Severe cases of neuroleptic-induced supersensitivity psychosis

Diagnostic criteria for the disorder and its treatment

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Tardive dyskinesia is thought to result from neostriatal dopaminergic receptor supersensitivity induced by chronic treatment with neuroleptics. Similarly, receptor supersensitivity occurring in other dopaminergic regions of the brain could result in the development of supersensitivity psychosis. As with tardive dyskinesia, severe forms of the disorder are rare. Ten such cases are described whose main characteristic is that psychotic symptoms can no longer be masked by increased dosages of neuroleptics. Diagnostic criteria for the disorder are proposed, and treatment with antiepileptic medication is described.

INTRODUCTION

Long-term administration of neuroleptics is currently the most efficacious treatment for schizophrenia. However, this treatment is not without serious risk, in particular for the central nervous system. Abnormal movements of choreoathetoid type called tardive dyskinesia have been reported to occur in 20–40% of patients receiving neuroleptics (APA Task Force Report, 1979) and can be potentially irreversible especially after the age of 40. We reported another long-term side effect which we called supersensitivity psychosis (Chouinard et al., 1978; Chouinard and Jones, 1980). Receptor changes in the dopaminergic pathways of the mesolimbic (Davis and Rosenberg, 1979) or other non-striatal dopaminergic regions of the brain could explain the disorder in the same way that changes in the neostriatum are thought to be responsible for tardive dyskinesia.

The phenomenon of supersensitivity psychosis is still under clinical investigation (Jain et al., 1988). However, several studies presented during the past 2 years have provided data compatible with its existence (Borison, 1987; Green et al., 1989; Oral et al., 1989; Sramek et al., 1989). So far, only one study has been negative (Singh et al., 1989), however, during that study the observation period for relapse after neuroleptic withdrawal was of only 2 weeks, which is of shorter duration than the 6 week period we recommend for oral neuroleptic discontinuation (Table 1). Hunt et al. (1988) conducted a chart review of 265 hospitalized schizophrenic patients and found 12 cases (4%) of probable but not definite supersensitivity psychosis. The worsening time varied between 1–6 weeks (which is in accordance with our criteria) and the improvement varied between 2 and 5 weeks with one patient showing no improvement in 8 weeks (this last patient could have been suffering from the severe form of the disorder). The lower incidence found in Hunt et al.'s study (1988) could be attributable to the fact that these patients were inpatients, the study was a chart review study (charts could be variable from one patient to another) and also to the fact that the authors were probably not the treating physicians. In our

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TABLE 1

Chouinard Research Diagnostic Criteria for Supersensitivity Psychosis

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(A) The patient must have a 3 month history of receiving antipsychotics

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(B) At least one of the following major criteria must be present:
   (1) reappearance of psychotic symptoms upon decrease or discontinuation of medication during the last 5 years — within 6 weeks for oral medication, 3 months for i.m. depot medication;
   (2) greater frequency of relapse (acute psychotic exacerbation) during continuous treatment with neuroleptics;
   (3) tolerance to the anti-psychotic effect of the neuroleptic (overall increase in dose by 20% or more during the last 5 years);
   (4) extreme tolerance: increased neuroleptic dosages do not mask the psychotic symptoms any more;
   (5) psychotic symptoms upon decrease of medication are new schizophrenic symptoms (not previously seen) OR are of greater severity;
   (6) psychotic relapse occurs upon sudden decrease ($\geq 10\%$) of medication but not if same decrease is gradual;
   (7) presence of drug tolerance in the past but presently treated with high doses of neuroleptics on at least a bid regimen.

(C) At least one of the following minor criteria must be present if only one major criterion is present:
   (1) tardive dyskinesia (a standard examination must be used);
   (2) rapid improvement in psychotic symptoms when the neuroleptic dose is increased after a decrease or discontinuation;
   (3) clear exacerbation of psychotic symptoms by stress;
   (4) appearance of psychotic symptoms at the end of the injection interval (for patients on long-acting intramuscular medication);
   (5) high levels of prolactin or neuroleptic activity (twice normal – at least once within the last 2 years).

(D) Exclusion criteria:
   (1) patients in the first acute phase of illness;
   (2) patients with continuous severe psychosis unresponsive to neuroleptics.

(E) *Subtypes*:
   Stage I: *Withdrawal type*: reversible when the only major criteria present are no. 1 and/or no. 6;
   Stage II: *Tardive type*:
       IIA — masked and mostly reversible when the only major criterion present is no. 3;
       IIB — masked and mostly irreversible when the only major criterion present is no. 7;
       IIC — overt and mostly irreversible when major criterion no. 1 is present with any other major criteria (other than no. 6);
   Stage III: *Severe type*: when major criterion no. 4 is present.

