Clozapine in the Treatment of Neuroleptic-Induced Blepharospasm: A Report of 4 Cases

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Background: Blepharospasm, the forcible closure of eyelids, is an infrequent consequence of neuroleptic treatment that, when severe, can interfere with the ability to walk, drive, or work. Like tardive dyskinesia, blepharospasm can be disfiguring and aesthetically distressing, contributing to the increased stigmatization of patients.

Case Reports: We report 4 patients with DSM-IV schizoaffective disorder, paranoid schizophrenia, or chronic undifferentiated schizophrenia who developed neuroleptic-induced blepharospasm. In all patients, blepharospasm remitted without the reemergence of psychosis within 3 to 5 months of treatment with clozapine, 100–200 mg/day.

Conclusion: The results suggest that clozapine may successfully treat neuroleptic-induced blepharospasm without the reemergence of psychosis in patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder.

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Blepharospasm is the forcible closure of eyelids that is an infrequent, albeit troublesome, consequence of neuroleptic treatment. When blepharospasm is severe, it can interfere with any activities of daily living, including the ability to walk, drive, and work. Not unlike the other neuroleptic-associated movement disorder tardive dyskinesia, blepharospasm can be disfiguring, aesthetically distressing, and contribute to increased stigmatization of patients. The few case reports in the literature have shown that the neuroleptic-induced disorder is indistinguishable from idiopathic Meige syndrome (blepharospasm and oromandibular dystonia). Blepharospasm can be secondary to a variety of neurologic, metabolic, and autoimmune disorders[1,2] and is often associated with abnormal movement disorders in other body regions.[2]

Wojcik et al.[3] reviewed 32 cases of tardive dystonia and noted that women had a shorter exposure time to neuroleptics until developing dystonia than men (2.3 versus 6 years). Of those patients presenting with segmental dystonia, more than 50% (10 of 18) presented with blepharospasm. Wojcik and colleagues also make the case for classifying blepharospasm with dystonia rather than with dyskinesia, given the dystonic nature of the movements.

Treatment of neuroleptic-induced blepharospasm and Meige syndrome is difficult; variable response has been reported to a variety of treatment strategies, including benzodiazepines, anticholinergic agents, and botulinum toxin type A.[4] While discontinuing neuroleptics has been successful in alleviating blepharospasm in some patients,[5] most patients with chronic psychoses require continued neuroleptic treatment. With the advent of atypical neuroleptics, alternative treatment approaches to chronic psychoses are now available. For example, clozapine has successfully been used in those patients unable to tolerate typical neuroleptics, as well as in the treatment of tardive dyskinesia.[6] In this report, we describe 4 patients in whom the blepharospasm associated with neuroleptic treatment responded to clozapine. All patients were followed up to 4 years after starting clozapine and have showed no reemergence of the blepharospasm, and all patients continue to do well psychiatrically. This is the largest case series reported to date and, combined with 5 prior single case reports, should establish clozapine as the drug of choice for treating blepharospasm in individuals with chronic psychosis.

CASE REPORTS

Case 1

Ms. A, a 34-year-old single white woman with a diagnosis of DSM-IV schizoaffective disorder of 14 years' duration, had been treated with a variety of low-dose typical neuroleptic medications. She was intermittently noncompliant due to complaints of side effects, especially akathisia. During the 10th year of treatment, while receiving perphenazine, 16 mg/day, she developed an increased rate of blinking and spasm of her eyelids. This impaired her ability to drive and caused significant subjective distress. She was seen by an expert psychopharmacologist in

another city who concurred with the presence of blepharospasm, as well as tongue and mouth movements.

Attempts were made to taper and eventually discontinue her neuroleptic over a 1-year period, with substitution of benzodiazepines and divalproex sodium. This strategy led to recurrence of her psychosis and hospital admission. In addition to neuroleptic treatment, she received electroconvulsive therapy, which appeared to diminish the blepharospasm. However, when the blepharospasm recurred on perphenazine therapy, clozapine was initiated and titrated up to 125 mg/day. After 3 months of treatment with clozapine, the blepharospasm resolved, as did the associated tongue and mouth movements. Two years later, the patient requested a trial of risperidone because of complaints about the blood work necessitated by clozapine and weight gain. She experienced a psychotic relapse during this time, as well as a return of the blepharospasm to a mild degree. When clozapine was restarted, the psychosis and blepharospasm remitted.

