The Emergence of Social Phobia During Clozapine Treatment and Its Response to Fluoxetine Augmentation

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Background: The underlying neurochemical basis of social phobia has yet to be fully explained, but there are suggestions of serotonergic and dopaminergic dysfunction. The atypical neuroleptic clozapine has been reported to induce anxiety symptoms, probably owing to its effect on serotonergic pathways. We report 12 cases of schizophrenic patients who developed social phobia during clozapine treatment.

Method: Patients were assessed using the Structured Clinical Interview for DSM-III-R, Patient Version, Scale for the Assessment of Negative Symptoms, Scale for the Assessment of Positive Symptoms, the Liebowitz Social Phobia Scale, and the Brief Psychiatric Rating Scale. They were reevaluated after 12 weeks of cotreatment with clozapine and fluoxetine.

Results: In 8 of the 12 cases, symptoms responded (≥ 35% reduction in Liebowitz Social Phobia Scale score) with an adjunctive regimen of fluoxetine.

Conclusion: Data are discussed in light of neurochemical mechanisms and cognitive adaptations that could explain the onset of anxiety spectrum disorders (such as social phobia) in clozapine-treated schizophrenic subjects during remission of psychotic symptoms.

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Several studies have suggested a dopaminergic dysregulation[1] in social phobia: markedly reduced striatal dopamine (D) reuptake site densities have been reported with single photon emission computed tomography (SPECT),[2] anomalies in basal ganglia volumes have been detected through the use of magnetic resonance imaging (MRI),[3] and alterations in cortical-thalamic-caudate areas have been revealed with magnetic resonance spectroscopy.[4] Furthermore, 2 studies have shown an increased rate of social phobia in patients who later developed Parkinson's disease.[5,6] Social phobia, which has received little study, is emerging as a common comorbid disorder in schizophrenia: on the basis of data obtained from the landmark National Comorbidity Survey, Kendler et al.[7] reported a lifetime comorbidity rate of 39.5%, while Cosoff and Hafner[8] reported a rate of 17%, and Cassano et al.[9] reported a rate of 16% among patients with schizophrenia spectrum disorders. Social phobic symptoms precipitated by clozapine treatment have not been reported until now.

The atypical antipsychotic clozapine is characterized by the combination of relatively high D_1, low D_2, and very high serotonin-2 ($5\text{-}HT_2$) receptor occupancy values,[10] even at low serum concentrations. This neurochemical profile may explain the lack of extrapyramidal side effects. Recently, however, a certain amount of evidence has been collected about anxiety disorders that appear during clozapine treatment, probably related to a secondary serotonergic dysfunction. In fact, treatment with clozapine has been associated with the development, de novo, of obsessive-compulsive symptoms in up to 10% of schizophrenic adults[11–13] and adolescents.[14] These obsessive-compulsive symptoms in schizophrenic patients seem responsive to an adjunctive selective serotonin reuptake inhibitor (SSRI) regimen.[13,15,16]

In this article we report on a group of schizophrenic patients, previously resistant or intolerant to typical neuroleptics, who developed social phobic symptoms 9 to 20 weeks after the beginning of clozapine treatment and who required pharmacologic augmentation.

METHOD

Twelve patients fulfilling DSM-III-R criteria for the paranoid type of schizophrenic disorder were considered for the present study. These patients represent 10% of a larger schizophrenic group longitudinally evaluated for separate neurophysiologic and psychopathologic research,[17,18] and 42.8% of the subgroup of patients who were treated with clozapine (N = 28).

