Clozapine Withdrawal–Emergent Dystonias and Dyskinesias: A Case Series

Shakeel Ahmed, M.D.; K. N. Roy Chengappa, M.D., F.R.C.P.C.; Venkat Rama Naidu, M.D.; Robert W. Baker, M.D.; Haranath Parepally, M.D.; and Nina R. Schooler, Ph.D.

Background: Severe psychotic decompensation during clozapine withdrawal has been reported previously. Less attention has been paid to movement disorders following abrupt clozapine withdrawal. This report describes 4 subjects who experienced severe dystonias and dyskinesias upon abrupt clozapine withdrawal.

Method: Current and past medical records of 4 subjects with DSM-IV schizophrenia or schizoaffective disorder were reviewed.

Results: All subjects had a history of neuroleptic-induced extrapyramidal symptoms, 1 had a history of severe dystonias, and 1 had neuroleptic malignant syndrome. All had mild orolingual tardive dyskinesia prior to clozapine treatment. All subjects had received clozapine for several months, and 3 of the 4 subjects stopped clozapine abruptly. Two subjects experienced cholinergic rebound symptoms within hours, which resolved quickly. These subjects had severe limb-axial and neck dystonias and dyskinesias 5 to 14 days after clozapine withdrawal. Two subjects were unable to ambulate, and 1 had a lurching gait. Two gagged while eating or drinking. Two subjects were returned to clozapine, 1 was started on low-dose risperidone treatment, and 1 was started on olanzapine treatment. All experienced significant improvements in their mental state and movement disorders.

Conclusion: Severe movement disorders, which may be worse than the movements prior to clozapine treatment, and cholinergic rebound symptoms may occur upon abrupt clozapine withdrawal and must be recognized in addition to the severe psychotic decompensation noted in some patients. Patients, families, and caregivers must be alerted to this possibility. Where possible, a slow clozapine taper, the use of anticholinergic agents, and symptomatic treatment may help minimize these withdrawal symptoms, and reintroduction of clozapine or treatment with the newer atypical agents can help in the clinical management of these symptoms.

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Received Aug. 20, 1997; accepted Jan. 15, 1998. From the Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, School of Medicine, Pittsburgh, Pa. (Drs. Ahmed, Chengappa, Parepally, and Schooler), the Special Studies Center, Mayview State Hospital, Bridgeville, Pa. (Drs. Chengappa and Parepally), the Veterans Affairs Medical Center, Highland Drive, Pittsburgh, Pa. (Dr. Naidu), and the Department of Psychiatry & Human Behavior, University of Mississippi Medical Center, Jackson (Dr. Baker).

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Reprint requests to: K. N. Roy Chengappa, M.D., F.R.C.P.C., Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, Special Studies Center, Mayview State Hospital, 3811 O'Hara St., Pittsburgh, PA 15213-2593 (e-mail: chengappakn@msx.upmc.edu).

There is renewed interest and debate concerning neuroleptic withdrawal in patients with schizophrenia.[1–7] Most of the data on withdrawal relate to the older neuroleptic drugs. However, anecdotal reports on clozapine-withdrawal psychoses and related phenomena have begun to appear.[8–15]

Several clinical and neurochemical effects other than the reemergence of psychoses have been described upon neuroleptic withdrawal.[1] These include, but are not limited to, cholinergic rebound (nausea, vomiting, drooling, diarrhea, malaise, diaphoresis, and insomnia), withdrawal-emergent dyskinesia and akathisia, and changes in sleep architecture, neurotransmitters and their metabolites, and neuropsychological test performance.

Described below are 4 patients who experienced adverse physical phenomena after clozapine withdrawal. All had withdrawal dyskinesia and/or dystonia.

METHOD

Medical charts of all current and past psychiatric admissions of the 4 patients described below were reviewed. These 4 subjects were drawn from approximately 350 patients in 2 hospitals who received clozapine after its approval in the United States. However, it cannot be definitively stated that the authors knew of all cases of clozapine withdrawal–emergent movement disorders that may have occurred at these 2 institutions, especially because the milder forms may not have come to clinical attention.

