Dr Gaebel and Mr Riesbeck Reply

To the Editor: We very much appreciate that the results of the second treatment year of the first-episode study[1] as part of the German Research Network on Schizophrenia[2] have elicited a discussion regarding the optimal long-term treatment strategy after a first episode in schizophrenia.

Suzuki et al summarize "several caveats" regarding our (secondary) conclusion that—besides maintenance treatment—alternative long-term strategies (including intermittent treatment) should be provided in individual cases. In our study, rates of relapse and of deterioration according to different measures were significantly

(up to 10-fold) higher for intermittent treatment (up to 50% of patients) compared to maintenance treatment (up to 5% of patients), although we had hypothesized noninferiority of intermittent treatment (on the basis of post hoc analyses from a previous study[3]). Accordingly, our primary conclusion here as well as in the article is that "maintenance treatment is more effective than targeted intermittent treatment … and should be the preferred treatment option"[1] even in the second postacute year after a first episode of schizophrenia.

Nevertheless, we retain our secondary conclusion that alternatives to maintenance treatment (including intermittent treatment) are needed and should be subject to future research. The main reason for this is that nonadherence to maintenance treatment is a major problem in long-term treatment, relating to dysfunctional treatment attitudes in first-episode patients already present in the first postacute year,[4,5] and many patients refuse to maintain treatment for the second year.[1] Thus, there is considerable need for effective alternatives to standard maintenance treatment—for example, maintenance treatment at a (very) low dose as applied in our German Research Network on Schizophrenia study with quite low doses (about 2–3 mg/d in haloperidol equivalents), which has also been suggested by Suzuki et al. However, since about 50% of the patients receiving intermittent treatment remained stable (ie, had neither a relapse nor a clinically relevant deterioration), intermittent treatment still seems a viable treatment strategy for some patients.

Preliminary results of our ongoing data analyses on identifying eligible patients for intermittent treatment (manuscript in preparation) indicate that combined maintenance treatment and psychological interventions during the first year predict a more successful course of intermittent treatment, whereas patients with superior symptom response to maintenance treatment during the first year are at higher risk of relapse if switched to intermittent treatment. To better understand success or failure of intermittent treatment, however, the validity of our decision algorithm in terms of occurrence, timeliness, and clinical effect of "early" drug intervention needs to be analyzed in more detail. (Please note that, contrary to the incorrect Suzuki et al quotation, the drug treatment restart-phase under intermittent treatment lasted on average 16.5 ± 9.4 days.) Unfortunately, the limited sample size of our study prevents too far-reaching conclusions.

In conclusion, like Suzuki et al we strongly support "well-balanced decision-making," and, we would like to add, this should entail a shared process in which the patient (and if possible his/her family) has been well informed about the evidence base of long-term treatment strategies. At present and in accordance with most of the available treatment guidelines, the foremost recommendation is to maintain antipsychotic treatment at the lowest dose possible for at least 2 years. Nevertheless, effective alternatives (including administration of long-acting medication strategies[6]) should be provided in case of nonadherence, which is mainly due to dysfunctional drug attitudes, intolerability, or insufficient response to maintenance treatment.

Intermittent treatment with early drug intervention should not be recommended for the majority of patients, but seems to be beneficial for some patients. It will be still a task for future research (of both basic and clinical interest) to identify who these patients are and why this treatment strategy works for them and not for others.

REFERENCES

1. Gaebel W, Riesbeck M, Wölwer W, et al. Relapse prevention in first-episode schizophrenia—maintenance vs intermittent drug treatment with prodrome-based early intervention: results of a randomized controlled trial within the German Research Network on Schizophrenia [published online ahead of print June 29, 2010]. *J Clin Psychiatry*.
2. Wölwer W, Buchkremer G, Häfner H, et al. German Research Network on Schizophrenia: bridging the gap between research and care. *Eur Arch Psychiatry Clin Neurosci*. 2003;253(6):321–329.
3. Gaebel W, Jänner M, Frommann N, et al. First vs multiple episode schizophrenia: two-year outcome of intermittent and maintenance medication strategies. *Schizophr Res*. 2002;53(1-2):145–159.
4. Gaebel W, Riesbeck M, Wölwer W, et al; German Study Group on First-Episode Schizophrenia. Maintenance treatment with risperidone or low-dose haloperidol in first-episode schizophrenia: 1-year results of a randomized controlled trial within the German Research Network on Schizophrenia. *J Clin Psychiatry*. 2007;68(11):1763–1774.
5. Gaebel W, Riesbeck M, von Wilmsdorff M, et al; EUFEST Study Group. Drug attitude as predictor for effectiveness in first-episode schizophrenia: Results of an open randomized trial (EUFEST). *Eur Neuropsychopharmacol*. 2010;20(5):310–316.
6. Gaebel W, Schreiner A, Bergmans P, et al. Relapse prevention in schizophrenia and schizoaffective disorder with risperidone long-acting injectable vs quetiapine: results of a long-term, open-label, randomized clinical trial. *Neuropsychopharmacology*. 2010;35(12):2367–2377.

Wolfgang Gaebel, MD
wolfgang.gaebel@uni-duesseldorf.de
Mathias Riesbeck

Author affiliations: Department of Psychiatry and Psychotherapy, Heinrich-Heine-University, Düsseldorf, Germany.

Potential conflicts of interest: **Dr Gaebel** has received speakers honoraria and research grants from Astra Zeneca, Janssen-Cilag, Lilly Germany, and Servier (Germany) and is or was a member of the advisory boards of Janssen-Cilag, Lilly Germany, and Lundbeck Institute (Denmark). **Mr Riesbeck** reports no financial or other relationships relevant to the subject of this letter.
Funding/support: The study discussed in this letter was conducted within the framework of the German Research Network on Schizophrenia, funded by the German Federal Ministry for Education and Research BMBF (grants 01 GI 9932 and 01 GI 0232). Risperidone and haloperidol were provided by Janssen-Cilag, Germany. Lorazepam was provided by Wyeth-Pharma.
doi:10.4088/JCP.10lr06452ayel