Sildenafil in the Treatment of Erectile Dysfunction in Parkinson's Disease

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Abstract: Background: Erectile dysfunction (ED) is a common nonmotor feature in patients with Parkinson's disease (PD). Data regarding the tolerability and efficacy of anti-ED medication in the PD population are limited. The aim of this work was to assess the safety and efficacy of sildenafil in treatment of ED in men with PD.

Methods: This was a double-blind, placebo-controlled, cross-over study consisting of two 4-week arms separated by a 2-week washout period. Treatment sequence (placebo-sildenafil vs. sildenafil-placebo) was randomized. Sildenafil was started at 50 mg and adjusted to 25, 50, or 100 mg after 2 weeks, depending upon side effects. The Erectile Function domain of the International Index of Erectile Function (IIEF-EF; primary outcome measure) and the Parkinson's Disease Quality of Life (secondary outcome measure) were obtained at baseline and end of each treatment period. The UPDRS was obtained at each study visit. The difference between group means was tested for statistical significance using *t* tests.

Results: Twenty men participated and completed both treatment arms of the study. There was one instance of headache as a side effect. There was a significant effect of sildenafil on sexual functioning as measured by the IIEF-EF domain ($P < 0.0001$; mean for sildenafil = 23.2 ± 7.0 ; mean for placebo = 12.3 ± 7.5). There were no treatment effects for quality of life ($P = 0.3$) or PD symptoms ($P = 0.86$).

Conclusions: Sildenafil was safe and improved ED in this sample of men with PD. Overall, PD symptoms and quality of life were not impacted by use of sildenafil.

The cardinal features of Parkinson's disease (PD) include bradykinesia, rigidity, tremor, and postural instability. The disorder is also characterized by nonmotor symptoms, including dysautonomia, that contribute to the patient's overall disability. Erectile dysfunction (ED) is a common, nonmotor symptom in men with PD and is viewed as a component of autonomic nervous system dysfunction in these patients. Other factors may contribute to the pathophysiology of ED in PD, including motor disability, medication side effect, and depression.¹ ED may have an impact on quality of life in men with PD.² Sildenafil citrate has been an effective treatment of ED in men without PD.³ Sildenafil has been suggested as a treatment for ED in PD by an American Academy of Neurology Practice Parameter,¹ but this recommendation was anchored in a single study of

12 subjects.⁴ The current study is a double-blind, placebo-controlled, cross-over study of sildenafil in 20 men with PD and ED.

Patients and Methods

Men were recruited from a university-based movement disorders clinic. All PD subjects were examined by a movement disorders neurologist (L.V.M.) and met UK PD Society Brain Bank criteria.⁵ All subjects were taking medication for PD and were instructed to continue taking their regular medication throughout the study. Efforts were made to not change subjects' medication throughout the course of the study. The study was approved by the institutional review board of Rush University

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Keywords: Parkinson's disease, nonmotor symptoms, sildenafil.

A portion of this study was presented at the 63rd Annual Meeting of the American Academy of Neurology, Honolulu, HI, April 2011. Relevant disclosures and conflicts of interest are listed at the end of this article.

Received 9 February 2016; revised 2 September 2016; accepted 24 September 2016.

Published online 20 November 2016 in Wiley InterScience (www.interscience.wiley.com). DOI:10.1002/mdc3.12456

(Chicago, IL); subjects gave written consent to participate in the study.

Subjects were required to have an H & Y stage of 1 to 3 in the ON state, between 35 and 75 years of age, and in a stable sexual relationship. ED has been defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance.⁶ There is no universally agreed upon criteria for duration of the problem or how often the problem needs to occur in order to fulfill the definition of ED. Because ED may be present from time to time in healthy men, the current study used a more-specific and more-rigorous definition: an inability to achieve an erection sufficient for intercourse more than 50% of attempts during the preceding 3 months. Exclusion criteria included: (1) history of stroke, myocardial infarction, or significant arrhythmia within the last 6 months; (2) taking nitroglycerine or any nitrate-based medication for cardiac or vascular disease; (3) taking three or more antihypertensive medications; (4) uncontrolled angina; and (5) failed cardiac stress test. Subjects were screened for depression using the Hamilton Depression Scale (HDS).⁷ Subjects with HDS total scores above 14, suggesting a mild level of depression, were excluded from the study.

Before enrollment, subjects received a urological evaluation in order to rule out other medical conditions that may contribute to ED in these subjects. Subjects underwent a measure of vibratory sensation by biothesiometry and dynamic color duplex Doppler ultrasound before and after intracavernous injection of 20 µg of prostaglandin E1. Biothesiometry is a test to indirectly assess penile sexual sensitivity. A RigiScan test was conducted at home for 4 nights after study medication use to assess nocturnal penile tumescence.