Table 1. Clinical Characteristics of 12 Schizophrenic Patients Who Developed Social Phobic Symptoms During Clozapine Treatment[a]

Patient	Sex	Age, y	Lifetime Comorbid Diagnoses	Onset of Social Phobia After Clozapine (wk)	SAPS Sum of Global Scores	SANS Sum of Global Scores	BPRS Total Score	LSPS FBF Total Score	LSPS Anxiety/ Fear Score	LSPS Withdrawal Score	Fluoxetine (mg/d)	LSPS Reduction After 12 Weeks of Fluoxetine (%)
1	M	28	Substance abuse	16	5	6	36	32	46	57	40	19.4
2	M	19	Simple phobia	12	3	5	19	16	29	32	40	49.2
3	M	24	Substance abuse	13	4	2	21	18	49	45	30	55.3
4	F	22	…	16	9	7	35	27	37	44	30	60.5
5	F	22	…	9	2	2	27	10	37	47	40	21.4
6	M	23	…	15	4	4	18	38	50	57	30	20.6
7	F	28	Panic disorder, substance abuse	18	3	2	31	20	28	38	40	12.1
8	F	23	…	15	5	4	24	19	51	51	50	45.1
9	F	27	…	20	8	6	38	24	26	36	30	41.9
10	M	20	Obsessive-compulsive disorder	14	7	5	36	31	29	38	30	37.3
11	M	29	…	18	7	4	36	9	44	47	30	50.5
12	M	24	Obsessive-compulsive disorder	12	5	9	30	22	36	44	40	60

[a]This assessment was made at the time of the diagnosis of comorbid social phobia, before starting fluoxetine treatment. Abbreviations: BPRS = Brief Psychiatric Rating Scale, FBF = Frankfurter Beschwerde Fragebogen, LSPS = Liebowitz Social Phobia Scale, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms.

All the subjects had been assessed by the Structured Clinical Interview for DSM-III-R, Patient Version (SCID-P) for Axis I diagnoses. The group consisted of 7 men and 5 women who started clozapine treatment after an unsatisfactory response to at least 2 different antipsychotic drugs or who were intolerant of typical neuroleptics and who developed social phobia during the clozapine regimen according to DSM-III-R criteria. No patient had reported social phobic symptoms during previous typical neuroleptic treatments.

These 12 schizophrenic patients did not differ significantly in demographic or clinical terms from the rest of the patients under clozapine treatment who did not show social phobia during the treatment. Patients were all right-handed, and their mean ± SD age was 24.12 ± 3.26 years (range, 19–28 years). The mean ± SD duration of illness, at recruitment, was 4.61 ± 2.24 years, and the mean ± SD number of weeks of prior hospitalization was 3.51 ± 3.60. The mean ± SD educational level was 8.93 ± 3.41 years, and the mean ± SD daily stabilized dose of clozapine was 325 ± 63 mg (range, 250–400 mg). No patient received other drugs during treatment with clozapine. Follow-up evaluations, by means of clinical interviews conducted by expert psychiatrists (S.P., L.Q., A.R.) with at least 10 years of clinical practice, were conducted every 2 weeks for the first 3 months, then monthly. In all cases, when the emergence of social phobia was assessed during follow-up evaluations, the therapy regimen was augmented with adjunctive SSRI fluoxetine (mean ± SD dose = 35.83 ± 6.68 mg/day). Fluoxetine was chosen from among the SSRIs on the basis of previous studies about its efficacy in social phobic symptoms,[19–22] the considerable literature data,[23–26] and our own clinical experience of its coadministration with clozapine. Patients were reevaluated after 12 weeks of treatment with clozapine and fluoxetine. All the patients were examined as outpatients in the day-hospital of the Institute for Neurosciences (Florence, Italy) following written informed consent.

The Brief Psychiatric Rating Scale (BPRS),[27] the Scale for the Assessment of Negative Symptoms (SANS),[28] the Scale for the Assessment of Positive Symptoms (SAPS),[28] the Liebowitz Social Phobia Scale (LSPS),[29] and the Frankfurter Beschwerde Fragebogen (FBF)[30] for the assessment of subjective cognitive complaints were employed.