RESULTS

Case 1

Mr. A, a 37-year-old African American man with DSM-IV chronic paranoid schizophrenia, had numerous hospitalizations over 18 years. He responded incompletely and adhered poorly to a variety of oral and depot neuroleptic drugs, and he experienced severe extrapyramidal side effects and akathisia on high-potency neuroleptic drugs. Eventually, Mr. A developed mild tardive dyskinesia evident mainly in both hands. He received his first clozapine trial in 1990, reaching a dose of 500 mg/day. The mild dyskinetic movements previously noted in both hands were no longer evident after 4 months of clozapine treatment. Chronic auditory hallucinations persisted, but at a lower intensity. He was readmitted approximately yearly for short periods mainly for depressive symptoms and suicidality.

In 1993, Mr. A had discontinued clozapine abruptly for 5 days and was then readmitted. He had experienced severe auditory and visual hallucinations, restlessness, and diaphoresis, and he had lordotic and twisting dystonias of his trunk, pill-rolling hand tremors, and a lurching abnormal gait. He had mild orofacial dyskinetic movements, and the mild dyskinetic movements in both hands reemerged. A urine screen for drugs and alcohol was negative. Mr. A was restarted on clozapine therapy, and although trunkal and extremity dyskinesia decreased and disappeared in 2 weeks, he continued to show pill-rolling movements and jerky choreiform movements of the hands, of which he was unaware. Clozapine was titrated to 900 mg/day, and the remaining abnormal movements and gait abnormality disappeared in the following week. Mr. A's mental status improved significantly over 1 month. He developed compulsive hand washing, which responded to the addition of 100 mg/day of sertraline.

Case 2

Ms. B, a 37-year-old African American woman with a 20-year history of schizoaffective disorder, was stabilized on clozapine therapy (250 mg/day) after having failed to respond to several neuroleptic drugs over the years. She had extrapyramidal side effects and mild orolingual tardive dyskinesia while taking older neuroleptic drugs. The orolingual tardive dyskinesia was barely evident at the time of discharge, nearly 6 weeks after clozapine initiation.

Two months after discharge, Ms. B began to refuse weekly blood monitoring, and clozapine was discontinued abruptly after admission to another hospital. She was given fluvoxamine for obsessions and lorazepam and was discharged 1 week later. However, her sister found her to be confused and shaky and so brought her to our hospital. At readmission, Ms. B was diaphoretic, mute, disoriented to time and place, and refusing of fluids and food, and she vomited twice. She had moderately severe trunkal dyskinesia, constant lip smacking and tongue thrusting, and choreiform movements of both hands. Because of the severe tongue thrusting, it was not clear if the milder orolingual dyskinesia that was present previously had recurred. Ms. B could follow simple oral commands. Benztropine was administered at a dosage of 3 mg/day, lorazepam was increased to 2 mg/day, and fluvoxamine was discontinued. The choreiform movements of the hands, lip smacking, tongue thrusting, and trunkal dyskinesia decreased significantly and disappeared in 4 days. Risperidone was started at 2 mg/day, and Ms. B was discharged from the hospital 3 weeks later with no evidence of these withdrawal-emergent movements. Benztropine was tapered and discontinued prior to discharge.

Case 3

Ms. C, an 18-year-old white woman with a 6-year history of undifferentiated schizophrenia, was admitted for the second time to a state hospital because of agitation and hallucinations. She had mild orofacial tardive dyskinesia on admission. Previous medication trials were notable for severe dystonia secondary to treatment with high-potency neuroleptic agents. Previous magnetic resonance imaging results and electroencephalogram were normal. Ms. C was initiated on clozapine therapy, which was titrated to a dose of 400 mg/day over several weeks. Psychotic symptoms improved, and the orofacial tardive dyskinesia and extrapyramidal symptoms resolved. Clozapine was tapered and discontinued over a 2-month period for reasons that are unclear. Ms. C was then treated with perphenazine up to 12 mg/day for 2 weeks, during which time mild dyskinetic movements of the hands and neck were noted.

Risperidone was then added and titrated to 5 mg/day over the next 4 weeks, and perphenazine was discontinued over a week. Ms. C developed severe choreoathetoid and dystonic movements of the neck, trunk, and hips. These movements increased until she was unable to sit in a chair owing to neck dystonias and opisthotonic arching of the back and trunk. She gagged while eating and had hemiballismic movements of her limbs. Notably absent were hand and body tremors and distal limb dyskinesias. Orofacial dyskinesias were very mild, and tongue movements were absent. All movements ceased during sleep.