Subjects were randomized using a random-length permuted block design to either 50 mg of sildenafil or placebo. The study coordinator assigned sequential subjects to treatment groups, and the master list was not disclosed to the investigators until all data were collected. After 2 weeks of study medication, if the subject did not experience side effects, the dose was increased to 100 mg or matching placebo equivalent for the second 2-week period. If side effects occurred but were considered mild, the dose was reduced to 25 mg for the rest of the study. Subjects were given six tablets at each visit with instructions to use at least three times within the next 2 weeks, and not more than once within a 24-hour period. Subjects were instructed to take the study medication 1 hour preceding sexual activity.

After the completion of the 4-week treatment, a 2-week period without sildenafil or placebo occurred. Plasma levels of sildenafil become very low after 24 hours.⁸ To avoid the possible reduction in sildenafil clearance by interaction of other medications used by study subjects, a 2-week washout period was used. Subjects then received the alternate treatment using the same titration and maintenance protocol. Drug and placebo were supplied by Pfizer, Inc.

The primary outcome measure was the Erectile Function (EF) domain of the International Index of Erectile Function (IIEF)⁹ and the secondary outcome measure was the Parkinson's Disease Quality of Life (PDQ-39).¹⁰ These questionnaires were

completed at baseline and at the end of each treatment period (weeks 4 and 10). The IIEF is a self-administered, psychometrically validated questionnaire of ED and was used to assess function during the 2 weeks of maintenance therapy. The first five items of the scale, which focus on erectile functioning, and item 15 comprise the EF domain of the IIEF, or IIEF-EF. The IIEF-EF has been used to as an outcome measure in treatment studies of erectile functioning.¹¹ These questions include: Question 1. How often were you able to get an erection during sexual activity? Question 2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration? Question 3. When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner? Question 4. During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner? (0 = No sexual activity, 1 = Almost never/never, 2 = A few times [much less than half the time], 3 = Sometimes [about half the time], 4 = Most times [much more than half the time], 5 = Almost always/always) Question 5. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse? (0 = Did not attempt intercourse, 1 = Extremely difficult, 2 = Very difficult, 3 = Difficult, 4 = Slightly difficult, 5 = Not difficult) Question 15. How do you rate your confidence that you could get and keep an erection? (1 = Very Low, 2 = Low, 3 = Moderate, 4 = High, 5 = Very High). IIEF-EF scores from 26 to 30 are classified as no ED, 22 to 25 is mild, 17 to 21 is mild to moderate, 11 to 16 is moderate, and 1 to 10 is severe ED.¹² The UPDRS Part III,¹³ a measure of motor function, was administered at each study visit by the movement disorders neurologist.

In order to monitor compliance, subjects were required to complete a diary form after each study medication use. The subject recorded the effectiveness of each use as well as satisfaction with intercourse. At each visit, subjects returned the diary forms, and medication use was verified by pill counts.

The primary outcome measure was the IIEF-EF score. Difference scores from week 0 to 4 were compared, as well as from week 6 to 10. A standard two-stage approach was applied to analyze the data from the cross-over study. Differential carry-over effect was first tested with a *t* test between the two sequences (sildenafil given before vs. sildenafil given after placebo), and if no statistically significant differential carryover effect was demonstrated, then data from the two periods would be combined to estimate the sildenafil effect with a *t* test. All statistical analyses were performed with SAS software (version 9.2; SAS Institute Inc., Cary, NC). A *P* < 0.05 was considered significant.

Results

Mean age of the cohort was 60 years (standard deviation [SD] = 7.7), and mean disease duration was 7.8 years (SD = 5.9). There were no instances of hypersexuality or impulsivity noted in any of the subjects at baseline or throughout the duration of the study. One subject dropped out before randomization because of traveling, and another subject

dropped out after the first visit without any follow-up data because of scheduling conflicts. All subjects were taking PD medications during the study, including the following: carbidopa/levodopa, pramipexole, ropinirole, amantadine, selegiline, entacapone, bromocriptine, and pergolide. Mean daily L-dopa equivalent dose¹⁴ for the total sample was 786.0 mg (SD = 424.4). One subject taking sildenafil reported mild headache after use of the medication, although the headache was transient, and did not interfere with the subject's participation in the study. This subject's maintenance dose was adjusted to 25 mg. All of the other subjects' doses were adjusted to 100 mg for maintenance.

There was no significant differential carryover effect between the placebo-sildenafil versus the sildenafil-placebo sequences ($P = 0.46$), and as planned, all sildenafil data were combined and compared to all placebo data. Sildenafil had a significant effect on erectile functioning, as measured by the IIEF-EF domain ($P < 0.0001$; see Table 1). The combined mean for the sildenafil group was 23.2 (SD = 7.0) and for the placebo group was 12.3 (SD = 7.5). Sildenafil did not have a significant impact on quality of life, as assessed by the PDQ-39 ($P = 0.74$). Likewise, sildenafil did not have an effect on UPDRS scores during the course of the study ($P = 0.86$; see Fig. 1).