RESULTS

Six of 12 schizophrenic patients exhibited lifetime comorbidity for psychiatric disorders, namely obsessive-compulsive disorder (N = 2), substance abuse (N = 3), panic disorder (N = 1), and simple phobia (N = 1) (Table 1). None of the patients fulfilled the criteria for a lifetime diagnosis of social phobia. Social phobia was diagnosed in this group of patients after a mean ± SD duration of 14.83 ± 3.07 weeks (range, 9–20 weeks) from the beginning of clozapine treatment. At the time of the social phobia comorbid diagnosis, the patients' mean ± SD sum of SAPS global scores was 5.17 ± 2.17, the mean ± SD sum of SANS global scores was 4.67 ± 2.15, and the mean ± SD BPRS total score was 29.25 ± 7.27. The LSPS showed a mean ± SD anxiety/fear subscore (range of scale, 0–72) of 38.5 ± 9.26 and a mean ± SD withdrawal subscore (range of scale, 0–72) of 44.7 ± 7.87. These scores resemble the elevated scores of subjects with moderate-to-severe social phobia. The FBF mean ± SD score was 22.2 ± 8.76, indicating mild subjective cognitive dysfunction. After 8 weeks of treatment

Table 2. Clinical Status in Schizophrenic Patients Assessed at After 12 Weeks Taking Clozapine Plus Fluoxetine

Scale	Score Mean	Score SD	Paired t Test (df = 11)	p
SAPS (sum of global scores)	5.02	2.24	1.01	NS
SANS (sum of global scores)	4.06	1.65	2.03	NS
BPRS (total score)	27.81	6.32	2.12	NS
FBF (total score)	20.53	7.12	1.65	NS
LSPS				
Fear/anxiety	24.81	7.65	2.67	< .05
Withdrawal	35.67	7.14	2.90	< .05

with fluoxetine, no significant variations were found in the mean BPRS and SAPS scores, while a significant reduction was found in SANS anhedonia (paired $t = 2.36$, $df = 11$, $p < .05$) and avolition (paired $t = 2.73$, $df = 11$, $p < .05$) scores. After 8 weeks of fluoxetine treatment, 4 of 12 patients showed an amelioration of social phobic symptoms of < 25% according to the LSPS, while 8 patients saw a ≥ 35% reduction in LSPS total score, of whom 3 patients saw a > 50% reduction. The LSPS mean score improved significantly after 12 weeks of fluoxetine treatment, in both fear/anxiety and withdrawal scores (Table 2).

A CASE REPORT

Mr. A (patient 3), a 24-year-old student, had a 7-year history of schizophrenia, chronic paranoid type. He had been hospitalized twice (at the ages of 18 and 20 years) and manifested a good response to typical neuroleptics (haloperidol plus chlorpromazine) at various phases, but his treatment compliance was complicated by low-dose–induced extrapyramidal symptoms (EPS) that led the patient to drop treatment after a 4- to 6-month period. Clozapine treatment (up to 250 mg/day) was followed by a reduction in the severity of psychotic symptoms (BPRS reduction of 45% after 6 weeks, 65% after 8 weeks). There were no significant extrapyramidal symptoms or complaints, and compliance was good. After 4 months of treatment, Mr. A described the emergence of phobic anxiety regarding various social situations. He experienced difficulties in speaking to others, particularly when among a group of friends, and shyness toward women, and he left the band in which he played the guitar. In these situations, he reported tremor, tachycardia, and sweating, and an increasing withdrawal from these situations was observed. His major complaint was shame. These symptoms had not been present during previous treatments. Clinical assessment demonstrated stabilized remission of psychotic symptoms (BPRS reduction of 70%), no EPS, reduction of subjective experience of cognitive complaints (FBF score reduction of 67%), social phobic symptoms (LSPS scale elevation: performance, 54%; withdrawal, 59%). Fluoxetine (up to 30 mg/day) was added. Social anxiety was substantially reduced after 40 days of SSRI treatment.

DISCUSSION

To our knowledge, this study is the first reporting the onset of social phobia in schizophrenic patients after clozapine treatment. None of the patients had experienced social phobic symptoms during previous traditional neuroleptic regimens. In this group of patients, fluoxetine ameliorated social phobic symptoms significantly in 8 of the 12 subjects (≥ 35% reduction of LSPS score).

