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Letters to the Editor

Dose-Induced Penile Erections in Response to Ropinirole Therapy for Parkinson's Disease

We note with interest the report by O'Sullivan and Hughes concerning apomorphine-induced penile erections in Parkinson's disease (PD).[1] As the authors themselves point out, there have been previous reports of this side effect following subcutaneous apomorphine use in both PD patients and healthy men.[2–5] We have also encountered one report of a persistent erection in a subject after intravenous lisuride injection.[6] Although changes in erectile function and sexual behavior are well-described in patients using levodopa and dopamine agonists,[7–9] to our knowledge, erections induced regularly in response to individual doses of commonly used oral dopamine agonists have not been reported. We want to draw attention to this side effect seen with the administration of ropinirole, one of the newer dopamine agonists used in the treatment of PD.

A 49-year-old man was diagnosed with PD after 2 years of investigation for pain, stiffness, and clumsiness of the left upper limb. Sinemet was introduced but was not tolerated because of excessive somnolence, involuntary jerking movements in the left arm, and gastrointestinal side effects. The clinical response to amantadine was considered to be inadequate, and ropinirole was therefore added to the patient's drug regime. At a dose of 3 mg three times a day his parkinsonism improved. However, he began to experience erections which occurred 20–30 minutes following each dose and were sustained for 10–15 minutes. These erections occurred with each individual dose of ropinirole. They were not associated with sexual arousal and caused considerable physical and emotional discomfort. The patient also had a persistent scrotal ache which began at approximately the same time. He had not experienced sexual dysfunction before the initiation of ropinirole.

On slowly reducing the dose of ropinirole, the frequency of ropinirole-induced erections began to diminish at a dose of 1 mg three times a day. They occurred only occasionally at a dose of 0.5 mg three times a day and ceased completely when stopping the drug. The scrotal pain subsided during the withdrawal period but only resolved completely a few days after drug termination. The patient remained on amantadine throughout this period, and low-dose Sinemet CR was re-introduced on withdrawal of the ropinirole.

Apomorphine-induced penile erections are thought to be mediated by central D2 dopamine receptor stimulation.[10] It is not surprising, therefore, that ropinirole, a potent, selective D2 receptor agonist, would produce similar drug-induced, individual dose-related erections. We suspect that this side effect may be more common than the literature would lead us to believe, but the information may not be volunteered by patients or specifically asked for by medical personnel.

The first of O'Sullivan and Hughes' case report describes a patient who, after starting apomorphine, began to experience erections after his first daily levodopa dose without concomitant apomorphine use. Although this observation is not specifically commented on by the authors, it suggests that, once primed, there is an alteration in the threshold for erectile function, and erections will be induced by a previously ineffective stimulus. It is interesting, in this regard, that our patient did not experience ropinirole-related erections until he reached an individual dose of 3 mg, but on withdrawing the drug, he continued to experience erections at much lower doses of 0.5 mg. Dopamine is thought to induce erections by stimulation of oxytocin release from the hypothalamic paraventricular nucleus.[10] Interestingly, the only report we came across of levodopa- or dopamine agonist-induced clitoral tumescence occurred in a postpartum woman using the dopamine agonist, bromocriptine, to suppress lactation.[11] In this case, an alteration of the threshold for stimulation of the dopamine–oxytocin neuroendocrine axis in the postpartum state may similarly account for the occurrence of this side effect.

Our patient reported no prior sexual dysfunction, and, like O'Sullivan and Hughes' patient who had normal erectile function, he experienced considerable discomfort when erections were drug-induced. However, three of the four patients reported by O'Sullivan and Hughes who had pre-existing sexual dysfunction found the increased erectile function associated with apomorphine desirable and used it to facilitate intercourse and enhance their sexual relationships. We suggest that consideration be given to the evaluation of ropinirole in patients with PD who are impotent.