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studies, we have been following these patients since 1972 (so far, up to 18 years).

Palmstierna and Wistedt (1987) did not report drug tolerance in a sample of 29 patients out of 255 individuals, using the criteria of an increase of 50% for drug tolerance and measurements of serum fluphenazine levels. (Serum fluphenazine levels are notoriously low and unreliable, and the authors should have provided the intra- and interassay coefficient variability with blind measurements. In our experience, these have been notoriously so variable even with MS-HPLC that we have never reported them in the literature.) Nonetheless, out of 28 patients, nine (31%) had increased doses or had potentially developed tolerance. Four of the nine had increased doses and were doing better, but this does not rule out supersensitivity psychosis, since it could be a stage I or withdrawal

psychosis. Two patients who deteriorated on a decreased dose may also have had the disorder. The other three had a definite increased dosage, among whom two appeared to have, in my opinion, a severe form of supersensitivity psychosis.

Supersensitivity psychosis is a drug-induced phenomenon which consists of psychotic relapse occurring upon decrease or withdrawal of neuroleptics. This psychotic relapse differs from a relapse related to the original illness in the following ways: (1) the relapse occurs immediately and invariably with drug withdrawal or dosage reduction and is correlated with a gradual decrease of the antipsychotic effect of the same levels of neuroleptic activity as measured by radioreceptor assay of neuroleptic activity or prolactin concentrations; (2) a greater frequency of relapses is seen in the patient when he is on continuous neuroleptic treatment as

opposed to when he was not treated regularly with neuroleptics; (3) tolerance to the antipsychotic effect can occur: higher doses of neuroleptics are needed to have the same therapeutic effect; (4) initially, the syndrome is characterized by the fact that the psychotic relapse will appear upon sudden decrease of medication but not if the same decrease of medication occurs gradually; (5) supersensitivity psychosis or drug-related relapse in its more severe form is characterized by an extreme tolerance to neuroleptic activity, i.e., increased neuroleptic dosages no longer produce the same therapeutic or masking effects: the illness appears worse than at any given time; and/or when the drug dosage is decreased, new schizophrenic symptoms or original symptoms of greater severity will appear.

A 6 week observation period for supersensitivity relapse after oral neuroleptic decrease or discontinuation was chosen following results from one open study ($n = 10$ patients) and two double-blind studies involving a total of 64 patients. During these studies, one group of chronically treated schizophrenic patients was randomized to continue taking classical neuroleptics, while the other group was randomly assigned to discontinue antidopaminergic drugs and was given a drug with no effect on the dopaminergic system. Since a plateau (or steady state) was reached for tardive dyskinesia and drug-induced parkinsonism after 6 weeks of standard neuroleptic discontinuation in those patients withdrawn from antidopaminergic drugs, we adopted this limit of 6 weeks after decrease of oral neuroleptics as the criterion for withdrawal psychosis. Studies done in normal volunteers (Hubbard et al., 1978), and in rats (Cohen et al., 1988), show that the effects and blood concentrations of neuroleptics could persist for several weeks after a single dose of haloperidol. Furthermore, one PET scan study showed that D_2 receptors occupancy persisted without falling 30 h (last imaging done) after discontinuation of neuroleptics (Farde et al., 1988). In addition, Cohen et al. (1988) suggested that neuroleptics given as a single dose 'might produce extended therapeutic effects as well as side effects'. As regards depot neuroleptics, a 3 month period was chosen because some data are suggesting a persistent effect of depot neuroleptic (Gitlin et al., 1988). Also, we found that the stabilization period necessary to adjust the dose of depot neuroleptic was at least of 2 months

duration in a double-blind study comparing haloperidol and fluphenazine decanoate (Chouinard et al., 1989).

The risk of central nervous system toxicity with long-term neuroleptic administration is a serious problem. We reported the prevalence of tardive dyskinesia and supersensitivity psychosis among 224 schizophrenic out-patients attending a special follow-up clinic for long-term maintenance treatment (Chouinard et al., 1988). This study revealed tardive dyskinesia to be present in 45% of patients (according to the research diagnostic criteria of Schooler and Kane (1982)) and definite supersensitivity psychosis was found in 22% of patients; the incidence was 43% if borderline cases are included (Chouinard et al., 1988). It could be argued that our population was different from that observed in other studies. In fact this does not appear to be the case. In a 5 year follow-up study (1975–1980) of these patients, we found the estimated annual incidence rate of tardive dyskinesia corrected for remissions to be 2.9% (Chouinard et al., 1988) which is similar to that reported by Kane et al. (1982) from a prospective study of TD development, although the latter study is of a younger and heterogeneous population of patients with schizophrenia or manic-depressive disorder.

