

Neuroleptic-Induced Supersensitivity Psychosis: Clinical and Pharmacologic Characteristics

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Tardive dyskinesia is thought to result from neostriatal dopaminergic receptor supersensitivity induced by chronic treatment with neuroleptics. The authors suggest that dopaminergic supersensitivity also occurs in the mesolimbic region after chronic neuroleptic exposure, resulting in the development of a supersensitivity psychosis. Neuroleptic-induced supersensitivity psychosis is illustrated by data from 10 patients that demonstrate the syndrome's clinical and pharmacologic characteristics. An implication of neuroleptic-induced mesolimbic supersensitivity is that the tendency toward psychotic relapse in such patients is determined by more than just the normal course of the illness.

Dopamine (DA) receptor binding sites have been shown to increase in the neostriatum after chronic treatment with neuroleptics, and this could account for the DA supersensitivity that induces tardive dyskinesia (1). We have proposed that similar changes occur in the mesolimbic pathway in response to the chronic DA blockade by these drugs (2, 3) and that psychotic symptoms following withdrawal or decrease of neuroleptics could be the clinical expression of a mesolimbic DA postsynaptic receptor supersensitivity. According to this hypothesis, the cessation of maintenance neuroleptic medication induces a relative increase in the mesolimbic DA function, leading to psychotic relapse or deterioration in the same manner as tardive dyskinesia can emerge or worsen when medication is stopped or decreased. We have proposed the term "supersensitivity psychosis" for this phenomenon (3).

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There is evidence from studies in both animals and humans which supports the theory of mesolimbic supersensitivity. In animal pharmacologic studies CNS tolerance to neuroleptic effect is well documented, and prolonged exposure to neuroleptics leads to increased dosage requirements to block the behavioral effects of apomorphine (4, 5). Muller and Seeman (6) reported an increase of dopamine-binding sites not only in the neostriatum but also in the mesolimbic region of rats chronically treated with neuroleptics. In human studies, Owen and associates (7) showed an increase of DA-binding sites in the mesolimbic region of schizophrenic patients; this increase was related to the length of treatment with neuroleptics. Recently, Lee and associates (8) also reported an increase of DA-binding sites in the brains of schizophrenics.

In an earlier paper, we presented evidence from two double-blind controlled studies that suggests the existence of this neuroleptic-induced supersensitivity disorder (3). In the present paper, we describe 10 cases of the disorder that illustrate the pharmacologic and clinical characteristics of the syndrome, which, like tardive dyskinesia, is a supersensitivity syndrome induced by long-term use of neuroleptic drugs. It consists of positive symptoms of schizophrenia, e.g., suspiciousness, delusions, or hallucinations, and does not include negative symptoms of the illness, e.g., emotional withdrawal or blunted affect. Like tardive dyskinesia, the supersensitivity psychosis has pharmacologic characteristics, described below, that are associated with its etiology of postsynaptic DA receptor supersensitivity.

1. Symptoms appear when neuroleptics are discontinued, when dosage is decreased, or, in the case of depot neuroleptics, at the end of the injection interval.

2. The syndrome is associated with a history of at least a few weeks of treatment with neuroleptics.

3. There are concomitant signs of DA supersensitivity (tardive dyskinesia) other than psychosis.

4. The syndrome is associated with high prolactin levels that result from the requirement for increased DA blocking to control psychotic symptoms induced by the DA supersensitivity. The high prolactin levels usually lead to signs of sexual dysfunction.

5. There is also an association with CNS tolerance to antipsychotic effect, i.e., a gradual increase in neuroleptic dosage is necessary to maintain a therapeutic effect.

6. As with tardive dyskinesia, the most efficacious treatment is the causative agent itself, the neuroleptic.

7. As with tardive dyskinesia, there may be different stages along a continuum (9). The first stage, analogous to withdrawal dyskinesia, is a reversible withdrawal supersensitivity psychosis that lasts only a few days. The second stage, analogous to "covert" dyskinesia, is a covert supersensitivity psychosis that appears only on withdrawal of neuroleptics but is persistent and may be irreversible. Finally, analogous to "overt" dyskinesia is an overt supersensitivity psychosis that appears even in the presence of neuroleptic treatment and is irreversible in most cases.