Case 2

Ms. B, a 49-year-old single white woman with a diagnosis of DSM-IV schizoaffective disorder and fibromyalgia of 25 years, had been treated for years with low doses of neuroleptics. She had a recurrence of psychosis when her fluphenazine decanoate was reduced because of complaints of restlessness. When her dose was increased from 5 mg every 2 weeks to 10 mg every 2 weeks, she developed increased blinking and bilateral spasm of her eyelids, as noted by multiple examiners. These side effects were very distressing, because she worked as a secretary and could not function at her job.

Lowering her dose again to 6 mg every 2 weeks did not reduce the blepharospasm. The fluphenazine decanoate was discontinued and a trial of clozapine was begun, since she could not tolerate being taken off neuroleptic treatment without the return of psychotic symptoms. The dose of clozapine was gradually titrated up to 150 mg/day, then reduced to 100 mg/day because of complaints of extreme fatigue. The blepharospasm fully remitted at this dose after 4 to 5 months. Ms. B was later treated for depressive symptoms with sertraline, 50 mg/day. The remission of her blepharospasm as well as her psychosis has now been maintained for 4 years.

Case 3

Ms. C, a 48-year-old married white woman with a 4-year history of DSM-IV paranoid schizophrenia, had psychotic symptoms that were well controlled with neuroleptics for 3 years. She subsequently developed blepharospasm along with jaw and lip movements while receiving haloperidol, 5 mg per day. When seen in consultation regarding the blepharospasm, she had been taken off neuroleptic therapy for 4 months, but was distressed by daily auditory hallucinations and paranoia.

Attempts at treating her blepharospasm with clonazepam to doses of 6 mg/day had no effect on her movements or her psychosis, so a trial of clozapine was begun. After 3 months on clozapine titrated gradually to 200 mg/day, she had remission of her blepharospasm as well as her psychosis, and both Ms. C and her husband noted return of her ability to function at home. This remission has persisted for 5 years of follow-up, although husband and patient report that, when fatigued and watching television, the patient shows a very mild return of increased blinking.

Case 4

Ms. D, a 34-year-old single white woman, had a 2-year history of chronic DSM-IV undifferentiated schizophrenia. While hospitalized, she showed an extreme sensitivity even to low doses of neuroleptics, manifested by akathisia requiring treatment with propranolol, benzodiazepines, and amantadine. After 3 to 4 months on neuroleptic therapy and haloperidol decanoate, 50 mg every 4 weeks, she developed moderately severe torticollis, movements of her forehead and jaw, and blepharospasm.

She was seen in a movement disorder clinic, where a trial of clozapine was recommended. She also had a single treatment with botulinum toxin type A. Before initiating clozapine, neuroleptics were discontinued and treatment with lithium and clonazepam was attempted, which, despite an improvement in abnormal movements, resulted in recurrence of her psychosis. When the psychosis emerged, a trial of risperidone was begun at 1 mg/day, but the patient complained of "shakiness" and refused to continue it. The blepharospasm returned to a mild degree. Clozapine was begun, but because of complaints of dizziness and sedation, as well as the patient's fear of medication side effects, titration was begun very slowly. Clozapine was increased by as little as 6.25 mg/week to a total dose of 200 mg, with a full remission of blepharospasm and no return of other abnormal movements after 4 months of treatment.

DISCUSSION

We describe here a small series of patients with neuroleptic-associated blepharospasm that successfully responded to clozapine monotherapy. Clozapine has been indicated for treatment-refractory schizophrenia, disabling tardive dyskinesia, and neuroleptic intolerance.[7] Although a relatively uncommon movement disorder, blepharospasm can be frightening and disabling to patients, often requiring urgent intervention. An increasing number of case reports in the literature show that clozapine is effective in the treatment of neuroleptic-induced blepharospasm.

Van Putten et al.[8] reported a single case of tardive Meige syndrome that was responsive to clozapine. The patient was a 30-year-old woman with a 9-year history of

schizophrenia that had been treated with moderate doses of neuroleptics. During the sixth year, she developed progressive squinting. Attempts to discontinue neuroleptics were associated with a florid psychosis. A trial with baclofen was associated with only modest improvement. The patient was gradually switched from thiothixene to clozapine, up to 250 mg/day. After 7 weeks of clozapine treatment, there was a profound improvement in the severity of blepharospasm. The authors noted that the patient eventually stopped clozapine, with the return of both the psychosis and the blepharospasm "full force."