In our latest epidemiological studies, high parkinsonism was predictive of development of tardive dyskinesia (Chouinard et al., 1990), but not supersensitivity psychosis (Chouinard et al., 1988, 1990). However, tardive dyskinesia was found to be the best predictor of the development of supersensitivity psychosis 10 years later.

Since supersensitivity psychosis may be difficult to differentiate from the original psychiatric disorder, we have established diagnostic criteria (Table 1), which are rated during an interview with the patient, during which information is obtained regarding relapses, drug withdrawal relapses, compliance and course of illness. The patient's chart is also reviewed as regards compliance with medication and relapses which have occurred when the patient discontinued medication by himself or upon physician's recommendation.

As with tardive dyskinesia, the most severe cases are of greatest concern. In general, severe cases of supersensitivity psychosis are characterized by an increased frequency of relapse, appearance of new schizophrenic symptoms and/or an increased

severity of previous symptoms after long-term neuroleptic treatment. As with tardive dyskinesia, the causative agent itself, the neuroleptic, could mask the supersensitivity symptoms for many years; however, in the most severe forms increasing the dosage of high-potency neuroleptics such as haloperidol or fluphenazine has little effect and in fact can lead to worsening.

In the present paper, we describe ten cases presenting severe forms of supersensitivity psychosis. Earlier, we reported ten cases which illustrated the overall characteristics of the syndrome (Chouinard et al., 1980). At that time, none of the patients presented evidence of the severe form of the disorder, and only two of these patients are included in the present report.

CASE REPORTS

Case 1

Mrs. A. was first seen on a psychiatric service at the age of 22 for delusions about sex. There was no history of drug or alcohol abuse and no family history of psychiatric disorder. She received no medication at that time, but became psychotic over the next 3 years, which led to hospitalization during which she was successfully treated with chlorpromazine and after 3 months was discharged on chlorpromazine 200 mg/day with the diagnosis of paranoid schizophrenia. She was 25 years old at that time. She was maintained on oral neuroleptic treatment over the following 10 years, was able to work full time and got married at the age of 34. Following participation in a research project on penfluridol, she was switched to fluphenazine enanthate 25 mg i.m. every 2 weeks. After 1 year this was increased to 31.25 mg every 2 weeks, and 18 months later to fluphenazine decanoate 137.5 mg i.m. every 3 weeks to achieve a similar therapeutic effect. Procyclidine, a central anticholinergic antiparkinsonian, was given for mild parkinsonian side effects. Over the next 2.5 years it was necessary to increase to 175 mg i.m. in order to achieve similar therapeutic effects, and she continued to work full time. Plasma prolactin concentration was 48 ng/ml. Over the subsequent months her medication was changed to haloperidol decanoate which needed to be increased gradually up to 525 mg i.m. every 2 weeks. At the age of 42, despite

these dosage increases, her psychosis continued to worsen: she became unable to work and developed more severe sexual delusions, auditory hallucinations and Capgras delusions, some of which were new psychotic symptoms. She also had mild buccolabial and upper extremity tardive dyskinesia, and mild akinesia. She was then switched to oral haloperidol 50 mg/day with little therapeutic effect. For the first time in 16 years of continuous neuroleptic treatment, hospitalization was required. She was treated with fluphenazine enanthate 150 mg i.m. every 2 weeks and oral fluphenazine 40 mg/day with some improvement. Plasma prolactin was 70 ng/ml and plasma neuroleptic activity was 91 nmol/ml (radioreceptor assay using [^{3}H]spiroperidol as a ligand and calf caudates) (Creese and Snyder, 1977; Lader 1980; Cohen et al., 1982). Because her psychosis did not remit, the medication was changed to pimozide, a diphenylbutylpiperidine derivative which has less affinity for neurophysiological pre-synaptic (Walters and Roth, 1976) and D_1-dopamine receptors, adenylcyclase linked (Christensen et al., 1984), than phenothiazine derivatives. She improved and was discharged on pimozide 32 mg/day and procyclidine 20 mg/day. At home she functioned marginally well but was unable to work. In the next few months pimozide was increased to 90 mg/day as she started to deteriorate again. Plasma prolactin was 68 ng/ml. Her psychosis had become more severe than at any time in the past. New psychotic symptoms had appeared and were consistent with the DSM-III disorganized subtype of schizophrenia, including talking in a child-like voice, defecating on the floor and lying in a fetal position for long periods of time. Finally, fluspirilene (an injectable diphenylbutylpiperidine) 40 mg i.m./week was added with little or no improvement of the psychosis. At the age of 43, her illness is worse than it has ever been. There was no evidence that this patient would develop this course of illness (she is a woman, got married, worked full time, etc.). Phenytoin 150 mg/day was initiated to treat her supersensitivity psychosis, which led to her discharge from the hospital and to a marked improvement in her daily functioning that was maintained up to 3 years.

