Amantadine Use Associated with Impulse Control Disorders in Parkinson Disease in Cross-Sectional Study

Daniel Weintraub, MD,[1,2,3] Mandy Sohr, PhD,[4]
Marc N. Potenza, MD, PhD,[5,6,7]
Andrew D. Siderowf, MD, MSCE,[2]
Mark Stacy, MD,[8] Valerie Voon, MD,[9]
Jacqueline Whetteckey, MD,[10]
Glen R. Wunderlich, PhD,[11]
and Anthony E. Lang, MD, FRCPC[12]

A recent controlled clinical trial suggested a role for amantadine as a treatment for pathological gambling in patients with Parkinson disease (PD). Analyzing data from a large cross-sectional study of impulse control disorders (ICDs) in PD, amantadine use (n = 728), vs no amantadine use (n = 2,357), was positively associated with a diagnosis of any ICD (17.6% vs 12.4%, $p < 0.001$) and compulsive gambling specifically (7.4% vs 4.2%, $p < 0.001$). This amantadine association remained after controlling for covariates of amantadine use, including both dopamine agonist use and levodopa dosage. Further research, including larger clinical trials, is needed to assess the role of amantadine in the development and treatment of ICDs in PD.

ANN NEUROL 2010;68:963–968

The cross-sectional prevalence of impulse control disorders (ICDs), specifically compulsive gambling, buying, sexual behavior, and eating, in Parkinson disease (PD) was recently reported to be 14% in a study of 3,090 patients (ie, the DOMINION study).[1] In this study, an association was observed between ICDs and treatment with dopamine replacement therapies (DRTs), including both dopamine agonists (DAs) and levodopa.

The management of ICDs in PD is complex. Case reporting and anecdotal experience suggest that ICD behaviors may resolve with dosage reduction or a change in DRT.[2–4] Selective serotonin reuptake inhibitors (SSRIs) are used clinically, but there is only mixed empirical evidence to support use for this indication in non-PD subjects,[5] and none in the PD population. Recent research suggests that nalmefene and naltrexone,[6,7] both opioid antagonists, and N-acetylcysteine (NAC),[8] a glutamate-modulating agent, are efficacious in the treatment of pathological gambling in the general population.

Amantadine is an aminoadamantane with modest antiparkinsonian activity used in early PD and increasingly as a treatment for dyskinesias and motor fluctuations.[9] A recent controlled study of 17 PD patients suggested that amantadine may be efficacious for the treatment of pathological gambling in patients with PD.[10] In light of this study and because amantadine has dopamine-enhancing effects,[11] a property associated with ICDs in PD, we performed a secondary analysis of the DOMINION data to determine the frequency of ICDs in PD patients treated with amantadine.

Patients and Methods

Study Participants and Design

Study participants and design were described in detail previously.[1] In summary, a semistructured interview using formal diagnostic criteria assessed current frequency of 4 ICDs (problem/pathological gambling, compulsive sexual behavior, compulsive buying, and binge-eating disorder) in treated idiopathic PD patients. Subjects were recruited from 46 movement disorders centers in the United States (n = 33) and Canada (n = 13). Inclusion criteria required treatment with a PD medication for a period of at least 1 year with demonstrated response. The recorded PD medications and dosages were those being taken at the time of assessment; these data included amantadine use (yes/no), but not amantadine dosage.

Procedures and Measurements

The following semistructured diagnostic instruments were administered by trained research staff: (1) Massachusetts Gambling Screen (MAGS)[12] for problem/pathological gambling; (2) Minnesota Impulsive Disorders Interview (MIDI)[13] for compulsive buying and sexual behavior; and (3) Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)[14] proposed research criteria for binge-eating disorder. Demographic and clinical data were obtained from patients in a semistructured interview and verified by chart review when necessary. Modified Hoehn and Yahr staging was obtained from a movement disorders clinician or by chart review.