Table 1. Demographic Characteristics of the Case Series and Treatment Parameters

Characteristic	Case 1	Case 2	Case 3	Case 4
Age, y	36	50	48	34
Sex	F	F	F	F
Race	W	W	W	W
Duration of illness, y	14	25	4	1
Neuroleptic	Perphenazine	Fluphenazine[a]	Haloperidol	Haloperidol[a]
Neuroleptic dose	16 mg/d	10 mg q 2 wk	5 mg/d	50 mg q 4 wk
Duration of blepharospasm	1 y	6 mo	1 y	4 mo
Time to remission of blepharospasm, mo	3	4–5	3	4
Clozapine response dose, mg/d	100	100	200	200

[a]Depot formulation.

Lamberti and Bellnier[9] reported a case of a 38-year-old man with schizoaffective disorder, depressed type, who had tardive dystonia with hyperextension of the neck and "marked blepharospasm." In addition, he showed horizontal jaw movements and athetoid movements of the mouth and tongue. Clozapine treatment was begun after the failure of reserpine and baclofen trials. Improvement was noted in 1 year. Abnormal Involuntary Movement Scale scores dropped from 24 to 18, and at 3 years blepharospasm was completely absent.

Shapleske et al.[10] reported a case of a 28-year-old woman with a 6-year history of schizophrenia and a 1-year onset of severe generalized tardive dystonia. Periodically, blepharospasm was noted. Trials of tetrabenazine, trihexyphenidyl, and diazepam (15 mg/day) resulted in no improvement at all. After several weeks on clozapine, 550 mg/day, the patient improved. After the addition of clonazepam, 3 mg/day, there was a dramatic improvement, and within 2 weeks almost all the abnormal movements had disappeared. At follow-up 2 years later, the patient showed no abnormal movements beyond minor finger and wrist movements. Although the response of the blepharospasm is not specifically noted, it would appear that it also resolved.

Zuddas and Cianchetti[11] reported a case of a patient with idiopathic spasmodic torticollis associated with blepharospasm that responded to treatment with risperidone. After 4 weeks of treatment with risperidone, 1.5 to 3 mg/day, a reduction in duration and amplitude of sustained movements ensued. This would suggest that further studies should include the newer atypical neuroleptics.

Friedman[12] also argued for the use of clozapine to treat patients "with severe drug-induced movement disorders, especially tardive dystonia, who require antipsychotic medication." He reported 3 cases of dystonia successfully treated with clozapine. His case 2 was a 37-year-old man evaluated by the author for blepharospasm. He was placed on clozapine therapy, and "1 year later there was no evidence of blepharospasm on examination."

Our 4 case examples showed some features in common: In each patient, blepharospasm progressed rapidly to a severely distressing and disabling level. In case 1, the patient reported severe difficulty walking and was unable to drive. In case 2, the patient, a secretary, was unable to perform at work due to the blepharospasm. In case 3, the patient had difficulty functioning as a homemaker or doing hobbies or crafts. Compared with most forms of tardive dyskinesia and even other forms of dystonia, the involvement of the eyes may be much more distressing to patients, and it requires aggressive treatment.

In several of the patients, neuroleptic withdrawal or reduction either did not decrease the blepharospasm or resulted in an equally distressing worsening of psychosis requiring neuroleptic treatment. Trials of anticholinergic medication or benzodiazepines in these cases were not effective. Clozapine-treated patients generally showed noticeable improvement early in the course of treatment, often within several weeks, and had remission by 4 months. This early response may reflect the fact that interventions were begun soon after the onset of blepharospasm.

The response to clozapine in these patients was quite dramatic. It is unlikely that this response was due only to the removal of the offending agent, as several patients had been withdrawn from medication with no improvement, and the response to clozapine treatment was rapid. It remains to be determined whether clozapine is curative or is simply masking blepharospasm. Ms. A, case 1, had a reemergence of blepharospasm while receiving risperidone transiently. Resumption of clozapine treatment resulted in remission of her blepharospasm. This reaction is similar to the experience of Van Putten et al.[8] with clozapine discontinuation. It would suggest that clozapine masks dystonia. However, continued clozapine treatment does not appear to result in reemergence or worsening of dystonia. Although in case 1, 2 years of clozapine treatment did not allow spontaneous remission of blepharospasm in the patient, perhaps a much longer interval is required for this phenomenon to occur.