Case 2

Mrs. B. was first seen on a psychiatric service for postpartum psychosis when she was 24 years old.

She received a course of ECT at that time. There was no history of drug or alcohol abuse but a family history of schizophrenia was recorded. In the first 22 years of her illness she had a total of five in-patient admissions for acute psychosis. She was last treated with thioridazine up to 500 mg/day for 2 years. At the age of 48 she became acutely psychotic with inappropriate affect, loosening of associations and mannerisms, which led to hospitalization. When she was discharged from hospital, she received fluphenazine 15 mg and thioridazine 100–300 mg daily. The diagnosis was hebephrenic schizophrenia, and she was referred to our clinic. Oral medications were stopped and treatment with fluphenazine enanthate 19.75 mg i.m. every 2 weeks was instituted. Over the next 2 months the depot neuroleptic was gradually increased to 50 mg i.m. every 2 weeks, but she remained severely psychotic. Fluphenazine enanthate was further increased to 125 mg every 2 weeks over the next few months, which did not prevent another admission for acute psychosis. After several months in hospital, she was discharged on fluphenazine enanthate 75 mg i.m. every 2 weeks. This was decreased to a minimal therapeutic dose of 50 mg i.m. every 2 weeks on which she remained for about 18 months. When she missed one injection, another acute relapse began. Fluphenazine enanthate 75 mg i.m. every 2 weeks was given with good effect for 6 months. The death of her daughter precipitated another relapse which failed to respond to a dosage increased up to 112.5 mg i.m. every 2 weeks, and she required hospital admission. After her discharge, she was stable on fluphenazine enanthate 50 mg i.m. every 2 weeks for a further 12 months. She missed a few appointments and began to relapse. The symptoms improved gradually with increasing doses of fluphenazine enanthate up to 225 mg i.m. every 2 weeks, but this was not sufficient to prevent another hospital admission. After discharge she was treated with fluphenazine enanthate 75 mg i.m. every 2 weeks for six months. Another failed appointment led to another relapse. At that time, fluspirilene 25 mg i.m. weekly was started, replacing all other neuroleptics. She recovered rapidly and was stable for 9 months until she missed a weekly injection. Then she relapsed, was readmitted and treated with fluphenazine. After her discharge the medication was changed to fluspiri-

lene 50 mg i.m. per week, and pimozide 80 mg orally twice a week was added gradually over a 6 month period because of worsening psychosis. She again required admission. She had few parkinsonian side effects and was receiving the anticholinergic antiparkinsonian procyclidine 20 mg/day. In hospital, she received haloperidol orally at 40 mg/day and procyclidine 20 mg/day for 10 days with some improvement, at which time she discharged herself from hospital against medical advice. She came back to the clinic 5 weeks later after taking no medication with a transient improvement in positive symptoms of her illness. Fluspirilene 25 mg i.m. per week was reinstituted since she was starting to show signs of relapse. Again, she missed an injection and required admission to hospital. In summary, she had five relapses of acute psychosis over the first 22 years of her illness, whereas over the last 10 years the frequency of relapse has increased to six acute relapses necessitating hospitalization. Indeed she has required two hospitalizations for acute psychosis in the present year. Finally, escalating doses of high potency neuroleptics (fluphenazine or haloperidol) have no more impact on her psychosis. Patient was also not responding anymore to the more atypical neuroleptic, fluspirilene.

Other cases
Data from the two patients presented above and eight other cases of severe supersensitivity psychosis are summarized in Table 2. All patients were diagnosed as schizophrenic according to DSM-III criteria (1980) and were followed at the Allan Memorial Institute in a special follow-up clinic for maintenance neuroleptic treatment. (The clinic consists of about 300 patients, and the following principles of drug treatment are applied: the minimum therapeutic dose of neuroleptic is tentatively prescribed; procyclidine is the only antiparkinsonism drug used; no other psychotropic drugs are given; patients are examined regularly for extrapyramidal side effects and medication is reviewed by the author at each visit.) This paper focuses on patients treated with high neuroleptic doses. The low dose group is also present in our clinic and represents about 10–20% of the patients. The daily neuroleptic dosages given in the clinic in the periods in which these patients were treated were reported in our two epidemiological

