

Zolpidem Improves Tardive Dyskinesia with and without Akathisia

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Background

- Tardive dyskinesia (TD) - group of delayed-onset, iatrogenic movement disorders caused by dopamine-receptor blocking agents (DRBA).
- TD frequently persists after eliminating offending drugs, and is often resistant to pharmacological treatment.
- Tetrabenazine (TBZ) is the most effective treatment of TD¹ if elimination of DRBA alone does not improve symptoms.
- Zolpidem - nonbenzodiazepine-related hypnotic drug that binds to the omega site of the GABA-benzodiazepine receptor complex found in high density in basal ganglia.²
- Zolpidem was previously reported to be effective in a variety of movement disorders (Table 1).²⁻¹³
- There were no human studies or reports of zolpidem effectiveness in TD.
- We present two patients with TD unresponsive to other medications who dramatically improved with oral zolpidem.

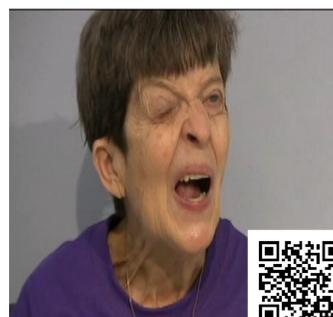
Table 1. Previous studies and case reports of movement disorders improved with zolpidem.

Study / Case report	N, total / improved	Diagnosis	Adverse effect of drowsiness	Comments
Daniele et al, 1997 (P-C)	10/6	PD ("off" symptoms)	4 out of 10 total	Improved rigidity, bradykinesia, gait, posture
Chen et al, 2008	1/1	PD ("off" symptoms, LID, dystonia)	No	
Ruzicka et al, 2000	1/1	PD ("off" symptoms and LID)	No	In "off" state, mostly improved gait initiation
Farver and Khan, 2001	1/1	Antipsychotic-induced parkinsonism	Sedation with 40 mg/day or + clozapine	Improvement in tremor
Miyazaki et al, 2012	34/8	Primary dystonia: generalized (n=9), focal: cranial (n=10), cervical (n=7), hand dystonia (n=8)	8 out of 34 total, 3 out of 8 responders to zolpidem	Improved generalized and hand dystonia but not cervical dystonia
Park et al, 2009	1/1	Myoclonus-dystonia syndrome	No	Improved myoclonus and dystonia
An et al, 2008	1/1	Cranial dystonia	No	
Garretto et al, 2004	3/3	Blepharospasm (n=1), cranial dystonia (n=2)	1 out of 3, only in the evening	
Evidente, 2002	3/3	X-linked dystonia-parkinsonism "Lubag" syndrome	Yes, at the dose more than 20 mg daily	Improved dystonia (all patients) and arkinsonism (2/3 patients)
Clauss et al, 2004	5/4	Spinocerebellar ataxia type 2 (one family)	Not reported	Improved tremor, ataxia and titubation
Cotter et al, 2010	1/1	Progressive supranuclear palsy	Yes, with IR formulation but not with SR	Improved bradykinesia, ocular motility, voice, facial expression and sialorrhoea
Daniele et al, 1999 (P-C)	10/2	Progressive supranuclear palsy	Yes, dose dependent	

P-C = Placebo-controlled; PD = Parkinson's disease; LID = levodopa-induced dyskinesia

Patient 1

67 y/o F was treated with neuroleptics for multiple personality disorder with psychosis and developed TD 17 years ago resistant to TBZ 37.5 mg daily.



Video 1a, OFF zolpidem.

The patient has oro-bucco-lingual stereotypies, b/l but asymmetric blepharospasm, repetitive jaw opening, moderate anterocollis with stereotypic head nodding (craniocervical dystonia), frequent loud inspiratory gasps (dystonic respiratory dysregulation), mild chorea in feet, rest tremor (TBZ-induced parkinsonism). The patient cannot drink water from a cup or swallow.

Video 1b, 50 minutes after 15 mg of zolpidem.

There is almost complete resolution of all symptoms except rare jaw opening dystonia. The patient is able to drink from a cup and swallow without difficulty. The patient has been taking 10 mg of zolpidem bid-tid for 11 months with the same benefits and no drowsiness.



Patient 2

25 y/o F with recurrent psychotic episodes treated with neuroleptics, developed generalized TD with akathisia unresponsive to TBZ 75 mg daily.



Video 2a, OFF zolpidem.

The patient is restless, unable to sit still (akathisia). She has bilateral blepharospasm, facial grimacing, intermittent torticollis to the right, chorea in the arms and hands, more on the left, truncal chorea with intermittent opisthotonic posturing.

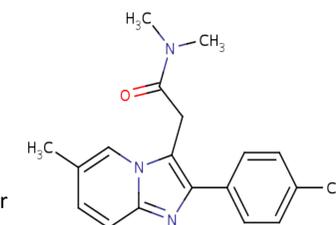
Video 2b, 5 hours after 10 mg of zolpidem.

The patient has mild chorea in the left hand with otherwise normal neurological examination. Akathisia, craniocervical and truncal dyskinesias resolved. The patient has been taking zolpidem 10 mg bid with the same benefit and no drowsiness.



Discussion

- Pathophysiology of TD remains poorly understood but it could result in part from GABAergic dysfunction and neurodegeneration of striatal interneurons from increased oxidative stress.
- Zolpidem binds to GABA-benzodiazepine receptor complex found in high density in basal ganglia.
- Exact mechanism of action of zolpidem in movement disorders is unknown; it may help restore basal ganglia GABAergic output influence on the thalamus and motor cortex.
- Zolpidem has also been suggested to exert antioxidant and neuroprotective properties and showed effectiveness in prevention and treatment of TD in animal study.¹⁴
- Our patients represent the first cases of documented improvement of TD and akathisia with zolpidem. Both patients had no daytime sedation with zolpidem, similar to previously reported cases of zolpidem use in other movement disorders (Table 1).



Conclusions

- Zolpidem can be safe and effective alternative treatment of TD with and without akathisia, resistant to other medications.
- Placebo-controlled study is needed to further investigate the effectiveness of zolpidem in TD.

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Poster available for download.

