Carbidopa-Levodopa–Induced Recrudescence of Premorbid Tic Disorder in Remission

Sir: Dopamine agonists, such as carbidopa-levodopa, have utility in alleviating symptoms of movement disorders, e.g., parkinsonism, and can reduce distressing movement disturbances arising from a variety of other conditions, e.g., restless legs syndrome, and tremor arising from head injury. We report a case illustrating that utilization of a dopamine agonist can precipitate tics in a patient with a clinically unrecognized history of tic disorder that had been in remission for years.

Case report. Mr. A, an 18-year-old man, was admitted to the hospital in late 2004 after sustaining multiple injuries from a motor vehicle accident. In addition to fractures, he had a left temporal contusion with intraventricular hemorrhage requiring ventriculostomy. After surgical intervention, he required intensive physical and occupational therapy and was admitted to the physiatry service to address his generalized deconditioning. A mild bilateral tremor was noted in both upper extremities, and although there was no associated cogwheel rigidity or bradykinesia, carbidopa-levodopa, 25 mg/100 mg t.i.d., was initiated.

After 2 days of treatment, psychiatric consultation was requested for "agitation." Specifically, Mr. A was noted to blurt out obscenities in a recurrent and compulsive manner; this was uncharacteristic of him earlier in his hospital course or even prior to the head injury. In addition, he was noted to exhibit rapidly occurring head tossing, facial twitching, frowning, and grimacing repeatedly throughout the day. There were no changes in his cognitive functioning as compared with his condition in previous days, and he had no notable inattentiveness or fluctuations in consciousness. There were no associated mood disturbances, perceptual disturbances, or delusions. There were no electrolyte disturbances noted, no hypoxia, and no evidence of infection. Computed tomography scan of the head failed to reveal any progression of the original central nervous system injury. The psychiatric consultants recommended discontinuation of carbidopa-levodopa. Within 3 days of discontinuation, the aforementioned tics abated completely.

Collateral information provided by Mr. A's mother revealed that he had a remote history of childhood tics, at approximately 9 to 10 years of age, that appeared to have remitted entirely by the time he entered adolescence. He displayed transient mild vocal tics (e.g., throat clearing and barking, but never coprolalia) and mild motor tics (e.g., facial twitching), generally for weeks at a time and occasionally exacerbated by periods of distress. The tics never interfered with his personal or social life and reportedly were never severe enough to warrant formal dopamine antagonist therapy.

Tourette's disorder consists of a combination of vocal and multiple motor tics that generally develop early in childhood, often before 7 years of age, and persist for at least 1 year.[1] There is wide variability in the presentation and severity of Tourette's disorder, i.e., number, type, and duration of symptoms.[2] In milder variants of the disorder, symptoms often decrease as an individual proceeds through adolescence. Mild tic disorders may go unrecognized and fail to receive medical attention. The patient described herein lacked the symptom cluster consistent with classic Tourette's disorder and never required formal dopamine antagonist therapy. His symptoms appeared to be consistent with the variant classified as transient tic disorder.[1]

Dopaminergic excess has been postulated to underlie the pathophysiology of Tourette's disorder.[2,3] This postulation has been based upon the observation that dopamine antagonists mitigate tics, while dopamine agonists, e.g., levodopa, and stimulants, e.g., methylphenidate, may exacerbate them.[3,4] However, data are emerging that suggest that dopamine agonists may have a role in reducing tic severity.[5] Such conflicting lines of evidence suggest that much has yet to be learned about the pathophysiology of Tourette's disorder and its variants.

What is striking in the case presented here is that administration of levodopa appeared to result in a recrudescence of a previously dormant tic disorder. The temporal relationship between the initiation of carbidopa-levodopa and the onset of motor and vocal tics in this patient, along with the rapid cessation of symptoms shortly after drug discontinuation, suggests that the medication was responsible for the tic recrudescence observed in our patient. It is possible that the central nervous system injury sustained may have rendered him vulnerable to untoward effects of dopamine augmentation. Use of dopamine agonists in medical and/or surgical patients can potentially complicate their clinical course, particularly if a current or remote history of tic disorder is overlooked or ignored.

Drs. Latif, Leo, and Bakhai report no financial or other relationship relevant to the subject of this letter.

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Panic Disorder, Alcohol and Substance Abuse, and Benzodiazepine Prescription

Sir: In a recent supplement of the *Companion*, the utilization of benzodiazepines in clinical practice was reviewed.[1] In that supplement, several authors advised caution in prescribing benzodiazepines to patients with histories of alcohol (p. 5) or substance abuse (p. 23). We were curious about the actual percentage of patients for whom this precaution might apply.