TABLE 2

Patient	Age (years)	Sex	Increased frequency of relapse	New symptoms or worsening of original illness	Neuroleptic dosage — Current	1 year previously	2 years previously	3 years previously	Prolactin (ng/ml) 0–10 (men) 0–20 (women)	Tardive dyskinesia[a] 1980 Total score	1982 Total score
A	43	F	+	+++	Pimozide 90 mg p.o. q. 1 day	Haloperidol decanoate 525 mg i.m. q. 2 weeks	Fluphenazine decanoate 175 mg i.m. q. 3 weeks	Fluphenazine decanoate 137.5 mg i.m. q. 2 weeks	68	9	31
B	56	F	+++	+	Fluspirilene 40 mg q. 1 week Pimozide 60 mg p.o. q. 1 week	Fluspirilene 25 mg i.m. q. 1 week	Fluphenazine enanthate 75 mg i.m. q. 3 weeks	Fluphenazine enanthate 50 mg q. 2 weeks	105	21	NA
C	32	M	+++	++	Fluspirilene 50 mg i.m. q. 1 week Pimozide 60 mg p.o. q. Thursday and 20 mg p.o. q. Monday	Fluspirilene 30 mg i.m. q. 1 week	Fluspirilene 40 mg i.m. q. 1 week	Fluphenazine enanthate 225 mg + fluphenazine decanoate 150 mg q. 1 week	29	18	NA
D	51	F	++	+++	Haloperidol decanoate 600 mg i.m. q. 3 weeks	Haloperidol decanoate 550 mg i.m. q. 2 weeks	Fluphenazine enanthate 200 mg i.m. q. 2 weeks	Fluphenazine enanthate 180 mg i.m. q. 2 weeks	76	26	NA
E	55	F	++	+++	Fluspirilene 40 mg i.m. q. 1 week Pimozide 70 mg p.o. q. Tuesday and q. Thursday	Haloperidol decanoate 250 mg i.m. q. 2 weeks	Fluphenazine enanthate 225 mg i.m. q. 2 weeks	Fluphenazine enanthate 75 mg i.m. q. 2 weeks	16.7	12	4
F	47	M	+++	+	Fluspirilene 60 mg i.m. q. 1 week Pimozide 50 mg p.o. q. Tuesday and q. Thursday	Haloperidol decanoate 780 mg i.m. q. 2 weeks	Fluphenazine enanthate 250 mg i.m. q. 2 weeks	Fluphenazine enanthate 225 mg i.m.q. 2 weeks	44	NA	18
G	40	F	+++	++	Haloperidol decanoate 600 mg q. 2 weeks	Haloperidol 20 mg p.o. q.i.d.	Fluphenazine decanoate 240 mg i.m. q. 2 weeks	Fluphenazine enanthate 200 mg i.m. q. 2 weeks	30	25	22

H	56	M	+++	+	Haloperidol 20 mg p.o. b.i.d.	Haloperidol 10 mg p.o. b.i.d.	Fluphenazine enanthate 125 mg i.m. q. 2 weeks	Fluphenazine enanthate 125 mg i.m. q. 2 weeks	NA	7	24
I	55	M	++	+++	Haloperidol 20 mg p.o. q. h.s.	Haloperidol 5 mg p.o. q. h.s.	Fluphenazine HCl 4 mg p.o. q. h.s.	Fluphenazine HCl 5 mg p.o. q. h.s.	27	NA	9
J	38	M	+++	++	Pimozide 20 mg p.o. b.i.d.	Haloperidol decanoate 250 mg i.m. q. 3 weeks Fluspirilene 35 mg q. 1 week Pimozide 10 mg p.o. b.i.d. Haloperidol 10 mg p.o. b.i.d.	Fluspirilene 20 mg q. 1 week Fluphenazine HCl 10 mg p.o. b.i.d.	Fluphenazine enanthate 150 mg i.m. q. 2 weeks Fluphenazine HCl 20 mg p.o. q. h.s.	21	NA	10

[a]Patients were examined by a neurologist during our epidemiological studies of tardive dyskinesia. The scale used was the Extrapyramidal Symptom Rating Scale (ESRS) of Chouinard et al. (1988, 1989). The ESRS total score for tardive dyskinesia ranges from 0 to 42 and each of the seven items ranges from 0 to 6. NA: data not available.

studies of tardive dyskinesia (Chouinard et al., 1978, 1988) and are lower (median: 400 CPZ units in 1978, and mean: 487 CPZ units in 1988) than those published in another major prospective study of tardive dyskinesia (Kane et al., 1982).

All patients reported here received neuroleptics for at least several years. Positive psychotic symptoms appeared in all patients with a decrease in neuroleptic dose, i.e., at the end of an injection interval or when oral or injectable medications were missed. Tolerance to the antipsychotic effects of neuroleptics was evident in all cases summarized in Table 2. For example, Mr. I.'s dosage was increased over three years from oral haloperidol 5 mg to 20 mg daily. Tolerance also occurred with atypical neuroleptics such as pimozide, but was of lesser magnitude. Mr. C. is an example of a case where fluphenazine was switched to fluspirilene 40 mg i.m. weekly which was subsequently increased over 2 years to fluspirilene 50 mg i.m. weekly and pimozide 60 mg p.o. twice a week. Furthermore, increases in high potency neuroleptics such as fluphenazine or haloperidol failed to ameliorate the schizophrenic symptoms. All patients described showed an increased vulnerability to external stresses, which often precipitated new relapses. Six of the ten cases had a marked increase in the frequency of psychotic relapses after several years of neuroleptic treatment. In addition, four of the ten had either a marked worsening of their original illness or the appearance of new schizophrenic symptoms.

