Dr Chan and Colleagues Reply

To the Editor: We appreciate the comments made by Peritogiannis and Tsouli regarding our recently published article.[1] We agree that researchers should focus on studying the use of other second-generation antipsychotics (SGAs) to treat patients with SGA-induced tardive dyskinesia. This kind of study has both clinical and etiologic implications for tardive dyskinesia. However, 3 points should be considered before study implementation.

First, the incidences and prevalence rates of tardive dyskinesia induced by SGAs are much lower than the rates of tardive dyskinesia induced by first-generation antipsychotics (FGAs). Correll and Schenk's[2] systematic review reported annualized tardive dyskinesia incidences of 3.9% for SGAs and 5.5% for FGAs and prevalence rates of 13.1% for SGAs and 32.4% for FGAs. The annual incidence rates

of SGA-induced tardive dyskinesia were even lower in children than in adults.[2] Therefore, prolonged study periods and increased numbers of study sites are needed in order to recruit enough patients with tardive dyskinesia, especially if younger psychotic patients are the target study population.

Second, the ethical problems with continuing the original SGA as one of the study arms should be considered. If we want to prove whether other SGAs are effective in ameliorating SGA-induced tardive dyskinesia, the most methodologically sound study design is to perform a randomized, double-blind comparison study comparing one group treated with other SGAs and one group treated with the original SGAs. An open-label switching study or a clinical trial comparing 2 other SGAs without original SGAs as the reference group will introduce placebo effect or observational bias. However, the question of whether it is acceptable to continue to use the original SGAs that already induced tardive dyskinesia is a debatable ethical issue.

Finally, investigations of the etiologies or subtypes of neuroleptic-induced tardive dyskinesia should be conducted by testing the effects of specific agents on clinical features and the brain. Positron emission tomography findings of abnormalities of neurotransmitters and various receptors of neurons may help us divide subjects into different groups such as dopamine receptor hypersensitivity, γ-aminobutyric acid (GABA) deficiency, and excessive free radicals.[3] Then, we can use different approaches to various patient groups; for example, we can try the SGAs with fast dissociation from the dopamine D_2 receptor[4] (eg, quetiapine) or dopamine partial agonists[5] (eg, aripiprazole) in the group with dopamine receptor hypersensitivity and use GABA agonists[6] (eg, valproate) in the group with GABA deficiency. The advantage of this kind of study is that only a small sample size is needed due to more homogeneous populations and more direct investigation of the pathophysiologic mechanisms of tardive dyskinesia. Hence, the combination of brain imaging and clinical assessment is one of the future directions of this kind of study.

REFERENCES

1. Chan HY, Chiang SC, Chang CJ, et al. A randomized controlled trial of risperidone and olanzapine for schizophrenic patients with neuroleptic-induced tardive dyskinesia. *J Clin Psychiatry*. 2010;71(9):1226–1233.
2. Correll CU, Schenk EM. Tardive dyskinesia and new antipsychotics. *Curr Opin Psychiatry*. 2008;21(2):151–156.
3. Margolese HC, Chouinard G, Kolivakis TT, et al. Tardive dyskinesia in the era of typical and atypical antipsychotics, part 1: pathophysiology and mechanisms of induction. *Can J Psychiatry*. 2005;50(9):541–547.
4. Kapur S, Seeman P. Does fast dissociation from the dopamine D_2 receptor explain the action of atypical antipsychotics? a new hypothesis. *Am J Psychiatry*. 2001;158(3):360–369.
5. Tamminga CA. Partial dopamine agonists in the treatment of psychosis. *J Neural Transm*. 2002;109(3):411–420.
6. Soares K, Rathbone J, Deeks J. Gamma-aminobutyric acid agonists for neuroleptic-induced tardive dyskinesia. *Cochrane Database Syst Rev*. 2004;(4):CD000203.

Hung-Yu Chan, MD, PhD
jan30@seed.net.tw
Susan S.-F. Gau, MD, PhD
Ching-Jui Chang, MD

Author affiliations: Department of General Psychiatry, Taoyuan Mental Hospital, Taoyuan, and Department of Psychology, Chung Yuan Christian University, Chung-Li (Dr Chan); Department of General Psychiatry, National Taiwan University Hospital and College of Medicine, Taipei (all authors); Department of Psychiatry, Cathay General Hospital, Taipei, and School of Medicine, Fu Jen Catholic University, Hsin-Chuang (Dr Chang), Taiwan.

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