Discussion

Results of this study suggest improved sexual functioning for men with PD using sildenafil. Erectile functioning, as measured by the IIEF-EF, was significantly higher for the sildenafil versus the placebo treatment group. Results of this study are similar to a previous smaller study, cited by the American Academy of Neurology Practice Parameter, suggesting a beneficial effect of sildenafil for PD men with ED.⁴ Our patient sample was larger than the earlier report, and all subjects who completed sequence 1 completed sequence 2.

In spite of improved erectile function, our study did not find improved quality of life in subjects using sildenafil versus placebo. This may be attributed to the measurement tool used, the PDQ-39, which is a general measure of health perception and does not focus specifically on sexual function and its impact on health. Whereas it is possible that quality of life may improve with longer treatment, the investigators believe that the robust effect of treatment for erectile function was not able to modify

Figure 1 IIEF-EF, PDQ-39, and UPDRS by sequence group. CI, confidence interval.

the effect of PD motor disability on the PDQ-39. There was earlier interest in sildenafil as an antidyskinetic agent in PD,¹⁵ but we cannot comment specifically on effects in this domain, because our patients did not have prominent dyskinesia at baseline. Although the UPDRS scores did not change with sildenafil, we cannot specifically negate any antidyskinetic effect because the cohort was not selected for this baseline behavior. There are other limitations of the study. Subjects did not receive cognitive testing before enrollment. However, the neuropsychologist for the study (B.A.B.) did not become concerned with the subjects' cognitive functioning or their ability to provide reasonable answers to the questionnaires. The small size of our sample does not support analyses controlling for covariates such as age or disease stage. Although the subjects of this study were not specifically screened for hypersexuality, impulse control disorder was not noted in their clinical history and was not reported during the study. Another limitation of this study is that motor fluctuations were not assessed, which may contribute to ED in PD. In this cohort, we are comfortable in stating that when PD patients are carefully screened for cardiac health, sildenafil was a safe treatment of ED in men with PD.

TABLE 1 IIEF-EF, PDQ-39, and UPDRS by sequence group

Outcomes	Week	Group/Sequence 1 (N = 11)						Group/Sequence 2 (N = 9)					
		Period 1 Placebo			Period 2 Sildenafil			Period 1 Sildenafil			Period 2 Placebo		
		0	2	4	6	8	10	0	2	4	6	8	10
IIEF-EF	Mean	12.45	—	12.82	8.54	—	24.4	12.33	—	21.78	12.89	—	11.56
	SD	7.23	—	6.88	6.25	—	6.17	5.5	—	7.96	8.07	—	8.5
PDQ-39	Mean	28.36	—	23.73	19.1	—	19.54	25	—	24.38	21.78	—	20.56
	SD	18.45	—	16.86	13.7	—	14.62	14.71	—	24.28	19.5	—	22.83
UPDRS	Mean	14.5	8.31	12.54	14.23	12.91	10.95	18	19.38	17.28	20.5	21.31	16.67
	SD	13.22	5.17	10.59	13.3	11.65	9.82	7.8	11.07	13.95	14.5	14.62	10.96

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

B.A.B.: 1B, 1C, 3A

L.V.M.: 1B, 1C, 3B

L.L.: 1B, 1C, 3B

B.O.: 2B

S.L.: 2A

C.G.G.: 1A, 1B, 1C, 3B

Disclosures

Ethical Compliance Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding Sources and Conflicts of Interest: B.A.B. received funding from Pfizer for this project. L.V.M. receives research funding from Pfizer. L.L. has received research funding from Pfizer, and he has been a consultant for Pfizer. Christopher Goetz is a consultant for Pfizer. The authors report no conflicts of interest.

Financial Disclosures for previous 12 months: L.V.M. receives research funding from Boston Scientific, US World-Meds, Pfizer, Adamas, and Osmotica. He has funding to Rush University Medical Center from NIH. L.L. is a speaker consultant for Coloplast, American Medical Systems, and Endo Pharmaceuticals. He is a speaker for AbbVie, and he is on the board for Absorption Pharmaceuticals. S.L. has funding to Rush University Medical Center from NIH. C.G.G. has consulting or advisory board membership with honoraria from Addex, Avanir, Boston Scientific, CHDI, Clevexel, Kanter Health, Oxford Biomedica, and Pfizer, WebMD. Grants and research funding include Rush University Medical Center from NIH and the Michael J. Fox Foundation. Dr. Goetz directs the Rush Parkinson's Disease Research Center that receives support from the Parkinson's Disease Foundation and some of these funds support Dr. Goetz's salary as well as his research efforts. He directs the translation program for the MDS-UPDRS and UDysRS and receives funds directed to Rush University Medical Center from the International Parkinson and Movement

Disorder Society (IPMDS) for this effort. He receives honoraria from the American Academy of Neurology, Captain James A. Lovell Federal Health Care Center, University of Pennsylvania, and University of Rochester. He receives royalties from Elsevier, Oxford University Press, and Wolters Kluwer.

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