Neuropsychiatric Disease and Treatment

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CASE REPORT

# Scopolamine alleviates involuntary lingual movements: tardive dyskinesia or dystonia?

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment
31 August 2017
Number of times this article has been viewed

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**Abstract:** Cholinergic hypofunction was believed to be associated with the pathogenesis of tardive dyskinesia, and therefore, anticholinergic treatment might exacerbate the condition. We describe herein a middle-aged male with feeble chewing movements, involuntary rolling motions of the tongue, and abnormally tightened cheeks which developed after consuming different psychotropic medications. These symptoms did not improve after routine treatment for tardive dyskinesia, but responded well to anticholinergic agents, such as scopolamine and benzhexol hydrochloride. This case extended our understanding of the complexity of extrapyramidal effects and their pharmacologic management.

**Keywords:** neuroleptic, scopolamine, tardive dyskinesia, dystonia

## Introduction

Among the various extrapyramidal side effects secondary to the medication use, tardive dyskinesia (TD) is a typical clinical phenomenology, which significantly affects the quality of life and attitudes toward treatment.[1] TD is characterized as late-onset, involuntary and persistent movements in an athetoid or choreiform pattern, generally involving the lower face, tongue and, sometimes, the extremities.[2] The stereotypic presentation of TD is involuntary and repetitive movements in the oro-facio-buccal-lingual regions. To date, the pathophysiology of TD remains unknown and the most acceptable hypothesis is the upregulation and hypersensitivity of the dopamine $D_2$ and possibly $D_3$ receptors. Iatrogenic TD is closely associated with exposure to dopamine antagonists.[1,3] Other possible mechanisms include maladaptive synaptic plasticity, disturbed neurotransmitter systems (eg, gamma-aminobutyric acid, serotonin and acetylcholine), oxidative stress, neurodegenerative changes and genetic susceptibility.[4–8] Pharmacologic options for TD, including clonazepam, ginkgo biloba extract, amantadine and the vesicular monoamine transporter 2 inhibitors, are limited and the outcome is indefinite.[9] Recently, deep brain stimulation has emerged as an alternative strategy for severe or refractory TD.[10]

In addition to dopaminergic hypersensitivity, cholinergic hypofunction was also considered to contribute to the development of TD.[11] The balance in dopamine–acetylcholine transmitter systems is essential for the maintenance of normal movement and behavior.[11] Based on this theory, agents of antimuscarinic class (eg, scopolamine and benzhexol) can exacerbate the severity of TD,[12,13] while cholinergic agents (eg, physostigmine) improve the condition.[14] However, the pathophysiology of tardive dystonia was poorly investigated, and one hypothesis referred to sensitization of the dopamine $D_1$ receptor-mediated striatal output.[15] In this case study, we would like to document a patient with TD-like symptoms, which were alleviated with scopolamine treatment.

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http://dx.doi.org/10.2147/NDT.S143970



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## Case presentation

A 50-year-old male patient was admitted to our hospital due to feeble occlusion and involuntary perioral movements. Two years before admission, this patient began to feel general malaise without obvious causes, including dizziness, abdominal distention, sore foot and other discomfort. He became upset and irritable. After visiting a local psychiatric hospital, he was prescribed duloxetine 60 mg/day and fluoxetine 20 mg/day and he took these drugs for nearly 1 year. However, his condition did not ameliorate. One year before admission, this patient visited our hospital and was diagnosed with somatoform disorder. He then began to take venlafaxine 225 mg/day monotherapy. One month after taking venlafaxine, paliperidone 3 mg/day was added as a synergist. His condition significantly improved and all of his discomfort remitted after adding paliperidone for 5 days. Nevertheless, this patient gradually began to feel weakness on mastication after taking paliperidone for ~1 month. He repetitively visited local hospitals, and investigations of single-fiber electromyography, repetitive nerve stimulation and the neostigmine test were all negative. About 6 months before admission, this patient complained of scattered rash on the trunk, which could be controlled with steroids and vitamin C. However, the rash recurred frequently when taking venlafaxine and paliperidone. This patient revisited our hospital and was prescribed with duloxetine 60 mg/day and olanzapine 5 mg/day instead of venlafaxine and paliperidone. After initiating these agents, the rash completely disappeared, but his feeble chewing movement did not improve. Although serum detection of anti-acetylcholine receptor antibody was negative, he took pyridostigmine bromide 60 mg three times a day for 1 month, which also did not help. Approximately 2 weeks before admission, his tongue began to roll in a spontaneous and purposeless pattern, with his bilateral cheeks feeling tightening.