In this small case series, it is interesting to note that all patients were women, a fact consistent with the idiopathic form of blepharospasm (Table 1). The mean age in our group was 41 years, which is younger than is typical in the

idiopathic form of Meige syndrome. It is also of interest that in this case series all patients showed sensitivity to neuroleptics at low doses, particularly manifested by akathisia. In all the patients, akathisia appeared prior to the onset of blepharospasm. It has been reported[13] that the presence of akathisia is a risk factor for the development of tardive dyskinesia. If akathisia indeed is a significant risk factor for the development of blepharospasm, this would support close monitoring for akathisia in patients taking standard neuroleptics. Clozapine has already been recommended for chronic treatment-refractory akathisia,[14] so that members of this population may have 2 indications for the use of clozapine, as they often have both akathisia and blepharospasm. As shown by this case series, one cannot assume that patients who are receiving low doses of standard neuroleptics are not at risk for dystonia, because these 4 patients were receiving the equivalent of 3–5 mg/day of haloperidol. Armstrong et al.[15] found that "a majority of patients who lacked CYP2D6 enzyme activity were suffering from chronic movement disorders." Thus, neuroleptic-sensitive patients may have a biological vulnerability to tardive dystonia, including blepharospasm. Their sensitivity to low doses (are they slow metabolizers?) may explain why they also responded to very low doses of clozapine. Such patients may require a slower titration of clozapine, begun in very low doses, if they are to accept the treatment.

Given the greater safety of the antipsychotics marketed since clozapine (risperidone, olanzapine, and quetiapine), it would be important to know if they can also be effective in treating blepharospasm. A multicenter study is currently underway to investigate the effects of olanzapine on tardive dyskinesia. Given the rarity of blepharospasm, a multicenter study would be required if this movement disorder were to be studied.

In summary, this article reports on the largest case series to date of neuroleptic-induced blepharospasm that is responsive to clozapine treatment. From these cases and the cases of withdrawal dyskinesias reported by Ahmed et al.,[16] clozapine appears to mask dystonia, with resulting reemergence when it is discontinued. In case 1, the patient showed a return of blepharospasm during a brief trial of risperidone after 2 years of clozapine treatment. Case 3 suggested that, despite the patient's being withdrawn from neuroleptics for 4 months, there was no reduction of blepharospasm until clozapine was started, thus supporting suppression as the mechanism. In this case, suppression was also supported by the fact that the patient had minimal nondisabling symptoms in a fatigued state, even with 5 years of clozapine treatment. The 4 cases showed remission of dystonia in about 4 months, which is more suggestive of suppression than allowing spontaneous remissions to occur.

This article emphasizes blepharospasm, a particular form of tardive dystonia, because of patients' demands for treatment as a result of the unusually disabling condition that results when the eyelids are affected. This demand for treatment contrasts with the rarity of complaints about other forms of tardive dystonia, unless gait is affected. As the literature has shown, clozapine is also the agent of choice for other forms of dystonia, when chronic psychosis requires antipsychotic treatment. We would also encourage the early detection of milder forms of blepharospasm such as increased blink rate. Given the relatively slow time course to remission, some patients may require treatment with botulinum toxin type A to relieve either the distress from the blepharospasm or any resulting severe impairments. Similarly, if there are cases of blepharospasm refractory to clozapine treatment, botulinum toxin type A injection in the obicularis oculi may become the treatment of choice.

Drug names: amantadine (Symmetrel and others), botulinum toxin type A (Botox), clonazepam (Klonopin and others), clozapine (Clozaril and others), diazepam (Valium and others), divalproex sodium (Depakote), haloperidol (Haldol and others), olanzapine (Zyprexa), perphenazine (Trilafon and others), propranolol (Inderal and others), quetiapine (Seroquel), reserpine (Serpasil and others), risperidone (Risperdal), sertraline (Zoloft), thiothixene (Navane), trihexyphenidyl (Artane and others).

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