From the [1]Departments of [1]Psychiatry and [2]Neurology, University of Pennsylvania School of Medicine, Philadelphia, PA; [3]Philadelphia Veterans Affairs Medical Center, Philadelphia, PA; [4]Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany; Departments of [5]Psychiatry, [6]Child Study, and [7]Neurobiology, Yale University School of Medicine, New Haven, CT; [8]Department of Neurology, Duke University Medical Center, Durham, NC; [9]University of Cambridge, Cambridge, England; [10]Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT; [11]Boehringer Ingelheim (Canada) Ltd., Burlington, Ontario, Canada; [12]Department of Neurology, University of Toronto, Toronto, Ontario, Canada.

Address correspondence to Dr Weintraub, 3615 Chestnut St., #330, Philadelphia, PA 19104. E-mail: daniel.weintraub@uphs.upenn.edu

Members of the DOMINION Study Group are listed in the Appendix on page xx.

Received Jun 10, 2010, and in revised form Jul 9, 2010. Accepted for publication Jul 16, 2010.

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.22164

TABLE 1: Impulse Control Disorder Frequencies by Amantadine Treatment Status

ICD Type	Amantadine Treatment Status	Current ICD, n (%)	No Current ICD, n (%)	*p* (CMH-test); Odds Ratio (95% CI)[a]
Any ICD	No amantadine use (n = 2357)	292 (12.4)	2065 (87.6)	<0.001; 1.49 (1.19–1.87)
	Amantadine use (n = 728)	128 (17.6)	600 (82.4)	
Problem/pathological gambling	No amantadine use	100 (4.2)	2257 (95.8)	<0.001
	Amantadine use	54 (7.4)	674 (92.6)	1.78 (1.27–2.50)
Compulsive sexual behavior	No amantadine use	71 (3.0)	2286 (97.0)	0.001
	Amantadine use	37 (5.1)	691 (94.9)	1.70 (1.13–2.56)
Compulsive buying	No amantadine use	119 (5.0)	2238 (95.0)	0.005
	Amantadine use	58 (8.0)	670 (92.0)	1.60 (1.15–2.22)
Binge-eating disorder	No amantadine use	100 (4.2)	2257 (95.8)	0.90
	Amantadine use	32 (4.4)	696 (95.6)	1.03 (0.68–1.54)

[a]Stratified by country.
CI = confidence interval; CMH = Cochran-Mantel-Haenszel test.

Statistical Analysis

A Cochran-Mantel-Haenszel (CMH) test with country stratification was performed, and odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated, for between-group comparisons in ICD frequencies. Breslow Day tests were applied for homogeneity of odds. Other between-group patient characteristics were compared by the CMH test or Wilcoxon-Mann-Whitney test. As preliminary analyses for the primary manuscript identified between-country differences in ICD frequencies, all univariate analyses for that and this manuscript were stratified by country. For secondary analyses, similar to what was done for the primary manuscript, variables associated with amantadine use on univariate analysis at $p < 0.10$ were entered into a stepwise logistic regression model to determine the independent effects of different covariates on ICD status.

The following conversion rates were used to calculate levodopa equivalent daily dosage (LEDD): 100mg regular levodopa = 133.3mg controlled-release levodopa = 80mg of levodopa + catechol-*O*-methyl-transferase inhibitor. Levodopa LEDD was divided at the median to examine levodopa dosing effects. Analyses were performed with SAS software, release 8.02 (SAS Institute, Inc., Cary, NC). A p value <0.05 was considered significant.

Results

Description of Study Population

A total of 3,085 patients participated and had data available for amantadine use. Approximately one-quarter (23.6%, n = 728) of patients were taking amantadine, two-thirds (66.1%, n = 2,038) were taking 1 or more DAs, and 86.8% (n = 2,678) were taking levodopa, at a median LEDD of 450mg/day.

ICD Frequencies by Amantadine Use

At least 1 active ICD was identified in 17.6% of amantadine-treated patients, compared with 12.4% of patients not taking amantadine ($p < 0.001$) (Table 1). The individual ICDs associated with amantadine use were problem/pathological gambling ($p < 0.001$), compulsive sexual behavior ($p = 0.001$), and compulsive buying ($p = 0.005$).