Risperidone was discontinued, and benztropine (oral and intramuscular in doses up to 6 mg/day) did not affect the dystonias. Lorazepam helped minimally. Vitamin E in doses up to 1600 IU/day produced equivocal results. Results of laboratory evaluations of serum ceruloplasmin, liver function, thyroid functions and antibodies, lupus-related antibodies, and erythrocyte sedimentation rate, results of antistreptolysin (ASO) titers and a slit-lamp examination, and electrocardiogram were normal or negative. Ms. C was eventually restarted on clozapine therapy 5 months after it was discontinued and was transferred to

a university neurology service for further evaluation. Tests for Huntington's disease and rare leukodystrophies were negative. In addition to clozapine, baclofen was added at 40 mg/day, trihexyphenidyl at 20 mg/day, and lorazepam at 4 mg/day.

On Ms. C's return to the psychiatry service, trihexyphenidyl and lorazepam were tapered over 4 months uneventfully. Clozapine was titrated to 600 mg/day. The choreoathetoid and dystonic movements improved gradually such that ambulation was possible with assistance. Opisthotonic movements and orofacial dyskinesias resolved after 2 months. Gait improved next, although she needed assistance while negotiating steps and retroflexive movements of the trunk would interrupt the smoothness of gait. Eating on her own was the next noted improvement. She was then able to sit on a chair. Some residual neck movements and an unsteady gait persisted. Six months after restarting clozapine, Ms. C could ambulate easily without assistance and eat without difficulty. Except for occasional side-to-side neck movements and mild akathisia, her neurologic symptoms are in remission. Ms. C's psychiatric condition improved significantly and led to eventual discharge from the hospital.

Case 4

Mr. D, a 60-year-old white man with schizoaffective disorder and mild mental retardation who resided at a long-term state hospital ward, was initiated on clozapine therapy because of several adverse effects from traditional neuroleptic drugs including orofacial tardive dyskinesia, extrapyramidal side effects, and neuroleptic malignant syndrome. Clozapine was titrated to 350 mg/day, and extrapyramidal symptoms and orofacial dyskinesia resolved in 3 months. Seventeen months after initiation of clozapine, fluoxetine was added for a major depressive episode. Owing to excess sedation, the clozapine dosage was halved over the next 18 months. Mr. D developed pneumonia and was transferred to another hospital. On the basis of a clinical picture of fever, diaphoresis, possible rigidity, tachypnea, tachycardia, an elevated creatine kinase level of 16,000 IU/L, and leukocytosis, a consulting psychiatrist diagnosed clozapine-induced neuroleptic malignant syndrome. Clozapine was abruptly stopped, although some of these adverse effects may have been due to pneumonia. Mr. D was returned to the state hospital on treatment with fluoxetine and lorazepam.

Ten days after his return, Mr. D was noted to have severe dystonias and dyskinesias affecting his face, neck, head, and trunk. He had frequent tongue thrusting, and he gagged while eating. Choreoathetoid movements of the distal hands and feet also were noted, and he had an ataxic gait and was unable to ambulate. Laboratory and other examinations as noted in Ms. C were done, and results were negative. Trihexyphenidyl up to 10 mg/day and lorazepam up to 6 mg/day had no effect. Mr. D was transferred to the neurology service, as was described in case 3 above. Baclofen was added at 40 mg/day, and lorazepam and trihexyphenidyl were discontinued. He was returned to the state hospital 3 days later and had the same movements as previously described within hours of return. Mr. D was then transferred to a community hospital and treated with reserpine at an eventual dose of 0.5 mg/day, and baclofen was discontinued. Olanzapine at 10 mg/day and lorazepam were added. Over the next 4 weeks, trunkal dyskinesia, tongue thrusting, and neck dystonias disappeared, and Mr. D could walk and eat independently. Minimal orofacial and hand dyskinesias persisted for an additional 4 weeks and then resolved. His mental status improved significantly as well.