On admission, physical examinations revealed no positive findings. Laboratory tests, including routine blood tests, biochemical indices, infectious biomarkers and thyroid hormones, were all within normal limits. Cranial magnetic resonance imaging demonstrated scattered ischemic foci in the frontal and parietal lobes, as well as an arachnoidal cyst in the cisterna magna. He had smoked for more than 20 years. He denied any experience of using illegal or toxic substances. No family history of mental illnesses or similar condition was reported. In consideration of the TD-like manifestations, the potential offending agents were all gradually tapered. Oral vitamin E 1,000 mg/day, clonazepam 1 mg per night, clozapine 12.5 mg per night and intramuscular injection of promethazine 25 mg per night were added to cope with his involuntary perioral movements. However, the outcome of these medications was not satisfactory. Given his tightened cheeks, the possibility of dystonia could not be completely excluded. After being fully informed, tentatively, intramuscular injection of scopolamine 0.3 mg was used. Surprisingly, all of his malaise disappeared about 30 minutes after scopolamine injection. His mastication became powerful, his cheeks felt relaxed, and the purposeless movements of his tongue apparently decreased. The outcome of scopolamine treatment could last for nearly 1 day, and his problems recurred as usual. To exclude the placebo effect, we had once tried intramuscular injection of mecobalamin, which turned out to be ineffective. As was requested by the patient, we injected 0.3 mg of scopolamine again and the result was satisfactory as before. During hospitalization, neurologic consultants also pointed to the diagnosis of dystonia. It was advised to titrate the dose of clonazepam to 2 mg three times a day if necessary. Accordingly, the dose of clonazepam was escalated to 1 mg twice a day and clozapine was discontinued. Besides, benzhexol hydrochloride 2 mg twice a day was added as an anticholinergic medication. The patient was content with the outcome and claimed that his condition had improved by at least half of the severity.

This case study was approved by the Institute Ethical Committee of the First Affiliated Hospital, Zhejiang University School of Medicine. Written informed consent was obtained from this patient for publication of the case details.

## Discussion

In this case study, we depict a middle-aged male patient with lingual stereotyped movements and oro-buccal abnormal feelings, which did not respond to regular anti-TD managements, but were dramatically relieved by scopolamine administration. This phenomenon went against the ideology that scopolamine treatment would exacerbate the symptoms of TD. Hence, the actual nature of the oro-buccal-lingual manifestations, including feeble chewing motions, involuntary lingual movements and tightened cheeks, needs further interpretation in our patient.

According to a systematic review, there was a paucity of evidence clarifying the effectiveness of anticholinergic medications, such as scopolamine, on treating neuroleptic-induced TD in humans.[14] Nevertheless, there are some exploratory animal studies that we can refer to. In a rat model of masticatory jaw movements induced by administration of different long-term neuroleptics for 4 months, prompt consumption of cholinergic compounds, such as pilocarpine

and physostigmine, worsened the condition, while the use of anticholinergic compounds, such as atropine and scopolamine, could significantly decrease the chewing behaviors.[16] In another study by the same authors, spontaneous or drug-related purposeless chewing behavior was elicited in Wistar rats after they received treatment of different neuroleptics for 3 weeks. Prompt use of scopolamine was also able to reduce these masticatory motions. However, the condition reverted to the control status when scopolamine was discontinued.[17] The authors, therefore, speculated that the behavior pattern in these rat models was more similar to acute dystonia rather than TD.[17] These findings were further confirmed by another study of subchronic treatment with haloperidol for 10 days.[18] It seemed that the spontaneous masticatory movements induced by neuroleptics were more related to Parkinsonian symptoms, but less similar to TD.[18]

According to the foregoing studies, involuntary perioral movements in rats may represent different conditions other than TD. As for our patient, his manifestations resembled persistent dystonia. The symptom of feeble chewing occurred shortly after adding paliperidone to venlafaxine. Accordingly, this condition could be a consequence of paliperidone treatment or the interaction between paliperidone and venlafaxine. Of note, the dose of paliperidone (3 mg) was small, and the weak masticatory motions did not improve or deteriorate after replacing the above drugs with duloxetine and olanzapine. Before the occurrence of other manifestations, pyridostigmine bromide, an acetylcholinesterase inhibitor, had been used for 1 month. Coincidentally, our patient responded well to the use of anticholinergic agents, including scopolamine and benzhexol hydrochloride. Hence, the deterioration of symptoms was possibly related to the administration of pyridostigmine and cholinergic hyperfunction. Moreover, diphenhydramine, a potent antihistaminergic and anticholinergic agent, has also been reported to be effective for extrapyramidal effects, especially akathisia.[19] Therefore, brain dysfunction of acetylcholine transmission should be carefully differentiated in various extrapyramidal manifestations.

In addition, cranial magnetic resonance imaging of our patient indicated ischemic foci in the frontal and parietal lobes. However, neuroimaging studies demonstrated that the basal ganglia region was the most relevant to the development of TD. Compared to schizophrenic patients without TD, those with TD had longer $T_1$ signal in regions of the putamen and the globus pallidus[20] and significant abnormalities of white matter in the cortico-basal ganglion circuits.[21] Using positron emission tomography, schizophrenic subjects with TD were found to have elevated pallidal synaptic activity.[22] Therefore, the ischemic foci in the frontal and parietal lobes seemed irrelevant to the TD-like symptoms in our patient.

To conclude, this single case study indicated that TD-like symptoms secondary to neuroleptics administration might be a manifestation of cholinergic hyperfunction and responded well to anticholinergic therapy. Therefore, clinicians should distinguish the actual TD from other similar conditions in clinical practice.

## Acknowledgments

This work was supported by grants of the Medicine and Health Program of Zhejiang Province (2014ZDA008, 2013RCA017, and 2015KYB136), National Key Basic Research Program (2016YFC1307104), the Public Welfare Project of Science Technology Department of Zhejiang Province (2015C33133), the National Clinical Research Center for Mental Health Disorders (2015BAI13B02), the Key Research Project of Zhejiang Province (2015C03040) and the Research Program of Education Department in Zhejiang Province (Y201430870). We acknowledge Dr Pornkanok Prukpitikul for helping to polish the language of this article.

## Disclosure

The authors report no conflicts of interest in this work.

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