Demographic and Clinical Characteristics by Amantadine Use

Patients treated with amantadine, compared with those not using amantadine, were younger, had longer PD duration, had more severe PD based on Hoehn and Yahr stage, were more likely to have undergone deep brain stimulation surgery, had more formal education, were more likely to be treated with a dopamine agonist (DA), and were taking a higher levodopa dosage (Table 2).

Logistic Regression Model of ICD Correlates

Examining the entire study population and using a stepwise logistic regression model, variables associated with amantadine use and also independently associated with diagnosis

TABLE 2: Demographic and Clinical Correlates of Amantadine Use

Variable	Amantadine Use, n = 728 (23.6%)	No Amantadine Use, n = 2357 (76.4%)	p[a]
Gender, male (%)	463 (63.6)	1515 (64.3)	0.6966
Age			<0.0001
mean (SD) years	62.4 (8.1)	64.3 (7.9)	
≤65 years (%)	446 (61.3)	1177 (49.9)	
Race, white (%)	706 (97.0)	2258 (95.8)	0.1855
Marital status, married (%)	584 (80.2)	1860 (78.9)	0.4767
PD duration, median years (25th–75th percentile)	10.0 (6.4–14.0)	5.7 (3.3–9.2)	<0.0001
Hoehn and Yahr stage, median (25th–75th percentile)	n = 724; 2 (2–3)	n = 2354; 2 (2–2.5)	<0.0001
History deep brain stimulation, yes (%)	94 (12.9)	206 (8.7)	0.0019
Country, United States (%)	547 (75.1)	1698 (72.0)	0.1009
Education, partial college or higher; yes (%)	534 (73.4)	1625 (68.9)	0.0415
Current smoking, yes (%)	33 (4.5)	85 (3.6)	0.2385
Current alcohol use, yes (%)	281 (38.6)	990 (42.0)	0.1322
Family history gambling problems, yes (%)	32 (4.4)	94 (4.0)	0.6330
Current family gambling problems, yes (%)	7 (1.0)	27 (1.2)	0.6998
Family history alcohol abuse, yes (%)	155 (21.3)	571 (24.2)	0.0972
Side predominance, n (%)			
Right	335 (46.0)	1143 (48.5)	0.1017
Left	303 (41.6)	981 (41.6)	
Symmetrical	90 (12.4)	233 (9.9)	
Dopamine agonist use, yes (%)	521 (71.6)	1517 (64.4)	0.0003
Levodopa use, yes (%)	639 (87.8)	2039 (86.5)	0.3648
Levodopa LEDD, median mg/day	468.75	450.0	0.0001

[a]Between-group comparison of amantadine use with no amantadine use; Cochran-Mantel-Haenszel test (stratified by country) or Mann-Whitney test.

of a current ICD were younger age (≤65 years), DA use, higher levodopa dosage, and amantadine use (Table 3). Based on the ORs, the strength of the association for the different medications was greatest for DA use, followed by higher levodopa dosage, and then amantadine use.

Discussion

This is the first study to present large-scale epidemiological data on the association between amantadine use and ICDs in PD. We found that amantadine use was associated with the presence of 1 or more ICDs, and at an individual ICD level this association was observed for compulsive gambling, sexual behavior, and buying. This association also was present on multivariable analysis after controlling for possible confounding clinical variables, including DA use and levodopa dosage. The strength of the association was stronger on univariate compared with multivariable analysis, and a possible explanation for this is that amantadine-treated patients were on higher levodopa dosages (since amantadine is typically used to treat dyskinesias associated with higher levodopa dosages), and higher levodopa dosage was also associated with ICDs.