Addendum

Subsequent to acceptance of our letter, a report was published[12] documenting nocturnal penile erections temporally related to the addition of a bedtime dose of sustained-release carbidopa/levodopa (CD/LD) to regular daily CD/LD in a single patient. These erections stopped while the patient took olanzepine and disappeared after withdrawal of the bedtime CD/LD.

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References

1. O'Sullivan JD, Hughes AJ. Apomorphine-induced penile erections in Parkinson's disease. *Mov Disord* 1998;13:536–539.
2. Stibe CMH, Lees AJ, Stern GM. Subcutaneous infusion of apomorphine and lisuride in the treatment of parkinsonian on–off fluctuations [Letter]. *Lancet* 1987;i:871.
3. Stibe CMH, Kempster PA, Lees AJ, Stern GM. Subcutaneous apomorphine in parkinsonian on–off fluctuations. *Lancet* 1988;i: 403–406.
4. D'Costa DF, Abbott RJ, Pye IF, Millac PAH. The apomorphine test in parkinsonian syndromes. *J Neurol Neurosurg Psychiatry* 1991;54:870–872.
5. Danjou P, Alexandre L, Warot D, Lacomblez L, Puech AJ. As-

sessment of erectogenic properties of apomorphine and yohimbine in man. *Br J Clin Pharmacol* 1988;26:733–739.
6. Quinn N, Marsden CD, Schachter M, Thompson C, Lang AE, Parkes JD. Intravenous lisuride in extrapyramidal disorders. In: Calne DB, ed. *Lisuride and Other Dopamine Agonists.* New York, NY: Raven Press, 1983:383–393.
7. Goodwin FK. Psychiatric side effects of levodopa in man. *JAMA* 1971;218:1915–1920.
8. Jeanty P, Van den Kerchove M, Lowenthal A, De Bruyne H. Pergolide therapy in Parkinson's disease. *J Neurol* 1984;231:148–152.
9. Uitti RJ, Tanner CM, Rajput AH, Goetz CG, Klawans HL, Thiessen B. Hypersexuality with antiparkinsonian therapy. *Clin Neuropharmacol* 1989;12:375–383.
10. Melis MR, Argiolas A, Gessa GL. Evidence that apomorphine induces penile erection and yawning by releasing oxytocin in the central nervous system. *Eur J Pharmacol* 1989;164:565–570.
11. Blin O, Schwertschlag US, Serratrice G. Painful clitoral tumescence during bromocriptine therapy. *Lancet* 1991;337:1231–1232.
12. Jiménez-Jiménez FJ, Tallón-Barranco A, Cabrera-Valdivia F, Gasalla T, Ortí-Pareja M, Zurdo M. Fluctuating penile erection related with levodopa therapy. *Neurology* 1999;52:210.

GABAa versus GABAb Hypothesis of Catatonia

I read with interest the report by Rosenfeld and Friedman.[1] They describe a case in which a 70-year-old woman with catatonia was responsive to lorazepam. The authors stated that lorazepam works better than other benzodiazepines for unknown reasons.[1]

Recent developments in the treatment of catatonia point to a new hypothesis. The GABAa versus GABAb hypothesis has developed from two separate lines of investigation. The first line of support was first described by Mastain et al who noted the favorable effect of zolpidem on catatonia.[2] They reported a 53-year-old woman with catatonia who was unresponsive to lorazepam and electroconvulsive therapy but responded dramatically to zolpidem. In a subsequent study, they noted favorable but short-term response to zolpidem in 11 patients with catatonia. Improvement was correlated with a serum level of zolpidem of 80–130 ng/mL.[3]

The second line of support was based on a case of catatonia induced after valproic acid was added to the regimen of a 42-year-old psychiatric patient on risperidone and sertraline.[4] This patient responded to lorazepam. The valproic acid-induced stimulation of GABAb receptors in the context of reduced GABAa efficacy was hypothesized to have promoted this episode of catatonia.[4]

Lorazepam is a benzodiazepine that is a strong GABAa agonist. Zolpidem is not a benzodiazepine but shares GABAa agonism. In his discussion, Lauterbach notes that stimulation of GABAb and serotonin HT1a receptors promote catatonia in experimental models,[4] whereas GABAa receptor stimulation is thought to ameliorate catatonia. Agents that block dopamine D2 receptors produce neuroleptic catatonia. Lorazepam is the most frequently used benzodiazepine for the initial treatment of catatonia. Other benzodiazepines that are also GABAa agonists may be equally effective, and other treatments may be necessary to maintain improvement in patients with catatonia.