Cassano et al.[9] found that social phobia has a 16.1% lifetime prevalence among schizophrenia spectrum disorders. This finding demonstrates that the co-occurrence of social phobic symptoms in schizophrenic patients is a significant phenomenon, even though social phobia has been underreported in the past because it was undistinguished from schizophrenic psychopathology. However, the lifetime comorbidity does not explain the precipitation of social phobia in our group of schizophrenic patients as reported by SCID-P assessment. Social phobia, as a pharmacologic side effect, was described as associated with haloperidol in patients with Tourette's disorder.[31] This finding, although limited to Tourette's disorder patients, gave rise to the hypothesis that central dopaminergic functions, antagonized by haloperidol, were involved in the precipitation of social phobic symptomatology. The role of dopamine in the symptoms of social phobia was also supported by the findings that novelty seeking and exploratory behavior are correlated with the striatal uptake of dopamine[32] and that long alleles of the D_4 receptor gene significantly characterized novelty-seeking individuals more than short D_4 receptor gene alles.[33] Lower striatal dopamine reuptake site densities were also found using SPECT in social phobic patients.[2]

Other studies have suggested the involvement of a serotonergic central dysfunction in the pathogenesis of social phobia.[19,34] It is possible that the social phobic disorder phenotype corresponds to an etiologic heterogeneity involving various neurotransmitter systems. Regarding clozapine, its particular pharmacochemical profile (higher D_1 than D_2 antagonism, 5-HT_2 antagonism) suggests that a serotonergic mechanism could be involved in certain undesired effects such as the emergence of obsessive-compulsive symptoms and, as found in our group, social phobic symptoms in some treated schizophrenics. We can speculate that some vulnerable schizophrenic patients could develop social phobia as a combined effect of dopaminergic and serotonergic loss of balance produced by clozapine. Both the emergence and latency mechanisms of social phobia observed in our group of schizophrenic patients are still unclear.

Fluoxetine appeared effective in ameliorating social anxiety in a significant subgroup of our schizophrenic pa-

tients. Systematic clinical reports and controlled trials have reported fluoxetine to be effective in the treatment of social phobia.[19,35] We did not monitor the plasma clozapine levels in our patients, but the possibility of a variation of plasma clozapine and/or norclozapine levels during fluoxetine cotreatment should be considered. The primary metabolism of clozapine is controlled by the cytochrome enzyme P450 1A2 (CYP1A2), which is not influenced by fluoxetine. However, fluoxetine inhibits the cytochrome CYP2D6, which is believed to be involved in the metabolism of the primary metabolites of clozapine. This CYP2D6 inhibition explains previous observations of increased plasma levels of clozapine analytes with fluoxetine,[36,37] despite the failure in other studies to find this pharmacokinetic interaction.[24] Paradoxically, we cannot exclude that the beneficial effect of adjunctive fluoxetine on social phobic symptoms in some schizophrenic patients could be due to an increase of plasma clozapine or norclozapine concentrations. Further studies are needed to relate the emergence and amelioration of this effect of clozapine with variations in its plasma levels.

Finally, from a psychopathologic point of view, the emergence of social phobic symptoms in clozapine-treated schizophrenics could be explained as the arrangement of a complex coping strategy after a cognitive "reset." The reduction of psychotic phenomena and the subjective cognitive improvement in memory, attention, and language, together with improved insight[18] during clozapine treatment, load the patient with a certain amount of social urge and expectations, coupled with incompletely formed relational and interpersonal competence and fitness. On the basis of this discrepancy, the onset of social phobic symptoms during the symptom-free phases is possible, as confirmed by Stern et al.[38] who did not find a correlation between severity of social phobic symptoms and positive and negative symptoms in schizophrenia.

Social inhibition, as recently hypothesized by Himmelhoch,[39] could also be related to a part or similar physiologic substrata of Parkinson's disease. Excessive social anxiety,[40] social dysfunction, and avoidant symptoms[41] have also been found to be frequent among the relatives of schizophrenic probands. Temperamental traits (i.e., avoidant or schizoid) could also favor the onset of social phobia in our group of patients. Further controlled studies are warranted to confirm social phobia as a trait elicited by atypical neuroleptics during psychosis remission in a subgroup of schizophrenic patients.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), fluoxetine (Prozac), haloperidol (Haldol and others).