DISCUSSION

The prevalence of supersensitivity psychosis appears to be similar to that of tardive dyskinesia (Chouinard et al., 1988), but only a small percentage of patients will develop severe forms of either disorder. Previously, we reported the clinical characteristics of patients presenting neuroleptic-induced supersensitivity psychosis and proposed a number of diagnostic criteria (Chouinard and Jones, 1980). All patients in the present report meet our original criteria as well as those proposed in this paper (Table 1). However, there are clinical characteristics which are more specific for the severe forms of the disorder.

First, there is little or no improvement with increased doses of classical neuroleptics. In fact, increasing doses could lead to worsening of the psychosis. An example is Ms. A. who began to relapse when fluphenazine decanoate 175 mg i.m. every 3 weeks was switched to haloperidol decanoate which was steadily increased over several months from 175 mg to 525 mg i.m. every 2 weeks. She was finally given oral haloperidol but failed to improve. It seemed that even large doses of high potency neuroleptics could not improve the positive psychotic symptoms. Presumably, classical neuroleptics continued to worsen the supersensitivity at the dopamine receptors (supersensitivity effect being greater than blockade). This characteristic of severe supersensitivity psychosis is also illustrated by Ms. B. During a recent relapse fluphenazine enanthate was increased from 50 to 225 mg i.m. every 2 weeks. Even additional oral haloperidol failed to improve the psychosis sufficiently to prevent admission for several months to an inpatient ward. In the other patients presented, escalating doses of classical neuroleptics had little or no effect in controlling schizophrenic symptoms. This is the most important characteristic of severe forms of supersensitivity psychosis; as in severe cases of tardive dyskinesia, neuroleptics can no longer mask the supersensitivity symptoms. This is in contrast with mild to moderate cases where increasing neuroleptics can cover up the two syndromes to a great extent (at least for several years).

Second, there is an increase in the severity of positive/productive psychotic symptoms of the original illness and/or the appearance of new schizophrenic symptoms when neuroleptic medication is decreased. Less severe cases exhibit this characteristic but to a lesser extent. This is evident in Ms. A. who had a good prognosis illness. Following one acute psychotic episode she was stable on neuroleptic treatment for more than 10 years. She worked full time at a demanding job and was married during this time. However, after she developed supersensitivity psychosis, she was unable to live independently nor care for her basic needs until phenytoin treatment was initiated. Originally, she had a paranoid subtype of schizophrenia which is now of the disorganized subtype. Supersensitivity psychosis appears severe in this case since she is presently worse than at any other

time due to the appearance of new schizophrenic symptoms. Three of the other patients reported in this paper have had a marked increase in the severity of their illnesses.

Third, there is an increase in the frequency of relapses. Again, this characteristic is also present in less severe cases but to a lesser degree. For example, Ms. B. had five relapses from 1952 to 1973 requiring hospitalization during the first 22 years of her illness, but had six similar relapses in the last 10 years of which two were in the last year. The rapidity of her psychotic relapses is remarkable: 2 days after missing an injection of fluspirilene she relapsed sufficiently to require hospitalization. High doses of haloperidol orally in the emergency room could not control her psychosis and prevent the last admission. It is also apparent in Table 2 that six other patients had a marked increase in the frequency of relapse. After many years of stable functioning, some required inpatient admission only in recent years. Patients will state that, a few years ago when they were on oral medication, they would relapse every 2–3 years if they did not take their medication. However, since they have been put on injectable neuroleptics, they relapse as soon as they miss one injection.

In the present cases there was clear evidence that the illness was worse after neuroleptic treatment (upon withdrawal) than it had ever been in the past. In previous studies (Chouinard et al., 1982) dosage increases were documented by radioreceptor assay of neuroleptic activity and prolactin measurements. As can be seen in case no. 1, routine prolactin measurements were carried out to ensure absorption of the drugs, and the levels were higher each time the dose was increased.

In our clinic, for standardization procedures, only one central anticholinergic antiparkinsonian drug (procyclidine) is given. All patients presented here were receiving procyclidine, and no psychotropic drugs were given other than the neuroleptics. We have no evidence from either animal studies or human studies that central anticholinergics may produce rebound or withdrawal psychosis upon continuous administration. However, in our 10 year follow-up study (Chouinard et al., 1990), we found in a stepwise multiple regression analysis in a cohort of 98 follow-up patients that neuroleptic dosage increases were good predictors of the presence of supersensitivity psychosis and to a

lesser extent, antiparkinsonian dosage increases. Our explanation is that antiparkinsonian dosage increase was found as a risk factor in the analysis because it was associated with neuroleptic dosage increase.