Amantadine use was relatively common in our study population, with approximately one-quarter of patients taking this medication. Amantadine is thought to have modest antiparkinsonian activity, and although used for this purpose, it is frequently used as a treatment for dyskinesias and motor fluctuations.[9]

Specific strengths of the study include: systematic evaluation of a large number of PD patients in routine clinical care; concurrent evaluation of gambling, sex,

TABLE 3: Multivariable Logistic Regression Model (Stepwise Selection) of ICD Correlates

Step	Variable[a]	Model	
		Odds ratio (95% CI)	*p*
1	Age (≤65 years vs >65 years)	2.40 (1.91–3.02)	<0.0001
2	DA use (yes vs no)	2.64 (2.01–3.46)	<0.0001
3	Levodopa LEDD (median ≥ 450mg/day)	1.50 (1.21–1.86)	0.0002
4	Amantadine use (yes vs no)	1.29 (1.02–1.63)	0.0342

[a]Clinical and demographic variables included were those with $p < 0.10$ on univariate analysis, only data for significant results presented. Other variables included in model were PD duration, Hoehn and Yahr stage, history deep brain stimulation, education, and family history of alcohol abuse.

shopping, and eating ICDs using standardized assessment instruments; and use of a priori defined recruitment procedure to minimize sampling bias (ie, recruitment of participants without prior knowledge of ICD or PD medication status). Regarding limitations, the study was not designed to define the etiological risk factors of ICDs in PD, since it was not a prospective randomized study of different DRTs. Thus, cause-effect conclusions cannot be drawn. Second, the protocol did not assess the frequency of other compulsive behaviors reported to occur in this population, such as punding[15] and dopamine dysregulation syndrome,[16] which may differ from ICDs in terms of their phenomenology and association with PD medications. Third, we were not able to examine specific aspects of amantadine use, such as indication, dosage, duration of exposure, and association with antipsychotic use, as these data were not collected. Finally, amantadine is prescribed primarily to treat dyskinesias, and if a direct association between dyskinesias and ICDs exists, amantadine use might be a confounder. However, dyskinesias and ICDs are typically comorbid in patients with DDS who are on high levodopa dosages, and dopaminergic therapy was controlled in the regression model.

The exact mechanisms of action of amantadine, including its effects in PD treatment, are unknown. Of relevance to PD and ICDs, it is reported to have both dopamine-enhancing effects (by increasing presynaptic dopamine release, blocking dopamine reuptake into presynaptic neurons, and possibly increasing D2 receptor availability) and antiglutamatergic properties.[11,17,18] Higher dopaminergic activity is 1 of several factors associated with the development of ICDs in PD. Conversely, amantadine's antiglutamatergic properties may have potential benefit as a treatment for ICDs.

Regarding preliminary evidence for the relationship between amantadine use and ICDs in PD, in a previous study amantadine treatment was associated with the presence of an ICD on univariate analysis, but not in a multivariable model.[19] However, the sample size in that study was nearly 10-fold lower than in this study, and only 55 patients were treated with amantadine in the previous study. In contrast, a recent controlled clinical trial (n = 17) found amantadine to be efficacious for the treatment of pathological gambling in patients with PD.[10] The authors of this latter study hypothesized that the antiglutamatergic properties of amantadine may have led to the positive results. Additional support for this hypothesis comes from a positive study of NAC, an amino acid that modulates glutamatergic activity, in the treatment of pathological gambling in the general population.[8]

It is possible that the complex, and not fully elucidated, pharmacologic properties of amantadine may explain these seemingly disparate findings. Chronic dopaminergic stimulation has been linked with both ICDs and dyskinesias, but amantadine appears to have *antidyskinetic* effects, which may be related to its antiglutamatergic properties.[20] Thus, the pro-dopaminergic activity of amantadine may contribute to ICD development in at-risk PD patients, while its antiglutamatergic properties may have beneficial effects when it is introduced in patients already suffering from ICDs.

This study demonstrates that amantadine use in PD is associated with ICDs in general, and compulsive gambling, buying and sexual behavior specifically. Further research is needed to define more precisely how amantadine may influence the development and treatment of ICDs in PD.

Acknowledgments

This study was funded by Boehringer Ingelheim.

We acknowledge the efforts of the principal investigators and research staff at the 46 participating centers (see list of participating sites and principal investigators in Appendix A), as well the Trial Data Manager, Ms. Joanne Zuck.