Mastain et al noted that zolpidem could act in two ways because of its specificity for benzodiazepine type I receptors: (1) it could diminish dopamine inhibition of the prefrontal cortex, and (2) it could increase activation of the supplementary motor area by upregulation of the thalamocortical glutamate circuit.[3]

Zolpidem's specificity suggests that GABAa receptors play a crucial role in catatonia. Thomas et al have used zolpidem successfully to test for catatonia.[5] This was replicated by Zaw and Bates.[6] Lauterbach based his conclusions, in part, on the known pathophysiology of parkinsonism.[4]

Daniele et al used zolpidem in a double-blind, placebo-controlled, crossover study of 10 patients with clinically diagnosed Parkinson's disease (PD).[7] They noted that the highest density of zolpidem-binding sites is in output structures of the basal ganglia: the ventral globus pallidus and the substantia nigra, pars reticulata. Zolpidem might act by inducing selective inhibition of GABAergic inhibitory neurons in the internal globus pallidus and substantia nigra, pars reticulata.[7] Their findings suggest that zolpidem therapy could be helpful for some patients with Parkinson's disease.

Selective GABAa agonists such as zolpidem that act within the basal ganglia may represent a new therapeutic approach in Parkinson's disease and catatonia.[3,7] The GABAa versus GABAb hypothesis offers the potential for new understanding of these movement disorders.

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References

1. Rosenfeld MJ, Friedman JH. Catatonia responsive to lorazepam: a case report. *Mov Disord* 1999;14:161–162.
2. Mastain B, Vaiva G, Guerouaou D, Pommery J, Thomas P. Effet Favorable du Zolpidem sur un Etat Catatonique (translated by Carroll SA). *Rev Neurol* (*Paris*) 1995;151:52–56.
3. Mastain B, Rascle C, Thomas P, Goudmand M. Zolpidem in catatonic syndrome: from a pharmacological test to a pathophysiological hypothesis. *Mov Disord* 1998;13(suppl 2):46.
4. Lauterbach EC. Catatonia-like events after valproic acid with risperidone and sertraline. *Neuropsychiatry, Neuropsychology and Behavioral Neurology* 1998;11:157–163.
5. Thomas P, Rascle C, Mastain B, Maron M, Viava G. Test for catatonia with zolpidem [Letter]. *Lancet* 1997;349:702.
6. Zaw ZF, Bates GDL. Replication of zolpidem test for catatonia in an adolescent [Letter]. *Lancet* 1997;34:1914.
7. Daniele A, Albanese A, Gainotti G, Gregori B, Bartolomeo P. Zolpidem in Parkinson's disease. *Lancet* 1997;349:1222–1223.

Reply

We appreciate the interesting pharmacologic hypothesis our case report[1] has generated. One problem in the formulation of the hypothesis, we think, is that catatonia is a clinical syndrome that has multiple causes.[2] The terms "medical catatonia"[2] and Dr Carroll's term, "neuroleptic catatonia," in contrast with "catatonia" arising from a primary psychiatric disorder blunts the use of the term. A withdrawn or psychotic patient rendered severely parkinsonian by drugs looks catatonic but is not. Such a patient will not respond to lorazepam. The beneficial effect of zolpidem on one patient with Parkinson's disease for 5 years and six of 10 PD patients for 2 hours after a single dose[3] only

suggests a possible clinical effect, not yet a unitary mode of action in both conditions. Our own experience with zolpidem has not revealed any benefit on motor function in PD.