'Rapid improvement' does not mean that the patients are the same as those described as rapid responders. Usually, what is meant by rapid responders are good prognosis patients, mostly female patients (Garver et al., 1988), who not only respond rapidly but completely to neuroleptics and in whom neuroleptics could be discontinued relatively rapidly (unless the patient has developed supersensitivity psychosis). In fact, some of Garver et al.'s patients (rapid responders) would be placebo responders or patients treated for a few days with neuroleptics which could then be discontinued (Chouinard, 1990). Patients classified as meeting the criteria of 'rapid improvement' are quite different from the rapid responders; rapid improvement means that acute symptoms improve rapidly but not necessarily completely. Both poor and good prognosis patients have this type of response, i.e., masking rapidly positive symptoms. Rapid improvement means that the symptoms are starting to improve, but are not necessarily completely gone. However, some rapid responders may be supersensitive. Rapid improvement is only a minor criterion in the diagnosis of the disorder.

Supersensitivity psychosis, in its clinical appearance, is similar to tardive dyskinesia in that it is thought to be caused by alteration of dopamine receptors secondary to prolonged neuroleptic blockade. Receptor changes in the neostriatum would result in the manifestation of tardive dyskinesia, whereas similar changes in the mesolimbic pathway or other neostriatal regions account for supersensitivity psychosis. This is supported by animal studies where there is also induction of dopamine receptor supersensitivity in the mesolimbic system after long-term neuroleptic treatment (Seeger and Gardner, 1979). As well, in postmortem studies, there is an increase in dopamine receptor binding sites in the mesolimbic pathway which correlates positively with the length of neuroleptic treatment (Owen et al., 1979).

The clinical characteristics of severe cases of supersensitivity psychosis will now be discussed in relation to the following proposed mechanism. Initially, dopamine blockade at the postsynaptic

membrane produces increased receptor binding. Later, new synaptic boutons may appear in the presynaptic receptor, a process termed 'sprouting', leading to the formation of new synaptic structures. These new synapses may result in permanent postsynaptic neuronal overactivity. Using this conceptual model proposed by Staton and Brumback (1980) we can look at stages of irreversibility. Stage I would correspond with an increased number of receptors without reinnervation sprout connections. The symptoms of supersensitivity psychosis appear only after the complete cessation of the neuroleptic or after an abrupt reduction and do not appear if the neuroleptic is gradually withdrawn. The emergence of symptoms is invariably rapid: within 6 weeks if the patient is on oral medication and within 3 months when the drug is administered in the long-acting intramuscular form. This is an important feature differentiating supersensitivity psychosis from a natural relapse of the schizophrenic disorder, which will occur at random within a two year period. Stage II disease is present when there is irreversible alteration of brain structures and function. Sprouting would have occurred producing reinnervation synapses. Here, symptoms appear at the cessation of neuroleptics and subsequently improve but residual symptoms persist. This improvement would coincide with the disappearance of those receptors not in contact with new synaptic boutons. Stage IIA disease is covert, mostly reversible neuronal overactivity. One of the main features is a tolerance to the neuroleptic, i.e., the drug has been gradually increased to achieve the same degree of symptom control. Finally, stage IIB disease is overt irreversible neuronal overactivity where symptoms are present during treatment and remain after cessation of neuroleptic drugs. Sufficient numbers of new synapses have appeared to result in permanent change in brain structure and function. At this stage, the patient presents the core feature of supersensitivity psychosis: relapse shortly after drug discontinuation or dose reduction. When the disorder has advanced to its most severe form (stage III), the patient has entered a vicious circle in which increased doses of neuroleptic lead eventually to worsening of psychosis.

Inasmuch as neuroleptics will treat the symptoms of supersensitivity psychosis, this only perpetuates the process of continued synapse forma-tion. Supersensitivity psychosis appears to be more reversible than tardive dyskinesia (Chouinard, 1983), suggesting stages I and IIA disease in many cases, as conceptualized above. Desensitization of the affected neurons, by a gradual decrease of neuroleptic dosage, often reverses the syndrome. However, there appear to be severe cases (stage III), as reported here, which may be irreversible. Worsening psychosis and frequent relapses make a gradual reduction in neuroleptic dose almost impossible. Moreover, increasing neuroleptic dose has little or no effect in these patients and ultimately leads to worsening of the psychosis.

