

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-

persensitivity psychosis was defined as consisting only of positive symptoms of schizophrenia, in particular suspiciousness, delusions, and hallucinations. We have proposed that positive symptoms of schizophrenia result from a relative DA hyperactivity in the mesolimbic region, whereas negative symptoms result from DA hypoactivity (2). Neuroleptic-induced supersensitivity in the mesolimbic region would thus appear clinically as an increased tendency toward positive symptoms. This has been our experience with the cases reported here. In contrast, negative symptoms, which we have not seen in the psychotic decompensation that is contingent in these cases on drug decrease, might be expected to improve over time on maintenance neuroleptic therapy because of DA supersensitivity induction. This is consistent with our clinical experience that negative symptoms of schizophrenia improve only after a few weeks of neuroleptic therapy or when neuroleptics are withdrawn.

The first characteristic of the syndrome is that it appears almost immediately after neuroleptics are discontinued or decreased. This is contrary to the normal course of most forms of schizophrenia, in which the illness would not be expected to worsen upon drug withdrawal. In the cases we have reported the deterioration is clearly evident when the neuroleptic dosage is reduced or the patient misses one or two injections. These patients show a similar pattern of deterioration with respect to the severity of their tardive dyskinesia. This is consistent with the proposed etiology of drug-induced DA supersensitivity for both the psychotic and dyskinetic deterioration. In questioning patients who have received maintenance neuroleptic treatment and have developed mesolimbic supersensitivity, one hears such statements as, "Before, I was not taking my medication regularly and I was readmitted once a year or every two years. Now since I take my medication regularly, I get sick as soon as I miss a single injection or stop taking my medication." The induced DA supersensitivity will not be clinically evident in its psychotic or dyskinetic symptom expression if it is covered by the neuroleptics themselves. Thus the syndrome may be masked in patients who are receiving divided doses of oral neuroleptics. In the cases we described, all patients were receiving only long-acting injectable medication when the syndrome became evident to us through psychotic decompensation late in the injection interval, a time when neuroleptic blood levels would be expected to be low. However, the syndrome may also be seen in patients taking oral neuroleptics once a day. An example of this would be Mr. A (case 1), who reported psychotic symptoms beginning in the afternoon when he was receiving only a single daily dose of oral neuroleptic at bedtime. We think that this may also explain the discrepancy in the literature regarding the incidence of tardive dyskinesia. The early surveys of tardive dyskinesia, done when neuroleptics were usually given in divided doses during the

day, showed an incidence of less than 1%, whereas the latest surveys, taken since the single daily oral doses and injectable neuroleptics have become common, report an incidence of 30%–40% (11). There is also evidence from one of our studies that patients treated with injectable neuroleptics show an even higher incidence of tardive dyskinesia when rated at the end of the injection interval (10).

The second characteristic is a history of consistent exposure to neuroleptics. Tardive dyskinesia is usually observed after several years of treatment; rare cases have been reported after 6 months. In our case 1, supersensitivity psychosis appeared after 6 months, whereas in the other cases it became clinically evident only after a number of years of neuroleptic treatment. However, the syndrome's clinical appearance varies according to the masking effect of neuroleptics or unmasking by a decrease of dosage.

The third characteristic is that other clinical signs of DA supersensitivity would be expected in patients who have developed supersensitivity psychosis. Animal and human studies show that DA supersensitivity develops to a similar degree in the neostriatum and mesolimbic region after exposure to neuroleptics that have approximately equal potency to block DA receptors in these areas (6, 7). Thus, tardive dyskinesia resulting from drug-induced neostriatum supersensitivity would be more prevalent and severe in patients manifesting supersensitivity psychosis. In the cases reported, tardive dyskinesia was seen and, as mentioned previously, worsened when patients experienced psychotic deterioration as a result of decreased neuroleptic levels. Similarly, in a double-blind controlled study we found a tendency for psychotic deterioration to be associated with increased severity of tardive dyskinesia in patients withdrawn from their regular neuroleptic medication (3). It should be noted, however, that the clinical signs of DA supersensitivity can be covered by neuroleptics. Thus in patients whose psychotic symptoms are controlled by increases in the neuroleptic dose, the expression of tardive dyskinesia may be suppressed similarly. It should also be noted that the relationship between the two supersensitivity disorders may be obscured by the use of anticholinergic drugs that affect the clinical manifestation of tardive dyskinesia but not the supersensitivity psychosis (12).

