

Response of Tardive and L-Dopa-Induced Dyskinesias to Antidepressants

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ABSTRACT: We report two patients with dyskinesia responding to antidepressants. The first is a 70-year-old man with depression, Parkinsonism and neuroleptic-induced tardive dyskinesia who presented with hysterical mutism. After recovery from the mutism, he was started on desipramine for depression. One week later the dyskinesia improved markedly. The second patient is a 61-year-old man with Parkinson's disease, dementia, depression and L-dopa-induced oro-lingual-facial dyskinesias. He was taking levodopa, trihexyphenidyl and bromocriptine. The depression was treated first with desipramine and later with trazodone. The dyskinesia improved significantly on both drugs. The response of the dyskinesias to antidepressant medication may be due to the fact that antidepressants decrease beta-adrenoreceptor sensitivity and density which in turn may result in a diminished release of dopamine since beta-adrenoceptors mediate the noradrenaline-stimulated release of dopamine.

RÉSUMÉ: Réponse au traitement par les antidépresseurs des dyskinésies tardives et de celles qui sont induites par la L-dopa. Nous rapportons les cas de deux patients dont les dyskinésies ont répondu au traitement par les antidépresseurs. Le premier est un homme âgé de 70 ans souffrant de dépression, de la maladie de Parkinson et de dyskinésies tardives induites par les neuroleptiques et qui a présenté un mutisme hystérique. Après avoir recouvré l'usage de la parole, il a reçu de la désipramine pour traiter sa dépression. En une semaine, les dyskinésies se sont améliorées de façon appréciable. Le second patient est un homme âgé de 61 ans souffrant de la maladie de Parkinson, de démence, de dépression et de dyskinésies oro-linguo-faciales induites par la L-dopa. Il prenait de la lévodopa, du trihexyphénidyle et de la bromocriptine. La dépression a été traitée d'abord avec de la désipramine et ensuite du trazodone. Les dyskinésies se sont améliorées de façon significative avec ces deux médicaments. La réponse des dyskinésies à la médication antidépressive est peut-être due au fait que les antidépresseurs diminuent la sensibilité et la densité des récepteurs bêta-adrénergiques ce qui peut occasionner une diminution de la libération de la dopamine, les récepteurs bêta-adrénergiques servant de médiateurs pour la libération de la dopamine sous stimulation noradrénergique.

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Neuroleptic-induced tardive dyskinesia is associated with a prolonged selective blockade of dopamine receptors,¹ dopamine supersensitivity,² and elevated densities of brain dopamine D₂ receptors.³ Tardive dyskinesia is more prevalent in the elderly and in females,⁴ and is related to the cumulative dose of neuroleptic.⁵ Tardive dyskinesia appears to have higher prevalence in patients with depression.^{6,7,8,9} Our first patient is a 70-year-old man with depression associated with parkinsonian symptoms and tardive dyskinesia who presented with hysterical mutism. Although this is an unusual presentation, Shulman and Silver¹⁰ also described an elderly patient with a conversion disorder on a background of possible depression whose conversion reaction responded to tricyclic antidepressants. The mutism in our patient responded to hospitalization, the sympathetic attitude and care of the staff, and attempts to increase the patient's social interaction. The other depressive features, as

well as the tardive dyskinesia and parkinsonism, responded to a tricyclic antidepressant.

Our second patient is a 61-year-old man who had Parkinson's disease and was being treated with L-dopa/carbidopa, trihexyphenidyl and bromocriptine. He presented with depression and severe oro-lingual-facial dyskinesias. The depression and dyskinesias responded first to desipramine and later to trazodone.

CASE REPORTS

Patient 1 A 70-year-old, right-handed man was admitted to the Baycrest Hospital Behavioural Neurology Unit with a one-year history of mutism. The mutism began one month following insertion of a cardiac pacemaker for complete heart block complicating a myocardial infarction. He also became completely withdrawn, sitting in a chair all day, rising only to eat. He was able to dress and feed himself but extremely slowly. Eleven years earlier he was admitted to hospital following a right

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occipital skull fracture sustained during a fight with a customer while employed as a parking lot attendant. He was started on haloperidol 2 mg. daily which he took until one month prior to the onset of the mutism.

On admission he was mute and had a stooped posture, shuffling gait, and at times seemed stuck to the floor. He had a positive glabellar tap reflex, mild bilateral grasp reflexes, cogwheeling in both arms, and increased muscle stretch reflexes on the left. The plantar responses were flexor bilaterally. He was withdrawn and, at times, tearful.

He had buccolingual masticatory movements. The only speech output was an occasional guttural noise. Auditory comprehension appeared impaired. He was unable to repeat or to name. He was able to write the letters "A" and "T" to dictation. For the word "house" he wrote "housy", for "E" he wrote "Y", and for "Y" he wrote "W". He was able to match letters but did not read aloud. Reading comprehension testing showed no response.

One week following admission, while the speech pathologist was encouraging him to phonate, he began to hum, then to imitate words which contained the initial "M" sound, and progressed to responding to questions with words and short phrases. This occurred during a ½-hour period. Later that day he began to speak in complete sentences but with severe dysarthria. His walking significantly improved over the next few days. He had not been treated with drugs at that time.