DISCUSSION

Neuroleptic drug withdrawal encompasses several distinct and sometimes overlapping syndromes.[16] Brooks[17] described these syndromes soon after the traditional neuroleptic agents were introduced into the marketplace, and similar reports[18–20] followed shortly thereafter. Antipsychotic withdrawal syndromes can be grouped into (1) autonomic and behavioral syndromes, (2) extrapyramidal and withdrawal-emergent dyskinesias, and (3) psychotic relapse.[16]

Autonomic and Behavioral Symptoms

In 1965, Simpson et al.[20] reported that discontinuing trifluoperazine and benztropine simultaneously resulted in a greater number of autonomic symptoms than discontinuing trifluoperazine alone. These symptoms included nausea, vomiting, diarrhea, abdominal colic, perspiration, rhinorrhea, insomnia, and restlessness and were attributed to a "cholinergic rebound." Low-potency neuroleptic agents with marked antimuscarinic activity such as chlorpromazine, thioridazine, and mesoridazine are more likely to be associated with such withdrawal symptoms.[21,22] Similar symptoms have occurred during withdrawal of anticholinergic tricyclic antidepressants and antiparkinsonian agents.[23,24] Typically, these symptoms occur within hours to days of drug withdrawal and subside in 1 to 2 weeks. Chronic cholinergic receptor blockade and consequent supersensitivity may account for these symptoms.

Three subjects in this report manifested some combination of these symptoms upon abrupt clozapine discontinuation. One subject benefited from the addition of benztropine, although another did not benefit from trihexyphenidyl. De Leon et al.[25] have suggested using a dose of 1 mg of trihexyphenidyl for every 40 mg of clozapine to treat or prevent cholinergic rebound upon clozapine withdrawal. Clozapine has strong antimuscarinic effects, and it has been suggested that cholinergic rebound effects may account for the symptoms noted in hours to days after abrupt clozapine withdrawal.[26]

Symptoms such as rhinorrhea may be due to adrenergic rebound and have been described in a case report of clozapine withdrawal.[27]

Movement Disorders

Abnormal involuntary movements such as dyskinesia, akinesia, and tremors have been described upon neuroleptic withdrawal.[16] These reports led to the concept of neuroleptic withdrawal–emergent dyskinesia. Animal models of dopamine supersensitivity induced by chronic neuroleptic therapy,[28] and human data, suggest that withdrawal-emergent dyskinesia may reflect a hyperdopaminergic state. It is interesting that the pattern of emergent dyskinesias described in these cases and in those reported by others appears to be quite intense in severity and more evident in the neck, trunk, and axial regions rather than the orobuccal region.[12,29,30] It is unclear if this pattern reflects the unique pharmacologic properties of clozapine. For instance, clozapine does not cause striatal dopamine supersensitivity in animal studies,[31,32] but it does induce supersensitivity of the α_1-adrenergic, muscarinic, and GABA receptors.[32–34] Whether the newer atypical agents will display similar patterns upon withdrawal remains to be seen. Another point of note is that clozapine has been used to treat severe dystonias and dyskinesias,[35] and it has not been clear if clozapine ameliorated these dyskinesias or "masked" them. These limited data concerning withdrawal suggest that the preexisting orofacial dyskinesias return in some individuals and resolve upon reintroduction of clozapine.

Extrapyramidal symptoms, including dystonias and dyskinesias, have been noted with the use of SSRI antidepressants.[36–40] It is suggested that serotonergic enhancement may inhibit dopaminergic neurotransmission. In 2 of our cases, fluoxetine and fluvoxamine may have contributed to the dystonic and dyskinetic reactions noted upon clozapine withdrawal. It is not possible to state whether this was an independent or additive effect.

Clozapine withdrawal–emergent dystonias and dyskinesias may be particularly relevant when switching to agents with low anticholinergic activity such as haloperidol and risperidone[30,41,42] or while discontinuing long-term anticholinergic treatment.[43] In such instances, it may be useful to undertake a slow taper (several weeks) of clozapine if necessary, and add anticholinergic agents for the short term.[25,26,43] However, as described earlier, despite a 2-month taper of clozapine followed by addition of risperidone 2 weeks after clozapine discontinuation, 1 of our subjects developed the most severe dystonias and dyskinesias ever seen by the authors. This emphasizes the assertion by Simpson and Meyer[43] that ongoing dopamine blockade combined with the lack of muscarinic blockade (risperidone), and in this instance cholinergic supersensitivity (clozapine withdrawal after months of treatment), may be particularly problematic in the vulnerable individual (history of dystonia while receiving older drugs).

