Dopamine supersensitivity psychosis as a pivotal factor in treatment-resistant schizophrenia

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\section{1. Introduction}

Although pharmacotherapy with antipsychotics has been a main strategy in treating schizophrenia, only 30–45\% of patients experience and adequate response to these drugs (Andreassen et al., 2005; Bertelsen et al., 2009). Patients who respond poorly to treatment with two or more antipsychotic drugs are diagnosed as treatment-resistant schizophrenia (TRS) (Kane et al., 1988; Brenner et al., 1990). Clozapine has been established as the only effective agent for treatment-resistant cases, but some patients poorly respond even to this drug (Chakos et al., 2001; Henna Neto and Elkins, 2007). These data suggest the existence of subtypes in TRS and the importance of clarifying these subtypes in developing strategies for the prevention and treatment of schizophrenia.

One possible type of TRS may be related to antipsychotic-induced dopamine supersensitivity psychosis (DSP), which was first reported by Chouinard et al. (1978) and was recently classified as iatrogenic supersensitivity psychosis (Iyo et al., 2013; Seeman and Seeman, 2013). DSP is considered to develop following increases in antipsychotic dosages accompanying with relapses in patients with schizophrenia, although we should also take account of natural deterioration as a feature of schizophrenia. They progressively may show severer positive symptoms and need higher doses of antipsychotics, reaching TRS. Possible clinical features of this psychosis co-existence of tardive dyskinesia (TD), relapse episodes immediately following treatment discontinuation (rebound psychosis) and/or developed tolerance to the drugs' antipsychotic effects despite continuous treatment (Chouinard, 1991; Moncrieff, 2006).

We recently proposed possible mechanisms underlying DSP and methods for the prevention and treatment of DSP on the basis of dopamine D2 receptor (DRD2) up-regulation (Iyo et al., 2013). In addition, antipsychotic-induced dopamine supersensitivity can be caused not only by an elevation in DRD2, but also by an increase in dopamine D2\textsuperscript{high} receptors, which are known to represent the functional high-affinity state of the DRD2 (Seeman et al., 2005). Briefly, patients with DSP have an up-regulation and increasing supersensitivity of brain DRD2 induced by long-term over-blockade by antipsychotics and need higher dosages of antipsychotics to suppress the excessive dopamine neurotransmission via the increased DRD2. Higher antipsychotic dosages may yield higher fluctuation in the antipsychotic levels in the body since the...
These criteria are according to the DSP research criteria proposed by Chouinard (1991) and are modified so as to be possible to apply easily to a retrospective chart review like the present study.

Table 1
Criteria for dopamine supersensitivity psychosis in the present study.

<table>
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<th>Criterion</th>
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<tr>
<td>(A) The patient must have a 3 month history of receiving antipsychotics</td>
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<td>(B) At least one of the following major criteria must be present at any time point during antipsychotic treatment:</td>
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<td>(1) Rebound psychosis episode:</td>
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<td>• reappearance of psychotic symptoms upon decrease or discontinuation of medication, within 6 weeks for oral medication, 3 months for i.m. depot medication;</td>
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<td>• reappeared psychotic symptoms include new schizophrenia symptom(s) for the patient.</td>
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<td>(2) Developed tolerance to antipsychotic effect:</td>
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<td>• greater frequency of relapse (acute psychotic exacerbation) during continuous treatment with neuroleptics;</td>
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<tr>
<td>• relapsed psychotic symptoms cannot successfully controlled by overall 20% or more dosage increase of antipsychotic(s).</td>
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</table>

*The episode(s) of (1) and (2) are required to be observed following clinically “stable” status.

(3) Tardive dyskinesia

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