His course was a fluctuating one. On certain days he was withdrawn, refused to eat, and had a shuffling gait, stooped posture and sad face. At these times his speech was more dysarthric and the buccolingual dyskinesias increased in severity. He was bradykinetic. On other days he was more socially interactive and walked with faster steps and straighter posture. Speech was more intelligible during these periods and the dyskinesias decreased. He slept much of the day, and at times sat in a chair. He repeatedly said that he felt depressed and that "nobody can help me, there's nothing you can do".

He often showed attention seeking behaviour. For example he had an episode during which he became very irritable and talkative, and fell slowly to the floor. He remained conscious, however, and answered questions appropriately.

Although the presentation was atypical, we felt that the diagnosis was conversion disorder as a manifestation of depression. He was started on desipramine 25 mg. daily. The dose was gradually increased to 125 mg. daily. The periods of withdrawal and psychomotor retardation became less frequent. The dyskinesias also improved markedly and, when present, were minimal. The Parkinsonian signs, ie. shuffling gait, stooped posture, hypomimic face and bradykinesia improved as well.

Patient 2 A 61-year-old man with a six year history of Parkinson's disease, and more recently dementia, depression and severe oro-lingual-facial dyskinesias was admitted to the Behavioural Neurology Unit at Baycrest Hospital. The dementia started two years prior to admission and was progressive. His major problem was that he had become very withdrawn and depressed.

On examination, he had a sad facial expression. There were almost continuous oro-lingual-facial dyskinesias that became even more pronounced during motor activities and writing. He had a low-amplitude, fast tremor of the outstretched hands, but no tremor at rest. There was cogwheel rigidity in both arms at the elbows and wrists. His movements were bradykinetic. He walked with a stooped posture and minimally slowed gait. He had decreased swinging of the arms. Attention span was reduced. He was disoriented to time and place and had recent and remote memory impairment. Spontaneous speech was hypophonic, tremulous and fading towards the end of a sentence, with word finding difficulties. Auditory comprehension was decreased. There was perseveration on copying a pattern with an alternating sequence. Abstraction ability was impaired.

He was taking L-dopa/carbidopa 100/10 mg. t.i.d. trihexyphenidil 4 mg. b.i.d., and bromocriptine 7.5 mg. daily. He had been on Cogentin and amantadine in the past, but not on phenothiazines or haloperidol. He was started on desipramine 10 mg. daily for depression. Four days later his dyskinesias improved markedly. He became agitated, however, and had visual hallucinations. The trihexyphenidil was discontinued and then the desipramine. The agitation and hallucinations subsided but the dyskinesias returned. He was then given trazodone 25 mg. daily and his dyskinesias improved a few days later. To further evaluate the relationship between the dyskinesias and the use of trazodone, we discontinued the trazodone with subsequent worsening of the dyskinesias.

On reinstating the trazodone the dyskinesias improved once again. The trazodone was then gradually increased to 125 mg. daily. Six months later his dyskinesias were still very mild, even with attempted activation by having him write.

DISCUSSION

In manic-depression, tardive dyskinesia may improve during mania and may be exacerbated during the depressed or euthymic phases.^{11,12} Cutler et al¹¹ described two patients with state-dependent dyskinesia. Rapid switches between the two states were accompanied by recurrence of the dyskinesia during depression and disappearance during mania. The switches were spontaneous and the patients were medication free. DePotter et al¹² reported a patient with rapid cycling between mania and the euthymic state. The patient had neuroleptic-induced oro-buccolingual dyskinesia and signs of parkinsonism. The dyskinesia was drug resistant, but remitted during the manic phase and relapsed during the euthymic phase. The parkinsonism did not change.

Unlike the above cases, our first patient did not have a bipolar affective disorder and the tardive dyskinesia improved in response to medication. The response occurred by about one week after the introduction of desipramine. It is of note that the depressive symptoms had not improved by that time.

Rosenbaum et al¹³ report improvement in depressed patients who have tardive dyskinesia. In their patients both the depression and the tardive dyskinesia improved in response to a combination of tricyclic antidepressants and lithium carbonate. The improvement occurred one to two months after the beginning of treatment.

The alleviation of tardive dyskinesia by antidepressants may be explained by the fact that antidepressants decrease beta-adrenoceptor sensitivity¹⁴ and density.¹⁵ Since beta-adrenoceptors mediate the noradrenaline-stimulated release of dopamine,^{16,17,18} a decrease in beta-adrenoceptor density would result in a diminished spontaneous release of dopamine with diminished dopaminergic dyskinesia. Slightly offsetting this mechanism is the fact that long-term antidepressants appear to sensitize animals to the post-synaptic locomotor effects of dopamine-mimetics.^{19,20} This post-synaptic sensitizing action may result from an antidepressant-induced subsensitivity of pre-synaptic dopamine receptors.^{21,22} This sensitizing factor, however, is small compared to the decrease in beta-adrenoceptors. The alleviation of tardive dyskinesia by antidepressants is unlikely to be explained by an anticholinergic action, since tardive dyskinesia is usually made worse by anticholinergic compounds.² Furthermore, the relatively rapid alleviation of the dyskinesia by antidepressants cannot here be accounted for by a spontaneous reduction in the dyskinesia, since such spontaneous reductions occur gradually over a matter of months.

