

## LETTER TO THE EDITORS

### Neuroleptic-Induced Supersensitivity Psychosis, the "Hump Course," and Tardive Dyskinesia

#### Editors:

We read with interest the article by Weinberger and associates,<sup>1</sup> published in the May issue of your journal, and would like to make the following comments.

First, although the authors hypothesized that neuroleptic-induced supersensitivity psychosis would manifest itself as an exacerbation of psychosis followed by an improvement (a "hump"), the possible courses of tardive dyskinesia during withdrawal of neuroleptics suggest that the hypothesis of the "hump" represents only one possible course. Our studies on abrupt withdrawal of oral neuroleptics show that tardive dyskinesia may follow three courses: (1) reversible dyskinesia, which appears or worsens at withdrawal and then improves and disappears toward the 6th week of withdrawal, or some overt dyskinesias that might improve and disappear during withdrawal; (2) mixed dyskinesia (reversible plus irreversible), which worsens at withdrawal and then improves without complete disappearance; and (3) irreversible dyskinesia, which worsens upon withdrawal and remains unchanged. We propose that supersensitivity psychosis may follow any of these courses. Thus, all eight patients who relapsed upon withdrawal of neuroleptics in Weinberger and associates' study may have been manifesting supersensitivity psychosis. Since it may be difficult to distinguish supersensitivity relapse from relapse related to the illness, Weinberger and associates proposed that a relapse related to supersensitivity would follow a "hump" course. We suggest that a more sensitive way of distinguishing normal relapse from supersensitivity relapse is the response of symptoms to reinstitution of medication: the supersensitivity relapse responding quickly compared with slow improvement after illness-related relapse. Unfortunately, the authors did not comment on the drug response of patients who relapsed when medication was restarted.

Our second comment regards the absence of correlation between supersensitivity relapse and tardive dyskinesia reported by Weinberger and co-workers. When we first found that relapses upon abrupt withdrawal of neuroleptics might be related to supersensitivity psychosis, we were investigating potential antipsychotic drugs that

had no effect on the dopaminergic system in poor prognosis patients.<sup>2</sup> However, when we surveyed the incidence of supersensitivity psychosis in 261 schizophrenic outpatients treated with neuroleptics, we found that it was more likely to be seen in good prognosis patients than in poor prognosis patients (G. Chouinard and colleagues, unpublished data). In contrast, when we studied the incidence of tardive dyskinesia in the same outpatient population, we found that patients less responsive to neuroleptics (presumably poor prognosis) were more likely to develop tardive dyskinesia.<sup>3</sup> This tendency for these two supersensitivity phenomena (supersensitivity psychosis and tardive dyskinesia) to be more prevalent in patients with different prognoses would obscure a relationship between the two syndromes. Furthermore, such a relationship is difficult to demonstrate in Weinberger and co-workers' study since only two of their patients had tardive dyskinesia. This low incidence may result from the absence of a standard examination to detect tardive dyskinesia.

Finally, it should be noted that the manifestation of supersensitivity psychosis depends on the type of neuroleptic that the patient is withdrawn from and, in particular, its preferential affinity for different dopaminergic regions of the brain, its half-life, and its anticholinergic activity.

Neuroleptics with different affinities for regional brain dopaminergic receptors would result in different prevalences of tardive dyskinesia and supersensitivity psychosis. Neuroleptics that have greater affinities for the mesolimbic dopaminergic regions as opposed to neostriatal regions would tend to have a greater incidence of supersensitivity psychosis as opposed to tardive dyskinesia. In contrast, neuroleptics that have an equal affinity for mesolimbic and neostriatal dopaminergic regions would tend to produce similar dopaminergic receptor supersensitivity in these two regions.

The half-life of neuroleptics and their active metabolites in the brain is most important as regards the appearance of supersensitivity psychosis, and the long half-life of the neuroleptics presently available is almost certainly responsible for difficulties in recognizing the syn-

drome. Withdrawal, rebound, or supersensitivity phenomena are more easily detected if the half-lives of the drug and/or its active metabolites are of short duration. The effects of neuroleptics on prolactin secretion show that a neuroleptic such as haloperidol (which has no active metabolites) is still active several days after discontinuation of the drug.<sup>4</sup> One would predict that metoclopramide, a shorter acting dopamine receptor blocking agent, when given to schizophrenic patients in high doses sufficient to have an antischizophrenic effect, would give clear evidence of supersensitivity relapse upon abrupt withdrawal. In Sweden, where clozapine has been extensively used, several cases of supersensitivity psychosis on withdrawal of the drug have been observed.<sup>5</sup> The diagnosis of supersensitivity psychosis in these cases was based on the clinical appearance of new psychotic symptoms or symptoms of greater severity when clozapine was withdrawn. This convincing evidence of clozapine's ability to induce supersensitivity psychosis might be related to both the short half-life of the drug and its greater affinity for mesolimbic dopamine receptors.

The type of neuroleptic may also be important as regards its effects on other neurotransmitters. Low potency neuroleptics at therapeutic doses are known to block  $\alpha$ -adrenergic, cholinergic, serotonergic, and histaminic receptors. Their abrupt withdrawal would tend to induce rebound phenomena in any of these neuronal systems and obscure the manifestation of supersensitivity psychosis. Review of the literature suggests that relapse occurring soon after neuroleptics are discontinued is more frequent in patients receiving high potency drugs despite equivalent doses of medication as translated into chlorpromazine units (B. D. Jones and G. Chouinard, unpublished data). A possible explanation for the lower incidence of supersensitivity psychosis upon withdrawal of low potency neuroleptics is the occurrence of rebound cholinergic activity which would block or cover up the expression of psychotic symptoms (this is supported by evidence that cholinergic agonists lessen the severity of

psychotic symptoms in mania). In Weinberger and coworkers' study, only eight of 20 patients were receiving high potency neuroleptics, and three of these patients had their antiparkinsonian medication stopped concomitantly with neuroleptic discontinuation. Thus, in 75% of their patients cholinergic rebound may have covered relapse related to drug-induced supersensitivity psychosis and resulted in a low incidence of potential cases. We found in a large sample of 300 schizophrenic outpatients chronically treated with high potency neuroleptics that 30% of patients showed signs of supersensitivity psychosis even without attempts of abrupt drug withdrawal.

In summary, neuroleptic-induced supersensitivity psychosis may appear most frequently in patients with a poor prognosis who are withdrawn abruptly from drugs with minimal central anticholinergic effect, short half-life, and preferential affinity for mesolimbic dopamine receptors. Its relationship to tardive dyskinesia may be obscured by several of the above mentioned factors.

**G. CHOUINARD, MD**

**B. JONES, MD**

*Allan Memorial Institute  
Royal Victoria Hospital  
Clinical Psychopharmacology  
and Research Department  
Louis-H. Lafontaine Hospital  
Montreal, Quebec, Canada*

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