CASE REPORTS

Case 1. Mr. A was first seen on a psychiatry service at the age of 19 because of persecutory feelings, for which he was treated without medication. Two years later he became acutely psychotic and was hospitalized with auditory hallucinations and persecutory delusions. During his 4-month hospitalization the patient improved slowly with oral neuroleptics. He was discharged without psychotic symptoms on trifluoperazine, 15 mg/day, with the diagnosis of paranoid schizophrenia. Mr. A had a mild relapse when the dose was reduced to 10 mg/day h.s. and he developed paranoid symptoms that occurred in the afternoon. Later, his medication was changed to fluphenazine enanthate, 6.25 mg I.M. every 2 weeks. The patient then reported that his persecutory feelings were under better control, except for the last 4 days before the injections; these feelings were not associated with an increase in his parkinsonian signs or symptoms, which actually improved toward the end of the injection interval. In terms of negative symptoms of schizophrenia, Mr. A had very mild emotional withdrawal that did not increase toward the end of the injection interval. He was able to continue in his occupation and normal way of life, but paranoid ideation occurred a few days before each injection. This continued for 6 months and necessitated the following dosage increases: 12.5 mg every 2 weeks; 6 months later 25 mg every 2 weeks; 2 months later 37.5 mg every week; 6 months later 50 mg every week. Over the next year, the pre-injection persecutory delusions and auditory hallucinations increased to such an extent that the patient was given fluphenazine enanthate, 375 mg every week, and haloperidol, 20 mg q.i.d. At this point, Mr. A was stable and working as a computer programmer. He received no other drugs with the exception of procyclidine, an antiparkinsonian agent. One week after his injection his ratings on the Extrapyramidal Symptom Rating Scale (ESRS) of Chouinard and Ross-Chouinard (10) indicated constant tremor of both legs, mild akathisia, occasional dyskinetic lingual movements with partial protrusion, and dyskinetic movements of one hand. There were no signs of what Gardos and associates (9) call "medical" withdrawal symptoms, such as nausea, vomiting, and sweating. The patient also complained of loss of libido and sexual drive and received a rating of 22 (moderate dysfunction) on a 7-point sexual dysfunction scale of 6 items. His prolactin level at that time, 7 days after the injection, was 64 ng/ml, and he showed positive and negative symptoms. In contrast, 5 days after the injection, there were no positive symptoms or dys-

kinetic movements, but his negative symptoms remained unchanged and his prolactin level was 94 ng/ml.

Case 2. Mr. B had been employed until his first psychiatric hospitalization, at the age of 34. Over the previous 4 years he had had an insidious onset of persecutory delusions. On admission he was noted to have auditory hallucinations of people whom he believed to be gangsters laughing at him, talking about him in his room, and following him on the street. Mr. B had no history of alcohol or drug abuse, and there was no family history of psychiatric illness. He was discharged on chlorpromazine, 100 mg q.i.d., and remained stable for 10 years, during which time he had mild negative symptoms consisting of blunted affect, poverty of thought, and apathy with only mild and occasional exacerbation of persecutory delusions. However, 12 years after his initial hospitalization he experienced a relapse characterized by a belief that the Mafia was out to get him and had entered his house. He was then treated with chlorpromazine, 400 mg b.i.d., and fluphenazine enanthate, 25 mg I.M. every 2 weeks. This was changed soon after to fluphenazine enanthate, 50 mg I.M. every 2 weeks and chlorpromazine, 400 mg/day, at which point he was stable. However 2 months later he had a mild exacerbation, missed an injection, and deteriorated further. After receiving his regular injection he again stabilized, but (3 months later) he missed another injection and again deteriorated; he heard voices and felt unable to leave his house for fear of being killed. At this point his medication was increased to fluphenazine enanthate, 75 mg every 2 weeks, and chlorpromazine, 600 mg/day. He remained stable for 2 months but then deteriorated immediately after his chlorpromazine dosage was decreased. With an increase of fluphenazine enanthate to 100 mg every 2 weeks and chlorpromazine to 600 mg/day, Mr. B improved. The injection was again increased to 125 mg but soon after this the patient missed an injection and quickly deteriorated. At this point, he also complained of persecutory delusions near the end of the injection interval, with no change in negative symptoms. The delusions were not associated with exacerbation of parkinsonian signs or symptoms such as akathisia. In fact, his parkinsonian symptoms improved toward the end of the injection interval. After 3 months on this regime, Mr. B's medication was changed to fluphenazine enanthate, 150 mg every 2 weeks. He remained stable for the next 11 months, at which point he again experienced marked persecutory delusions over the 4 days before his next injection. Therefore he was placed on fluphenazine enanthate, 100 mg per week. He remained stable for 4 months, when he missed an injection and subsequently deteriorated. An attempt was made to return him to 2-week injection intervals. He remained stable until a further attempt to decrease the dose from 100 mg to 87.5 mg resulted in an immediate relapse. After stabilization on a 100-mg dose, he was switched to fluphenazine decanoate, 200 mg every 4 weeks. Within 2 months he was again deteriorating over the last 4 days before his injection and the interval was changed to 3 weeks. He then remained stable for 1 month, when he began to deteriorate during the week before his injection. He was therefore returned to fluphenazine enanthate, 100 mg every 2 weeks, and has since received increases of his injection to control recurring relapses near the end of the injection interval. At present Mr. B is receiving 175 mg of fluphenazine enanthate every 2 weeks. On this dose his prolactin level 2 weeks after the injection, at which time persecutory delusions and nega-