The fourth characteristic of the syndrome is its association with high prolactin levels, which may produce clinical signs of sexual dysfunction. Development of DA supersensitivity in the tubero-infundibulum has not been demonstrated, and our own studies do not suggest such supersensitivity (13). Thus if neuroleptic doses are increased to control emerging psychotic symptoms in patients with supersensitivity psychosis, there will be progressive increases in DA-blocking activity in the tubero-infundibulum. These increases will be unopposed because of the lack of DA supersensi-

tivity development there. Prolactin, which is inhibited by dopamine, will then increase in such patients to levels that are in accord with the degree of DA-blocking needed to counteract mesolimbic DA supersensitivity. Thus patients who have developed supersensitivity psychosis would be expected to show abnormally elevated prolactin levels and sexual dysfunction. In the cases reported, elevated prolactin levels and symptoms of sexual dysfunction were present. Furthermore, we have found that patients who deteriorate when neuroleptics are withdrawn tend to have greater prolactin decreases than patients who remain stable (3).

The fifth characteristic is that the syndrome is usually associated with CNS tolerance to antipsychotic effect, i.e., a gradual increase in neuroleptic dosage is necessary to maintain the therapeutic effect. In animal studies, this tolerance is well recognized (4, 5). In addition, Bowers and Rozitis (14) have reported a tolerance to neuroleptic-induced increases in HVA concentration in the mesolimbic region. We also reported that during a 7-month double-blind controlled study with esters of fluphenazine (3), 44% of the patients required dosage increases. Of the cases presented here, case I is the best example of such a drug tolerance. We think that drug tolerance to antipsychotic effects will be seen most easily in outpatients who are employed in jobs that involve a certain amount of stress. Patients receiving long-term care in mental hospitals are less likely to display such tolerance because they are under minimal stress and have less need for medication. It might be argued that this is a metabolic drug tolerance and that measurements of blood levels therefore would be necessary. However, based on our experience with gas chromatography-mass spectrometry, we do not think that reliable measurements of fluphenazine levels can be made at this time. The unreliability of available methods results from the tendency of fluphenazine to concentrate in the red blood cells. Furthermore, we think that prolactin measurements reflect the DA-blocking activity of neuroleptics and that their elevation with increasing drug dosage rules out a metabolic tolerance to neuroleptics. That such increases in neuroleptic dosage have not been noted previously in the literature probably results from the lack of long-term studies of patients receiving only one injectable neuroleptic and no other medications except anti-parkinsonians. Only in this patient population will such variables as gastrointestinal absorption, liver metabolism, and patient compliance be controlled.

The sixth characteristic of the syndrome is that the causative agent, the neuroleptic, is the most efficacious treatment, as is true in tardive dyskinesia. This is well demonstrated in the cases we have presented. Each time the neuroleptic medication was increased, the supersensitivity psychosis improved. We also think that the more potent neuroleptics with a strong DA-blocking effect are better suppressors of the super-

sensitivity syndrome, as they are in tardive dyskinesia.

The seventh characteristic of the syndrome is that it may exist on a continuum, as is true in tardive dyskinesia (9). The cases presented here illustrate the later stages of the syndrome, in which the covert supersensitivity psychosis is uncovered by a dosage reduction and finally becomes apparent during neuroleptic treatment, necessitating further increases in dosage. Thus, the need for neuroleptic therapy to control the supersensitivity psychosis would be expected to be continual.

In addition, one might speculate on one further characteristic of the supersensitivity psychosis syndrome: schizophrenic patients may be more prone to develop supersensitivity psychosis than nonschizophrenic patients. We have proposed that schizophrenia is a dopamine deficiency disease and that the positive symptoms of schizophrenia are due to postsynaptic receptor DA supersensitivity resulting from this dopamine deficiency (2). DA-blocking drugs are thus efficacious in controlling the symptoms of the supersensitivity psychosis, as they are in masking tardive dyskinesic symptoms. However, the DA-blocking effect of these drugs, added to the existing DA deficiency, will lead to further development of dopaminergic supersensitivity in schizophrenic patients. This would be in contrast to nonschizophrenic patients, who do not have dopamine deficiency as an original element of the disease and thus would be expected to have less tendency to develop dopaminergic supersensitivity in response to neuroleptics. It has been our clinical experience that most bipolar manic patients do not show signs of supersensitivity psychosis on neuroleptic withdrawal and have less tendency to develop tardive dyskinesia. The proneness of schizophrenic patients to develop neuroleptic-induced dopaminergic supersensitivity in the mesolimbic region may be similar to the increased tendency in parkinsonian patients to develop dyskinesia in response to L-dopa treatment (15). However, the fact that animal studies show dopaminergic supersensitivity in the mesolimbic region, despite presumably normal preneuroleptic dopamine function, suggests that supersensitivity psychosis may not be confined to schizophrenic patients. Finally, elderly patients and those for whom the neuroleptic has little therapeutic effect might be more likely to develop the syndrome, just as they are more likely to develop tardive dyskinesia (11).

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