REFERENCES

1. Potts NLS, Davidson JRT. Social phobia: biological aspects and pharmacotherapy. Prog Neuropsychopharmacol Biol Psychiatry 1992;16:635–646
2. Tiihonen J, Kuikka J, Bergstrom K, et al. Dopamine reuptake site densities in patients with social phobia. Am J Psychiatry 1997;154:239–242
3. Potts NLS, Davidson JRT, Krishnan KR, et al. Magnetic resonance imaging in patients with social phobia. Psychiatry Res 1994;52:35–42
4. Davidson JRT, Krishnan KRR, Charles HC, et al. Magnetic resonance spectroscopy in social phobia: preliminary findings. J Clin Psychiatry 1993;54(12, suppl):19–25
5. Lauterbach EC, Duvoisin RC. Anxiety disorders in familial parkinsonism [letter]. Am J Psychiatry 1987;148:274
6. Stein MB, Heuser IJ, Juncos JL, et al. Anxiety disorders in patients with Parkinson's disease. Am J Psychiatry 1990;147:217–220
7. Kendler KS, McGuire M, Gruenberg AM, et al. Schizotypal symptoms and signs in the Roscommon Family Study: their factor structure and familial relationship with psychotic and affective disorders. Arch Gen Psychiatry 1995;52:296–303
8. Cosoff SJ, Hafner RJ. The prevalence of comorbid anxiety in schizophrenia, schizoaffective disorder and bipolar disorder [see comments]. Aust N Z J Psychiatry 1998;32:67–72
9. Cassano GB, Pini S, Saettoni M, et al. Occurrence and clinical correlates of psychiatric comorbidity in patients with psychotic disorders. J Clin Psychiatry 1998;59:60–68
10. Nordstrom AL, Farde L, Nyberg S, et al. D1, D2, and 5-HT2 receptor occupancy in relation to clozapine serum concentration: a PET study of schizophrenic patients. Am J Psychiatry 1995;152:1444–1449
11. Patil VJ. Development of transient obsessive-compulsive symptoms during treatment with clozapine [letter]. Am J Psychiatry 1992;149:272
12. Baker RW, Chengappa KNR, Baird JW, et al. Emergence of obsessive compulsive symptoms during treatment with clozapine. J Clin Psychiatry 1992;53:439–442
13. Patel B, Tandon R. Development of obsessive-compulsive symptoms during clozapine treatment [letter, comment]. Am J Psychiatry 1993;150:836
14. Levkovitch Y, Kronnenberg Y, Gaoni B. Can clozapine trigger OCD? [letter] J Am Acad Child Adolesc Psychiatry 1995;34:263
15. Allen L, Tejera C. Treatment of clozapine-induced obsessive-compulsive symptoms with sertraline [letter]. Am J Psychiatry 1994;151:1096–1097
16. Poyourovsky M, Hermesh H, Weizman A. Fluvoxamine treatment in clozapine-induced obsessive-compulsive symptoms in schizophrenic patients. Clin Neuropharmacol 1996;19:305–313
17. Pallanti S, Quercioli L, Pazzagli A. Relapse in young schizophrenic patients: a prospective study of stressful life events, P300 measures, and coping. Am J Psychiatry 1997;154:792–798
18. Pallanti S, Quercioli L, Pazzagli A. Effects of clozapine on awareness of illness and cognition in schizophrenia. Psychiatry Res 1999;86:239–249
19. Van Ameringen M, Mancini C, Streiner DL. Fluoxetine efficacy in social phobia. J Clin Psychiatry 1993;54:27–33
20. Black B, Uhde TW. Treatment of elective mutism with fluoxetine: a double-blind, placebo-controlled study. J Am Acad Child Adolesc Psychiatry 1994;33:1000–1006
21. Dummit SE, Klein RG, Tancer NK, et al. Fluoxetine treatment of children with selective mutism: an open trial. J Am Acad Child Adolesc Psychiatry 1996;35:615–621
22. Taylor LvH. Fluoxetine efficacy in social phobia [letter]. J Clin Psychiatry 1997;58:124–125
23. Centorrino F, Baldessarini RJ, Kando J, et al. Serum concentrations of clozapine and its major metabolites: effect of cotreatment with fluoxetine or valproate. Am J Psychiatry 1994;151:123–125
24. Eggert AE, Crimson ML, Dorson PG. Lack of effect of fluoxetine on plasma clozapine concentrations [letter]. J Clin Psychiatry 1994;55:454–455
25. Buchanan RW, Kirkpatrick B, Bryant N, et al. Fluoxetine augmentation of clozapine treatment in patients with schizophrenia. Am J Psychiatry 1996;153:1625–1627
26. DeVane CL, Nemeroff CB. Psychotropic drug interactions. Primary Psychiatry 1998;5:36–75
27. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychol Rep 1962;10:799–812
28. Andreasen NC. Schizofrenia: Scale per la Valutazione dei Sintomi Positivi e Negativi. Moscarelli M, Maffei C, eds. Milan, Italy: Cortina; 1987
29. Liebowitz MR. Social phobia. In: Klein DF, ed. Modern Problems in Pharmacopsychiatry: Anxiety. Basel, Switzerland: Karger; 1987:141–173
30. Sullwold L. FBF: Questionario dei Sintomi-Base. Stanghellini G, Strik WK, Cabras PL, eds. Florence, Italy: Organizzazioni Speciali; 1991
31. Mikkelsen EJ, Detlor J, Cohen DJ. School avoidance and social phobia