Catatonia is rare and therefore difficult to study. PD on the other hand is common. At this point it will be of interest to see if more cases of zolpidem-responsive catatonia or PD are reported.

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References

1. Rosenfeld MJ, Friedman JH. Catatonia responsive to lorazepam: a case report. *Mov Disord* 1999;14:161–162.
2. Gelenberg AJ. The catatonia syndrome. *Lancet* 1976;1:1339–1341.
3. Daniele A, Albanese A, Gainotti G, Gregori B, Bartolomeo P. Zolpidem in Parkinson's disease. *Lancet* 1997;349:1222–1223.

Carvedilol-Induced Myoclonus

Several drugs have been reported to cause myoclonus.[1] We add one more to this long list of medications We report what we think is the first case of drug-induced myoclonus from carvedilol, a new nonselective beta-adrenergic blocking agent with alpha-1 blocking activity used for the treatment of congestive heart failure (CHF) and hypertension.

The patient is an 81-year-old man with ischemic cardiomyopathy, recurrent CHF, and paroxysmal atrial fibrillation who was admitted for cardiac pacer placement. The procedure was done without complications. He was later started on 3.125 mg carvedilol orally per day and maintained on 0.125 mg digoxin per day, 80 mg furosemide twice a day, and 81 mg aspirin per day. Three days later, the carvedilol dose was increased to 3.125 mg twice a day (the standard initiating dose). Within hours, he was noted to have myoclonic jerks involving the face, trunk, and bilateral extremities.

Our neurologic examination was normal except for myoclonus. The myoclonus was intermittent, arrhythmic, and multifocal. It persisted but did not worsen with posture or action. This did not interfere with his gait and no ataxia was noted. He was afebrile and the general physical examination was unremarkable.

Complete blood count, serum electrolytes, and digoxin level were within normal limits except for increased blood urea nitrogen (BUN; 57 mg/dL; normal = 6–20 mg/dL) and creatine (1.5 mg/dL; normal = 0.5–1.2 mg/dL), which was unchanged from his baseline. Carvedilol was discontinued while all other medications were kept at the same dose. The myoclonus resolved within 36 hours. The BUN and creatinine levels remained elevated.

Nonselective beta-blockers have not been reported to cause myoclonus. The adrenergic system has not been implicated in the pathophysiology of myoclonus.[1] On the contrary, propranolol, the prototypic nonselective beta blocker, was found to have a protective effect against picrotoxin-induced myoclonus in rats.[2]

We think the myoclonus exhibited by our patient was the result of carvedilol intake based on the temporal association with increased dosage and resolution with discontinuation. All other drugs taken in conjunction with carvedilol had been taken prior to his admission without dose adjustments. The BUN and creatinine level remained unchanged throughout the hospital course.

Despite the lack of electrophysiological evidence, the patient's myoclonus is consistent with a subcortical origin, as are most examples of drug-induced myoclonus.[1] Unlike cortical myoclonus, no worsening was noted with posture, action, or sensory stimuli.[3] We have no etiologic or clinical basis to implicate myoclonus of spinal origin.

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References

1. Gimenez-Roldan S. Neuropharmacology and treatment of myoclonus. In: Jankovic J, Tolosa E, eds. *Parkinson's Disease and Movement Disorders*, 3rd ed. Baltimore, MD: Williams and Wilkins, 1998:467–490.
2. Paul V, Krishnamoorthy MS. The synergistic protective effect of propranolol and aminooxyacetic acid against picrotoxin-induced myoclonus in rats. *Indian J Med Res* 1990;92:17–20.
3. Shibasaki H. Myoclonus and startle syndromes. In: Jankovic J, Tolosa E, eds. *Parkinson's Disease and Movement Disorders*, 3rd ed. Baltimore, MD: Williams and Wilkins, 1998:453–466.