Potential Conflicts of Interest

Dr. Weintraub has received consulting fees or honoraria or grant support from Boehringer Ingelheim, BrainCells, EMD Serono, Novartis, Ovation, and Wyeth. Dr. Potenza has received consulting fees or honoraria from Boehringer Ingelheim, has consulted for and has financial interests in Somaxon, has received research support from Mohegan Sun Casino, the National Center for Responsible Gaming and its affiliated Institute for Research on Gambling Disorders, and Forest Laboratories pharmaceuticals, and has consulted for law offices and the federal public defender's office in issues related to impulse control disorders. Dr. Siderowf has received consulting fees or honoraria from Boehringer Ingelheim, Merck Serono, and Teva. Dr. Stacy has received consulting fees or honoraria from Allergan, Boehringer Ingelheim, Osmotica, Biogen, General Electric, Kyowa, Neurologix, Novartis, Synosia, and Teva. Dr. Lang has received consulting fees or honoraria from Boehringer Ingelheim, Ceregene, Eisai, Medtronic, Novartis, Prestwick, Merck Serono, Solvay, Taro, and Teva.

Appendix A: DOMINION Study Group (Principal Investigators)

United States: R. Pahwa, University of Kansas School of Medicine, Kansas City, KS; W. Ondo, Baylor College of Medicine, Houston, TX; B. Scott, Duke University School of Medicine, Durham, NC; P. Barbour, Lehigh Valley Hospital, Allentown, PA; J. Friedman, Neuro-Health, Inc., Warwick, RI; J. Morgan, Medical College of Georgia, Augusta, GA; E. Driver-Dunckley, Mayo Clinic Arizona, Scottsdale, AZ; M. Menza, University of Medicine and Dentistry, New Jersey (Robert Wood Johnson Medical School), Piscataway, NJ; H. Fernandez, University of Florida School of Medicine, Gainesville, FL; D. Weintraub, University of Pennsylvania and Veterans Affairs Medical Center, Philadelphia, PA; N. Leopold, Crozer Chester Medical Center, Upland, PA; D. Jennings, Molecular NeuroImaging, L.L.C., New Haven, CT; T. Simuni, Northwestern University School of Medicine, Chicago, IL; L. Marsh, The Johns Hopkins University School of Medicine, Baltimore, MD; W. Marks, Veterans Affairs Medical Center, San Francisco, CA; M. Nirenberg, Weill Medical College of Cornell University, New York, NY; D. Margolin, Margolin Brain Institute, Fresno, CA; S. Isaacson, Parkinson Disease and Movement Disorders of Boca Raton, Boca Raton, FL; A. Diamond, Colorado Neurology, Englewood, CO; G. Liang, The Parkinson's Institute, Sunnyvale, CA; J. Schneider, Thomas Jefferson University, Jefferson Medical College, Philadelphia, PA; H. Shill, Sun Health Research Institute, Sun City, AZ; M. Baron, Veterans Affairs Medical Center, Richmond, VA; J. Murphy, Associate Neurologists, P.C., Danbury, CT; P. LeWitt, Clinical Neuroscience Center, Southfield, MI; D. Higgins, Albany Medical College, Albany, NY; J. Sutton, Pacific Neuroscience Medical Group, Inc., Oxnard, CA; M. Thomas, Neurology Specialists of Dallas, Dallas, TX; T. Davis, Vanderbilt University School of Medicine, Nashville, TN; W. Grainger, Neurological Physicians of Arizona, Mesa, AZ; W. McDonald, Emory University School of Medicine, Atlanta, GA; D. Kreitzman, Parkinson's Disease and Movement Disorders of Long Island, Commack, NY

Canada: M. Guttman, Markham Professional Centre, Markham, ON; E. Pourcher, Quebec Memory & Motor Skills Disorders Clinic, Québec City, QC; M. Panisset, Hôtel-Dieu de Montreal, Montréal, QC; A. Goodridge, Health Science Centre, St. John's, NF; D. Grimes, The Ottawa Hospital - Civic Campus, Ottawa, ON; D. Hobson, Deer Lodge Centre, Winnipeg, MB; W. Martin, Glenrose Rehabilitation Hospital, Edmonton, AB; R. Ranawaya, Department of Clinical Neurosciences Area 3 Neurology, Calgary, AB; D. Stewart, Neurocare Research Consulting Corporation, Kitchener, ON; J. Miyasaki, Toronto Western Hospital, Toronto, ON; A. Rajput, Royal University Hospital, Saskatoon, SK; M. Jog, Canadian Foundation for Innovation, London, ON; D. King, Dalhousie University, Halifax, Nova Scotia.