triggered by haloperidol in patients with Tourette's disorder. Am J Psychiatry 1981;138:1572–1576
32. Cloninger CR, ed. The Temperament and Character Inventory (TCI): A Guide to Its Development and Use. St. Louis, Mo: Center for Psychobiology of Personality; 1994
33. Benjamin J, Patterson C, Greenberg BD, et al. Population and familial association between the D4 dopamine receptor gene and measures of novelty seeking. Nature Genetics 1996;12:81–84
34. Tancer ME. Neurobiology of social phobia. J Clin Psychiatry 1993;54 (suppl 12):26–30
35. Black B, Uhde TW, Tancer ME. Fluoxetine for the treatment of social phobia. J Clin Psychopharmacol 1992;12:293–295
36. Centorrino F, Baldessarini RJ, Frankenburg FR, et al. Serum levels of clozapine and norclozapine in patients treated with selective serotonin reuptake inhibitors. Am J Psychiatry 1996;153:820–822
37. Spina E, Avenoso A, Facciola G, et al. Effect of fluoxetine on the plasma concentrations of clozapine and its major metabolites in patients with schizophrenia. Int Clin Psychopharmacol 1998;13:141–145
38. Stern RG, Frank D, Mera H, et al. High social phobia scale scores in schizophrenia do not correlate with psychosis symptom severity scores. In: New Research Program and Abstracts of the 152nd Annual Meeting of the American Psychiatric Association; May 18, 1999; Washington, DC. Abstract NR239:131
39. Himmelhoch JM. The paradox of anxiety syndromes comorbid with bipolar illnesses. In: Goldberg JF, Harrow M, eds. Bipolar Disorder: Clinical Course and Outcome. Washington, DC: American Psychiatric Association Press; 1999:237–258
40. Torgersen S, Onstad S, Skre I, et al. True schizotypal personality disorder: a study of co-twins and relatives of schizophrenic probands. Am J Psychiatry 1993;150:1661–1667
41. Kendler KS, Gallagher TJ, Abelson JM, et al. Lifetime prevalence, demographic risk factors, and diagnostic validity of nonaffective psychosis as assessed in a US community sample: The National Comorbidity Survey. Arch Gen Psychiatry 1996;53:1022–1031