Table 1. Lifetime Prevalence of Alcohol and Substance Abuse Among Study Participants With Panic Disorder

Study	Year	N	Sample Characteristics	Lifetime Prevalence, n (%)
Himle and Hill[3]	1991	70	Epidemiologic Catchment Area Study	Alcohol abuse/dependence: 15 (21.4)
Lepine et al[4]	1993	100	Outpatients	Substance abuse/alcohol: 23 (23.0)
Dick et al[5]	1994	47	Random sample of households	Alcohol abuse/dependence: 25 (53.2); drug abuse/dependence: 20 (42.6)
Katerndahl and Realini[6]	1999	97	Community sample with panic disorder	Alcohol abuse: 31 (32.0); substance abuse: 27 (27.8); any substance abuse: 38 (39.2)
Mavissakalian and Guo[7]	2002	306	Evaluations for long-term drug program	Alcohol abuse: 51 (16.7); other substance abuse: 61 (19.9)
Marquez et al[8]	2003	274	Clinical sample with panic disorder	Alcohol use disorder: 26 (9.5)
Sbrana et al[9]	2005	50	Outpatients/inpatients with panic disorder	Alcohol use disorder: 2 (4.0) Any substance use disorder: 3 (6.0); subthreshold substance use: 13 (26.0)
Total		944		Alcohol: 150/844 (17.7)[a]; other substance abuse: 111/500 (22.2)[b]

[a]Data from the Lepine et al. study[4] were excluded.
[b]Data are from the 4 studies in which data on substance abuse other than alcohol abuse (Dick et al.,[5] Katerndahl and Realini,[6] Mavissakalian and Guo,[7] and Sbrana et al.[9]) were reported.

To explore this, we undertook a literature search dating back to 1990 using the PsycINFO and MEDLINE databases. We entered the search terms *panic disorder*, *substance abuse*, and *alcohol*. After identifying and gathering articles, we excluded those that had already been addressed in review articles, were written in foreign languages, or reported studies that comprised adolescent participants.

We first examined the lifetime prevalence of alcohol and substance abuse in studies in which participants were identified by a diagnosis of panic disorder. As a prelude to our findings, we encountered a 1990 review article by Brady and Lydiard[2] that reported 2 earlier studies in which the prevalence of alcohol abuse or alcoholism was 7% to 8% among panic disorder samples. We located 7 studies published since 1990 (Table 1) that explored the lifetime prevalence of alcohol and substance abuse in participants with panic disorder.[3–9] Because the study by Lepine et al.[4] did not separate alcohol from substance abuse, we elected to exclude it from the present analysis, bringing the subsequent working sample size to 844 participants. In this subsample, 150 participants (17.7%) with panic disorder were also diagnosed with alcohol abuse or dependence. As for "other substance abuse," again excluding the Lepine et al. study,[4] 4 studies comprising 500 participants were relevant. The prevalence of other substance abuse was confirmed in 111 participants (22.2%). In summary, these data indicate that in studies since 1990, approximately 20% of panic disorder patients had lifetime histories of either alcohol or other substance abuse.

To augment the preceding findings, we examined 2 large community studies that explored the prevalence of alcohol and substance abuse in panic disorder participants during the 12 months preceding assessment. In the first study,[10] the prevalence rate of panic disorder among 9282 participants was 2.7%; the correlations between panic disorder and alcohol abuse, alcohol dependence, drug abuse, and drug dependence were 0.27 (significant at $p < .05$), 0.25, 0.16, and 0.27, respectively. In the second study,[11] the prevalence of any comorbid alcohol use disorder during the preceding 12 months in panic disorder participants with and without agoraphobia was 18.8% and 15.3%, respectively, while the prevalence of any comorbid substance abuse disorder was 24.2% and 17.3%, respectively.

We next examined the prevalence of panic disorder in study samples of alcoholics or substance abusers. Brady and Lydiard[2] summarized these data up to 1993. Averaging various samples, these authors found that 8.8% (range, 1.0%–20.0%) of participants met the criteria for panic disorder. In the 2 subsequent studies[12,13] that emerged during our literature search, the lifetime prevalence rate for panic disorder among alcoholics was 4.1% (144/3475), and among those who abuse or are dependent on sedative/hypnotics, the lifetime prevalence rate was 13.2% (58/441). These rates are substantially less than the rates of alcohol/substance abuse reported in panic disorder samples.

Understandably, it is difficult to accurately assess and compare prevalence rates among studies because of varying assessment tools, different time frames (preceding 12 months vs. lifetime prevalence rates), the timing of the assessment in relationship to detoxification in alcohol and substance abuse populations, patient candor, and varying characteristics of the study population (e.g., primary vs. tertiary care, clinical vs. nonclinical). In addition, we may have missed studies presented at meetings and abstracts, as well as published articles that were not accessed by our search terms. However, these data suggest that approximately 20% of panic disorder patients have lifetime histories of alcohol and/or substance abuse. Because of the substantial rate of comorbidity between panic disorder and alcohol/substance abuse, clinicians need to screen for these disorders at the outset and exercise caution in prescribing benzodiazepines in this subgroup other than for detoxification.

Drs. R. Sansone, Griffith, and L. Sansone report no financial or other relationship relevant to the subject of this letter.

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