Risks of Intermittent Antipsychotic Treatment in Schizophrenia

To the Editor: We read with great interest an important contribution by Gaebel et al[1] in which they compared antipsychotic maintenance treatment with discontinuation and intermittent treatment in first-episode schizophrenia. We note several caveats in interpreting their crucial findings for well-balanced decision-making.

The authors found that about half of patients in the intermittent treatment group remained stable (as is partly reflected by the data from 8 completers in Table 3 of the article) and concluded that alternative long-term strategies including intermittent treatment should be provided in individual cases. However, the magnitude of worsening in the rest of the patients needs to be contemplated in light of the cost of stability in some others, to allow for a neutral risk/benefit consideration. Table 2 in the article shows that at the end of the second year, the mean Positive and Negative Syndrome Scale (PANSS) total score had increased by 12.3 points and the mean Global Assessment of Functioning (GAF) score had decreased by 9.9 points in the intermittent treatment group. Also, the standard deviations of scores at endpoint (compared with baseline) were consistently larger, indicating a wider score distribution, which would translate into a suggestion that some patients became even substantially worse. How such a magnitude of deterioration compares with some more reduction in adverse effects and increase in the Subjective Well-Being Under Neuroleptics scale score remains a question. In addition to symptomatic perspectives, we believe that a 10-point change in global functioning represents a clinically pertinent one.[2]

Patients in this study were fairly well controlled at baseline: their mean PANSS total score was less than 40, with good functioning as represented by a mean GAF score in the 70s. In this context, irreversibility of worsening in the intermittent treatment group is a concern. However, 8 patients did not improve enough upon restarting antipsychotics (even at the higher dosages shown in Table 5) and had to be dropped from the study. Although the mean time from restart to dropout of 8 ± 16.5 days was too short to draw any conclusions, irreversibility of worsening may result in a higher antipsychotic maintenance dose, which has been found to be correlated with the number of relapses and total duration of psychotic episodes.[3] Higher antipsychotic doses in the end might actually result in higher cumulative dosage in the long run in these worsened patients (in comparison with a simple continuation whereby deterioration could have been avoided considering a 0% relapse rate in the maintenance treatment group).

The authors also plausibly acknowledged that some patients insisted on discontinuing drug treatment (sooner or later), a typical clinical situation that poses a challenge to clinicians. We think that their findings add nicely to the well-known importance of continuous adherence to antipsychotics and provide a sound basis for psychoeducation to clients. The results indeed do not rule out a possibility of discontinuation of antipsychotics and intermittent treatment in *some* patients (on an individual basis), but they overall argue against such an approach. This is because the rates of clinical worsening (including hospitalization) and premature attrition were far superior in the maintenance treatment group. In fact, a treatment recommendation[4] indicates that intermittent treatment (or a targeted strategy) should not be used routinely. Finally, this critical study still leaves a possibility that first-episode patients once stabilized may be treated with even lower antipsychotic doses (rather than discontinued from antipsychotic treatment completely).

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Takefumi Suzuki, MD, PhD
takefumi@oak.dti.ne.jp
Kensuke Nomura, MD
Koichiro Watanabe, MD, PhD

Author affiliations: Department of Neuropsychiatry, School of Medicine, Keio University, Tokyo, Japan.

Potential conflicts of interest: Within the last 5 years, **Dr Suzuki** has received grants from the Mochida Memorial Foundation, Kanae Foundation, Japanese Society of Clinical Neuropsychopharmacology, and Government of Canada Post-Doctoral Research Fellowships. **Dr Nomura** has received honoraria from Eli Lilly, Janssen, and Meiji. **Dr Watanabe** has received grants or consultant fees from Dainippon Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, and Pfizer and speakers honoraria from Astellas, Dainippon Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, Meiji, Otsuka, Pfizer, and Yoshitomiyakuhin. ***Funding/support:*** None reported.
doi:10.4088/JCP.10lr06452yel