In the second patient both desipramine and trazodone improved the dyskinesias. Trazodone shares with the tricyclic antidepressants the property of decreasing adrenoceptor sensitivity and density.

Although the dyskinesias in our two patients each had a different etiology, the implication of the above effect and mechanism of action of desipramine and trazodone, if further validated, is that antidepressants could be a useful treatment for tardive dyskinesia and levodopa-induced dyskinesias, even in the absence of depression.

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REFERENCES

- Seeman P, Lee T, Chau-Wong M, Wong K. Antipsychotic drug doses and neuroleptic/dopamine receptors. *Nature* 1976; 261: 717-719.
- Tarsy D, Baldessarini RJ. The pathophysiologic basis of tardive dyskinesia. *Biol Psychiat* 1977; 12: 431-450.
- Muller P, and Seeman P. Brain neurotransmitter receptors after long-term haloperidol: dopamine, acetylcholine, serotonin, alpha-noradrenergic and naloxone receptors. *Life Sci* 1977; 21: 1751-1758.
- Smith JM, Baldessarini RJ. Changes in prevalence, severity, and recovery in tardive dyskinesia with age. *Arch Gen Psychiat* 1980; 37: 1368-1373.
- Ezrin-Waters C, Seeman MV, Seeman P. Tardive dyskinesia in schizophrenic outpatients: prevalence and significant variables. *J Clin Psychiat* 1981; 42: 16-22.
- Davis KL, Berger PA, Hollister LE. Tardive dyskinesia and depressive illness. *Psychopharmacol Commun* 1976; 2: 125-130.
- Rosenbaum AH, Niven RG, Hanson NP, Swanson DW. Tardive dyskinesia: relationship with a primary affective disorder. *Dis Nerv Syst* 1977; 38: 423-427.
- Rush M, Diamond F, Alpert M. Depression as a risk factor in tardive dyskinesia. *Biol Psychiatry* 1982; 17: 387-392.
- Yassa R, Nair V, Schwartz G. Tardive dyskinesia and the primary psychiatric diagnosis. *Psychosomatics* 1984; 25: 135-138.
- Shulman KI, Silver IL. Hysterical seizures as a manifestation of "depression" in old age. *Can J Psychiatry* 1985; 30: 278-280.
- Cutler NR, Post RM, Rey AC, Bunney WE. Depression-dependent dyskinesias in two cases of manic-depressive illness. *N Engl J Med* 1980; 304: 1088-1089.
- dePotter RW, Linkowski P, Mendlewicz J. State-dependent tardive dyskinesia in manic-depressive illness. *J Neurol Neurosurg Psych* 1983; 46: 666-668.
- Rosenbaum AM, Auger RG, Maruta T, Martin DK, Duane DD, Brenengen EE. Tardive dyskinesia in depressed patients: Successful therapy with antidepressants and lithium. *Psychosomatics* 1980; 21: 715-719.
- Vetulani J, Sulser F. Action of various antidepressant treatments reduces reactivity of noradrenergic cyclic AMP-generating system in limbic forebrain. *Nature (London)* 1975; 257: 495-496.
- Banerjee SP, Kung LS, Riggi SJ, Chanda SK. Development of beta-adrenergic receptor subsensitivity by antidepressants. *Nature (London)* 1977; 268: 455-456.
- Anden NE, and Grabowska M. Pharmacological evidence for a stimulation of dopamine neurons by noradrenaline neurons in the brain. *Eur J Pharmacol* 1976; 39: 275-282.
- Reisine TD, Chesselet MF, Lubetzki C, Cheramy A, Glowinski J. Striatal beta-adrenergic receptors regulate dopamine release. *Soc Neurosci Abstr* 1981; 8: 526.
- Langer AZ. Presynaptic regulation of the release of catecholamines. *Pharmacol Rev* 1981; 32: 337-362.
- Spyraki C and Fibiger HC. Behavioural evidence for super-sensitivity of postsynaptic dopamine receptors in the mesolimbic system after chronic administration of desipramine. *Eur J Pharmacol* 1981; 74: 195-206.
- Serra G, Argiolas A, Klimek V, Fadda F, Gessa GL. Chronic treatment with antidepressants prevents the inhibitory effect of small doses of apomorphine on dopamine synthesis and motor activity. *Life Sci* 1979; 25: 415-424.
- Chiodo LA, Antelman SM. Repeated tricyclics induce a progressive dopamine autoreceptor subsensitivity independent of daily drug treatment. *Nature* 1980; 287: 451-454.
- Serra G, Argiolas A, Fadda F, Gessa GL. Hyposensitivity of dopamine "autoreceptors" induced by chronic administration of tricyclic antidepressants. *Pharmacol Res Commun* 1980; 12: 619-624.