includes poorer therapeutic response and greater severity of negative symptoms (2). Since these patients do not respond as well to single medications, they are administered polypharmacy schedules of medications with more side effects as a result and poorer response based on subtype of illness but not necessarily as a reflection of multiple antipsychotic medication use. While the authors do briefly address the option of treatment resistance as a limitation, it is not emphasized enough, and this point may in fact be an obvious fatal flaw of the study. Furthermore, the comparison of the two study subgroups as analyzed by the authors appears incorrect. It clearly seems that the patients who were treated and who quickly improved with monotherapy only were in a less severe state compared to the patients treated with polypharmacy, a treatment modality used as "the last resort" in overcoming treatment resistance. In order to determine whether polypharmacy is "good" or "bad," studies are required to compare similar populations of schizophrenic patients. One option, for example, would be to divide treatment-resistant patients into two groups—one treated with monotherapy and the second with polypharmacotherapy.

#### References

1. Lerner V, Libov I, Kotler M, Strous RD: Combination of "atypical" antipsychotic medication in the management of treatment-resistant schizophrenia and schizoaffective disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2004; 28:89–98
2. Chakos MH, Alvir JM, Woerner MG, Koren A, Geisler S, Mayerhoff D, Sobel S, Kane JM, Borenstein M, Lieberman JA: Incidence and correlates of tardive dyskinesia in first episode of schizophrenia. *Arch Gen Psychiatry* 1996; 53:313–319

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TO THE EDITOR: In discussing the methodological limitations of their important assessment of the risks and benefits of antipsychotic polypharmacy, Dr. Centorrino et al. did not include the potential shortcomings of one of their primary outcome measures, the Positive and Negative Syndrome Scale scores extracted from medical records. We are aware of no work establishing the validity and reliability of a retrospective Positive and Negative Syndrome Scale instrument and wonder if scoring patients without interviews may have underestimated the differences among subjects and biased results toward the authors' findings of no baseline or outcome differences between monotherapy and polytherapy groups. In particular, negative items like poor rapport, difficulty in ab-

stract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking may be difficult to rate reliably from routine inpatient clinical charts on the Positive and Negative Syndrome Scale's seven-point scale. Absent more specific prospective measures, inclusion of prospective Global Assessment of Functioning (GAF) scale scores likely to be available in charts along with raters' retrospective GAF scale scores might be of value in assessing the clinical characteristics and outcomes of psychotic patients treated with antipsychotic monotherapy or polytherapy.

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#### Dr. Centorrino and Colleagues Reply

TO THE EDITOR: We appreciate the response of Dr. Citrome et al. and agree with their points on the use of antipsychotic polytherapy. Polytherapy may, in fact, be a result of shortened length of inpatient hospitalization and the subsequent perceived need to treat patient symptoms more aggressively. It is also possible that the patients discharged receiving polytherapy may be a subset of more refractory patients; however, we were not able to gather such information from this specific study. We recognize the limitations of a retrospective study. The brief period over which the patient information was recorded leaves room for interpretation as to whether the rate of polytherapy was due, at least in part, to cross-titration or was rather a deliberate long-term plan. There is no doubt that more randomized, double-blind studies are needed to ascertain the clinical benefits of antipsychotic polytherapy.

The points addressed by Drs. Strous and Lerner are valid and warrant further investigation. Combination antipsychotic therapy may be used more frequently in patients who have failed to respond to monotherapy. Failure to respond to monotherapy treatment and the need to treat nonresponsive patients more aggressively, therefore, may result in a longer length of stay and an increased incidence of adverse events. Because of the retrospective nature of this study and the limited period of time over which patient information was gathered, it was not possible to separate the cohort by level of treatment responsiveness. However, patients in the monotherapy and polytherapy groups were matched by diagnosis and severity of illness (as assessed by the Clinical Global Impression scale and the GAF scale) in order to make more accurate comparisons. A prospective study in which monotherapy and polytherapy are compared in a group of patients who are more homogenous in terms of level of responsiveness to antipsychotic medications would be a worthy and valuable endeavor.

We agree with Dr. Case and his associates that there are inherent limitations in the retrospective rating of symptoms in a review of inpatient medical records and, more specifically, that there are items in the Positive and Negative Syndrome Scale that are more difficult than others to score retrospectively. However, since all items of the Positive and Negative Syndrome Scale were scored in the same manner for both the