Neuroleptic-Induced Supersensitivity Psychosis

BY GUY CHOUINARD, M.D., M.SC. (PHARMACOL), BARRY D. JONES, M.D., AND LAWRENCE ANNABLE, DIP. STAT.

Dopamine receptor binding sites have been reported to increase in the neostriatum after chronic treatment with neuroleptics, which could account for the dopamine hypersensitivity that induces tardive dyskinesia (1). We propose that similar changes may occur in the mesolimbic region in response to the chronic dopamine blockade of these drugs. Three kinds of clinical evidence are compatible with this hypothesis: 1) central nervous system (CNS) drug tolerance; 2) psychosis following neuroleptic withdrawal, which is correlated with signs of dopamine supersensitivity and which we would therefore term "supersensitivity psychosis"; and 3) psychosis associated with a sudden decrease in prolactin levels following neuroleptic withdrawal.

Study Reports

CNS drug tolerance. In a double-blind controlled study we compared fluphenazine enanthate given every 2 weeks

with fluphenazine decanoate given every 4 weeks in the maintenance treatment of 48 schizophrenic outpatients (2). Before entering the trial, patients had received fluphenazine enanthate routinely for periods of 1 to 42 months (median=14). All patients underwent a further 1-month period of stabilization with fluphenazine enanthate. The bimonthly dosages of the fluphenazine enanthate-treated patients on entering the trial ranged from 2.5 to 125 mg (median=25 mg, mean=39.3 mg) and after 7 months of treatment ranged from 2.5 to 325 mg (median=50 mg, mean=69.1 mg). Thus, substantial increases in dosage were required to maintain the mean therapeutic effect at the same level. In animal studies, prolonged exposure to neuroleptics leads to increased dosage requirements to block the behavioral effects of apomorphine (3, 4).

Psychosis associated with signs of dopamine supersensitivity. In a 6-week double-blind trial of tryptophan-benserazide we studied the relationship between tardive dyskinesia and psychotic relapse in 32 patients with process schizophrenia (5). Half of the subjects received tryptophan-benserazide instead of their regular neuroleptic medication and half received chlorpromazine. In the tryptophan group, the severity of tardive dyskinesia (assessed on a 9-point clinical impression scale of the Extrapyramidal Symptom Rating Scale [2]) tended to be greater in the 8 patients who deteriorated than in the 6 patients who did not (means±SD=5.4±1.4 and 3.8±1.7, respectively, t=1.85, p <.10). However, there was no difference in severity of tardive dyskinesia between the deteriorated (N=2) and nondeteriorated (N=14) chlorpromazine patients (means±SD=3.5±0.7 and

REFERENCES


A more complete bibliography is available on request from the authors.
Another implication is the possibility that this supersensitivity may explain why Hogarty and associates (10) were unable to identify "good prognosis" patients who do not relapse when maintenance neuroleptics are discontinued. Another implication is the possibility that this supersensitivity is irreversible. This is accepted to be true of tardive dyskinesia unless it is diagnosed early and medication is discontinued. If the same irreversibility is occurring in the mesolimbic region, the result would be patients who must remain on neuroleptics for the rest of their life regardless of the natural course of their illness. In the studies done by Hogarty's group, two-thirds of patients thought to be suitable for drug withdrawal after 2 years of drug therapy relapsed following drug discontinuation, causing the authors to state that "the need for maintenance chemotherapy may be indefinite" (10). In some of these cases, the need for continued neuroleptic treatment may itself be drug-induced.

**Discussion**

The association between dyskinesia and psychotic relapse has been observed by others (8, 9). The hypothesis that tardive dyskinesia and supersensitivity psychosis may be caused by a similar mechanism occurring in different areas of the brain is suggested by the common factors that can alter the clinical picture of both syndromes: increasing the neuroleptic dosage decreases the severity of dyskinesia and psychosis, decreasing the dosage makes both worse, stress exacerbates both dyskinetic and psychotic symptoms, and L-dopa and amphetamine can increase the severity of both.

We suggest that neuroleptics can produce a dopamine supersensitivity that leads to both dyskinetic and psychotic symptoms. An implication is that the tendency toward psychotic relapse in a patient who has developed such a supersensitivity is determined by more than just the normal course of the illness. This may explain why Hogarty and associates (10) were unable to identify "good prognosis" patients who do not relapse when maintenance neuroleptics are discontinued.

**REFERENCES**