TABLE 1
Antipsychotic Treatment Histories of 10 Patients Who Developed Supersensitivity Psychosis

Patient	Age (years)	Sex	Schizophrenia Subtype	Symptom Responsible for Dosage Increases	Fluphenazine Enanthate Dose (mg/2 weeks)				Prolactin (ng/ml) ^a	Tardive Dyskinesia Score ^a	Sexual Dysfunction Score
					Three Years Previously	Two Years Previously	One Year Previously	Current			
1	26	M	Paranoid	Persecutory delusions	6.25	37.5	400	800 ^b	64	6	22
2	51	M	Paranoid	Persecutory delusions	150	100	100	175	25	13	— ^c
3	25	M	Paranoid	Delusions of reference	25	31.25	25 ^c	62.5 ^d	28	16	5
4	25	M	Paranoid	Auditory hallucinations	25	25	125	125	77	0	31
5	33	M	Paranoid	Delusions of being controlled	100	100	200	350	30	0	— ^c
6	39	F	Undifferentiated	Somatic delusions	37.5	37.5	50	50	121	3	12
7	35	F	Hebephrenic	Capgras delusions	50	50	125	150	89	11	— ^c
8	31	F	Hebephrenic	Delusions of being controlled	62.5	75	165 ^d	165 ^d	86	5	15
9	24	F	Hebephrenic	Auditory hallucinations	6.25	100	200	225	119	3	— ^c
10	50	F	Paranoid	Persecutory delusions	37.5	37.5	175	237.5 ^b	62	3	23

^aProlactin levels and tardive dyskinesia scores were obtained immediately before the next injection of fluphenazine enanthate.

^bPatient also receiving fluphenazine decanoate; dose given is fluphenazine enanthate plus decanoate.

^cValues not assessable.

^dPatient receiving only fluphenazine decanoate.

tive symptoms were present, was 25 ng/ml, and his rating for tardive dyskinesia on the ESRS was 13, indicating moderate dyskinesia (abnormal movement of the tongue and lips and choreoathetoid movements of the lower extremities). In contrast, 5 days after the injection the prolactin level was 38 ng/ml, tardive dyskinesia and positive symptoms were absent, and negative symptoms were still present.

Other Cases

Table 1 summarizes the data for these 2 patients and 8 others regarding neuroleptic doses over a 3-year period. All patients were diagnosed as schizophrenic. During this period they had been treated as outpatients in a special follow-up clinic for long-term treatment of schizophrenia. This clinic has an average patient population of 300 actively involved in treatment. The patients presented here are typical of those manifesting the supersensitivity psychosis and required a gradual increase in medication over time. However, this was not always so, as can be seen in the case of Mr. B. Since the policy at the clinic is to give the minimum therapeutic dose, a reduction in the medication will be expected for those patients who will have a remission of their illness. However, the appearance of the neuroleptic-induced psychosis in the patients presented did not permit complete withdrawal of the neuroleptic drug. Before adjusting a patient's neuroleptic dose, a full assessment of extrapyramidal signs and symptoms was always done to rule out the possibility of neuroleptic-induced extrapyramidal reactions associated

with psychotic decompensation. All patients described in table 1 have shown the most characteristic feature of the syndrome, a relapse manifested by an increase in positive symptoms immediately after decreases in neuroleptic dosage. In contrast, negative symptoms in these patients, as in the two patients described previously, did not increase in the same circumstances.

The syndrome is associated with an elevated prolactin level that usually leads to sexual dysfunction. Male patients tended to have a smaller prolactin elevation than female patients, but their levels are above the normal range of 0-10 ng/ml. The prolactin measurements were made immediately before the patients received their injections and are conservative estimates because neuroleptic blood levels are very low at that time. The low scores for tardive dyskinesia seen in some of these patients can be explained by the fact that they were receiving high doses of injectable neuroleptics, and some were receiving oral neuroleptics at the end of the injection interval, both of which would cover the manifestations of tardive dyskinesia.

DISCUSSION

We have described the neuroleptic-induced supersensitivity psychosis and its seven characteristics. These characteristics are necessary to establish the existence of the supersensitivity disorder. The su-