Therapeutic strategies are limited in these patients. We recommend the use of anticonvulsant drugs such as valproic acid, carbamazepine and phenytoin. In patient no. 1, we used phenytoin with great success. This patient was the first one to be treated for supersensitivity psychosis with antiepileptic drugs. The rationale for giving antiepileptics was to correct a hypothesized pharmacological kindling induced by long-term neuroleptic administration. We suggested that chronic administration of high doses of neuroleptics, drugs known to reduce seizure threshold, were, upon repeated administration, inducing a phenomenon similar to kindling, which anticonvulsant drugs would counteract. In a first paper, we described (Sultan et al., 1990) the first five schizophrenic patients with supersensitivity psychosis that we have treated with antiepileptic drugs. All patients were treated in our special follow-up clinic for schizophrenia (clinic described under case no. 2) in an open label study with regular blood concentrations monitoring and up to 3.5 years. Patients were assessed independently by the treating nurse on a Clinical Global Impression Scale of Improvement. In addition, we recently reported (Chouinard and Sultan, 1990) an additional 30 schizophrenic patients (DSM III criteria, 1980) treated with antiepileptic drugs and found 51% (18 out of 35) were rated as at least much improved. Compliance and dose adjustments were monitored through regular measurements of anticonvulsant blood levels (every 2 weeks for the first 3 months and then every month for the next 3 months and then every 3 months). 60% of patients ($n = 21$) were treated with carbamazepine (dose range: 100–400 mg/day), 12 patients with valproic acid (dose range: 750–1000 mg/day), one patient with

phenytoin 150 mg/day and one patient with combination of valproate 1500 mg/day and carbamazepine 100 mg every 2 days.

For these supersensitivity psychosis patients, we recommend the use of atypical neuroleptics such as benzamides (sulpiride and remoxipride) and diphenylbutylpiperidines (pimozoide and fluspirilene) which have greater affinity for D_2 and D_1 dopamine receptors, adenylcyclase linked (Christensen et al., 1984). The low level of dopamine blockade at presynaptic and D_1 receptors by the diphenylbutylpiperidines and benzamides may explain their lesser efficacy in treating acute schizophrenic symptoms as compared with classical neuroleptics (Chouinard and Annable, 1976, 1982). However, this action may limit the formation of new synapses, which may result in fewer irreversible forms of supersensitivity psychosis. In our experience, we found the diphenylbutylpiperidine neuroleptics easier to decrease over time than classical neuroleptics. Regarding how these patients would do on thioridazine or clozapine, our prediction would be that it would make the syndrome worse. In Scandinavia where clozapine has been available for several years, cases of withdrawal or rebound psychosis have been described (although very few have been published) (Ekblom et al., 1984). As far as thioridazine is concerned, the drug gives multiple withdrawal syndromes upon discontinuation, which makes it difficult to find the minimal therapeutic dose (Chouinard et al., 1984).

Another important therapeutic consideration is the marked vulnerability to stress observed in these patients. Stress often precipitates relapses or contributes to worsening of psychosis. One could predict that patients with high EE (expressed emotion) families would be more likely to develop supersensitivity psychosis. Consequently, admission to an inpatient service or day hospital ward may decrease stress sufficiently to allow less potent atypical neuroleptics to effectively control the psychosis. Thus escalating doses of classical neuroleptics could be avoided.

In patients with the least severe form of the disorder (stage I), gradual decrease of neuroleptics (10% of the dose every 3 months) is indicated to achieve minimal therapeutic dose through gradual desensitization of dopaminergic receptors. In stage II and III, hospitalization, stress management and

abrupt discontinuation of classical neuroleptics by substitution of atypical neuroleptics (diphenylbutylpiperidines and benzamides) may be needed. When the patient is stabilized with the atypical neuroleptic a very slow reduction of the dose should be tried. When the patient presents the most severe form of the disorder, anticonvulsant therapy must be initiated and patient must be kept on a constant neuroleptic dose (no further increase), even though he may still complain of the presence of productive symptoms of psychosis such as delusions or hallucinations. Furthermore, we recommend giving an anticonvulsant such as carbamazepine or valproic acid instead of increasing the neuroleptic dose once the diagnosis of supersensitivity psychosis is made.

Recognition of the concept of supersensitivity psychosis is important since it leads to the minimal therapeutic dose by a gradual decrease of neuroleptic dosage which makes it possible to distinguish between true schizophrenic relapse and supersensitivity psychotic relapse. The latter occurs at an early stage (withdrawal type — stage I) when medication is rapidly discontinued but does not appear during gradual reduction of medication and at an early stage responds rapidly to the antipsychotic drug. In conclusion, the recognition of supersensitivity psychosis and its subtypes is important in the drug treatment of schizophrenic patients in order to avoid the most severe forms of the disorder.

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