References

1. Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol 2010;67:589–595.
2. Driver-Dunckley E, Samanta J, Stacy M. Pathological gambling associated with dopamine agonist therapy in Parkinson's disease. Neurology 2003;61:422–423.
3. Dodd ML, Klos KJ, Bower JH, et al. Pathological gambling caused by drugs used to treat Parkinson disease. Arch Neurol 2005;62: 1–5.
4. Mamikonyan E, Siderowf AD, Duda JE, et al. Long-term follow-up of impulse control disorders in Parkinson's disease. Mov Disord 2008;23:75–80.
5. Grant JE, Potenza MN. Impulse control disorders: clinical characteristics and pharmacological management. Ann Clin Psychiatry 2004;16:27–34.
6. Grant JE, Potenza MN, Hollander E, et al. Multicenter investigation of the opioid antagonist nalmefene in the treatment of pathological gambling. Am J Psychiatry 2006;163: 303–312.
7. Kim SW, Grant JE, Adson DE, et al. Double-blind naltrexone and placebo comparison study in the treatment of pathological gambling. Biol Psychiatry 2001;49:914–921.

8. Grant JE, Kim SW, Odlaug BL. N-acetyl cysteine, a glutamate-modulating agent, in the treatment of pathological gambling: a pilot study. Biol Psychiatry 2007;62:652–657.
9. Thomas A, Iacono D, Luciano AL, et al. Duration of amantadine benefit on dyskinesia of severe Parkinson's disease. J Neurol Neurosurg Psychiatry 2004;75:141–143.
10. Thomas A, Bonnani L, Gambi F, et al. Pathological gambling in Parkinson disease is reduced by amantadine. Ann Neurol (in press). DOI:10.1002/ana.22029.
11. Mizoguchi K, Yokoo H, Yoshida M, et al. Amantadine increases the extracellular dopamine levels in the striatum by re-uptake inhibition and by N-methyl-$_D$-aspartate antagonism. Brain Res 1994;662:255–258.
12. Shaffer HJ, LaBrie R, Scanlan KM, et al. Pathological gambling among adolescents: Massachusetts gambling screen (MAGS). J Gambl Stud 1994;10:339–362.
13. Christenson GA, Faber RJ, deZwaan M. Compulsive buying: descriptive characteristics and psychiatric comorbidity. J Clin Psychiatry 1994;55:5–11.
14. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. text revision. Washington, DC: American Psychiatric Association, 2000.
15. Evans AH, Katzenschlager R, Paviour D, et al. Punding in Parkinson's disease: its relation to the dopamine dysregulation syndrome. Mov Disord 2004;19:397–405.
16. Giovannoni G, O'Sullivan JD, Turner K, et al. Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies. J Neurol Neurosurg Psychiatry 2000; 68:423–428.
17. Volonté MA, Moresco RM, Messa C, et al. A PET study with [11-C]raclopride in Parkinson's disease: preliminary results on the effect of amantadine on the dopaminergic system. Neurol Sci 2001;22:107–108.
18. Blanpied TA, Clarke RJ, Johnson JW. Amantadine inhibits NMDA receptors by accelerating channel closure during channel block. J Neurosci 2005;25:3312–3322.
19. Weintraub D, Siderowf AD, Potenza MN, et al. Association of dopamine agonist use with impulse control disorders in Parkinson disease. Arch Neurol 2006;63:969–973.
20. Voon V, Fernagut P-O, Baunez C, et al. Chronic dopaminergic stimulation in Parkinson's disease: from dyskinesias to impulse control disorders. Lancet Neurol 2009;8: 1140–1149.