Withdrawal Psychoses

Psychoses associated with neuroleptic withdrawal have been reviewed extensively.[1] Anecdotal case reports and series of patients experiencing clozapine-withdrawal psychoses with intense decompensation have been described.[9–14,44] Two of our patients experienced a severe psychotic decompensation that took several weeks to stabilize, and they were returned to clozapine with significant benefits. Two others did not experience such severe decompensation, and 1 improved on risperidone treatment and another benefited from olanzapine.

Possible Pathophysiology of Clozapine Withdrawal Phenomena

Clozapine has a short half-life and is rapidly extracted from the brain (12 hours) compared with the older agents (20 to 30 hours).[8] This may account for the rapid cholinergic rebound symptoms noted in subjects from whom clozapine is abruptly withdrawn. Chronic cholinergic receptor blockade and cholinergic supersensitivity may account for the delirium that can accompany clozapine withdrawal.[29] The later onset of dystonias and dyskinesias (1 to 2 weeks) may be related to GABA supersensitivity, which develops 1 week after clozapine withdrawal and resolves after 2 weeks.[32] The movement disorders were noted 5 to 14 days after clozapine withdrawal among our subjects. GABA agonists have been useful in the treatment of tardive dyskinesia.[45] Interestingly, unlike with the older neuroleptic agents, chronic treatment with clozapine increases GABA turnover in the substantia nigra.[46]

CONCLUSION

In the susceptible individual, abrupt or rapid withdrawal from clozapine may be accompanied by severe psychotic decompensation, autonomic instability, symptoms of cholinergic rebound, and withdrawal-emergent dystonias and dyskinesias. Individuals with a history of neuroleptic-induced severe extrapyramidal symptoms and dystonia may be more vulnerable to withdrawal movement disorders, although these patients are often the ones chosen for clozapine treatment. The cholinergic rebound and autonomic instability may be seen in hours to days, and subjects may appear "organic." A recent study indicates that some patients meet criteria for DSM-IV substance withdrawal delirium.[29] If possible, a gradual taper of clozapine (several weeks) combined with anticholinergic agents may minimize these rebound phenomena. However, in certain situations, abrupt clozapine withdrawal is indicated, for instance, agranulocytosis and neuroleptic malignant syndrome secondary to clozapine. Withdrawal dystonias and dyskinesias may not be evident

until a few days after discontinuation. Patients, their families, and caregivers may need to be advised about these potential problems if a switch from clozapine is planned. This may be especially relevant when the switch occurs to agents with minimal anticholinergic potential such as haloperidol, risperidone, and quetiapine.

It remains to be seen if these phenomena will be noted when clozapine-treated patients are switched to the yet-to-be-marketed agents such as sertindole or ziprasidone, which have low antimuscarinic activity. It has been suggested that switching or adding an agent with high antimuscarinic affinity such as thioridazine (in doses of 100 to 200 mg/day) may help minimize some of the rebound symptoms during clozapine withdrawal.[29] Olanzapine, a recently marketed antipsychotic agent, has significant anticholinergic activity. One in vitro study indicated that olanzapine is more anticholinergic than clozapine,[47] although the clinical use of olanzapine does not appear to bear this out. However, no data have shown if olanzapine can minimize clozapine withdrawal phenomena. Overall, empirical and clinical data to guide clinicians on the switch process remain sparse, although such trials are currently under way. It is possible that SSRI agents may worsen these clozapine withdrawal movements, but again the data are too limited to come to any definitive conclusions.

Drug names: baclofen (Lioresal), benztropine (Cogentin and others), chlorpromazine (Thorazine and others), clozapine (Clozaril), fluoxetine (Prozac), fluvoxamine (Luvox), haloperidol (Haldol and others), lorazepam (Ativan and others), mesoridazine (Serentil), olanzapine (Zyprexa), perphenazine (Trilafon), quetiapine (Seroquel), reserpine (Serpasil and others), risperidone (Risperdal), sertindole (Serlect), sertraline (Zoloft), thioridazine (Mellaril and others), trifluoperazine (Stelazine), trihexyphenidyl (Artane and others).

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