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Erectile function with nightly sildenafil
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·*Clinical Experience*·

Improved spontaneous erectile function in men with mild-to-moderate arteriogenic erectile dysfunction treated with a nightly dose of sildenafil for one year: a randomized trial

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Abstract

Aim: To test the hypothesis that sildenafil (50 mg nightly for one year) can improve spontaneous erectile function (EF) in men with mild-to-moderate arteriogenic erectile dysfunction (ED) responsive to erectogenic treatment. **Methods:** In a prospective open-label trial, 112 men with ED were randomized to sildenafil 50 mg nightly or sildenafil 50 or 100 mg as needed for 12 months, followed by one-month and 6-month non-medicated periods. Non-randomized, non-medicated men with ED were also assessed. The EF domain of the International Index of Erectile Function (IIEF EF) and the peak systolic velocity (PSV) of penile cavernous arteries were used to measure the efficacy. **Results:** After sildenafil treatment and a subsequent non-medicated month, IIEF EF was normal in 29 of 48 (60.4%, 95% confidence interval [CI]: 45.3–74.2%) of the nightly group *vs*. 4 of 49 (8.2%, 95% CI: 2.3–19.6%) of the as-needed group. PSV improved by 11.2 cm/s (95% CI: 4.7–21.4; $P = 0.012$) in the nightly group but only by 3.4 cm/s (–5.1–14.7; $P = 0.435$) in the as-needed group. IIEF EF normalized in 1 of 18 (5.6%, 95% CI: 0.1–27.3%) non-medicated men and the PSV declined slightly. Six months after treatment, the IIEF EF remained normal and PSV was stabilized in most (28/29, 97%) nightly group men who had initially normalized. **Conclusion:** Sildenafil nightly for one year resulted in ED regression that persisted well beyond the end of treatment, so that spontaneous EF was characterized as normal on the IIEF in most men. The results from this open-label, randomized trial warrant verification under double-blind, placebo-controlled conditions. *(Asian J Androl 2007 Jan; 9: 134–141)*

Keywords: phosphodiesterase; sexual dysfunctions; psychological; sildenafil citrate; erectile funcion

1 Introduction

Although erectile dysfunction (ED) can be treated with an erectogenic agent (e.g. an oral phosphodiesterase type 5 [PDE5] inhibitor, sublingual apomorphine, or application of alprostadil [intracavernosal or injection]) prior to anticipated sexual activity, these "as-needed" treatments have not been shown to alter the underlying clinical dysfunction [1].

Endothelial dysfunction and the resulting reduction in the release of nitric oxide (NO) from the endothelium contribute to the pathophysiology of vascular ED [2].

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In addition, increased fibrous tissue and decreased smooth muscle content might result from an insufficient oxygen supply to the organ in the absence of sexually-stimulated or nocturnal erections [3].

Sildenafil citrate (Pfizer Inc., NY, USA), a selective PDE5 inhibitor, reduces the turnover of cyclic guanosine monophosphate (cGMP), the NO second messenger, in the vascular muscles, thereby increasing the physiological activity of NO and improving endothelial function [4]. Longer-lasting effects on endothelial function have been described following the nightly intake of sildenafil 25 mg for a period of 2 weeks [5]. Moreover, nightly intaking of sildenafil at bedtime improves nocturnal erections in healthy men and men with ED [3, 6, 7]. Building on these results, we investigated the improvement and maintenance of improvement in erectile function (EF) and in penile arteriogenic reactivity after treatment for one year with sildenafil taken nightly at bedtime compared with sildenafil taken as needed for anticipated sexual activity, in men with mild-to-moderate arteriogenic ED who had responded to erectogenic treatment at baseline.

2 Materials and methods

2.1 Trial design

The 18-month, open-label, parallel-group, prospective trial randomized 112 men with ED (defined as a score < 26 on the EF domain of the International Index of Erectile Function [IIEF]) to either of two treatment groups: sildenafil 50 mg every evening at bedtime only and sildenafil 50 or 100 mg as needed for anticipated sexual activity. The trial was conducted at the Urology Clinic of the University Medical Centre of Cologne, where all data were collected. Patients were randomized to the different therapeutic arms with the help of a computer program (SAS Institute, Cary, NC, USA). Hospital physicians enrolled participants and assigned them to treatment groups. After a 4-week, non-medicated, run-in period sildenafil treatment, which was obtained by prescription and paid by the patient, was initiated and continued for 12 months, followed by a 4-week, non-medicated, washout period. Patients in the sildenafil nightly group who had normal EF (IIEF EF domain score ≥ 26) after the 4-week washout period were evaluated again after 6 months without medication. Also included was a third, non-randomized group of 18 age-matched patients who fitted the inclusion and exclusion criteria but declined pharmacological treatment.

Patients provided written informed consents. The trial protocol was approved by the Institutional Review Board of the University of Cologne.

2.2 Patients

The inclusion criteria were: age from 20–70 years; ED history of ≥ 6 months that was mild (IIEF EF domain score of 22–25), mild to moderate (score of 17–21), or moderate (score of 11–16) [8], arteriogenic in aetiology, and responsive to erectogenic treatment (oral PDE5 inhibitor or intracavernous injection); and participation in a stable heterosexual relationship. Penile arteriogenic reactivity was measured as the peak systolic velocity (PSV) of the penile cavernous arteries, and arteriogenic ED was confirmed by the measurement of a PSV of less than 35 cm/s. The inclusion criteria allowed patients with well-controlled diabetes (defined as $HbA_{1c} \leq 7.5\%$) or who had had erections following radical prostatectomy but had ED at the time of trial enrolment. However, no patient who had undergone radical prostatectomy was recruited and no recruited patient underwent prostatectomy during the trial or the follow-up.

The exclusion criteria included penile anatomical abnormalities, primary hypoactive sexual desire, ED of endocrine origin (assessed according to testosterone level), veno-occlusive insufficiency (diastolic flow rate > 5 cm/s), radical pelvic surgery without erection, poorly controlled diabetes ($HbA_{1c} > 7.5\%$), or clinically significant liver, kidney, cardiovascular or central nervous system disorders. Non-responders to erectogenic treatments (e.g. eight trials of sildenafil 100 mg or intracavernous injection of 40 μg of vasoactive prostaglandin E_1) were also excluded from all three groups, as were patients being concurrently treated with nitrates, androgens or anticoagulants.

2.3 Objectives and outcomes

We tested the hypothesis that sildenafil 50 mg nightly for 1 year can improve spontaneous EF in men with mild-to-moderate arteriogenic ED that is responsive to erectogenic treatment. Our objectives were to assess EF and penile arterial reactivity, the primary outcomes, in men who were treated for 1 year with sildenafil taken nightly at bedtime *vs*. sildenafil taken as needed for anticipated sexual activity, and to document long-term, post-treatment maintenance of improved spontaneous EF in the men treated with nightly sildenafil.

The IIEF EF domain was used to assess EF. Subjects with an EF domain score ≥ 26 were defined as having

normal EF. Penile arterial reactivity was measured as the PSV of the penile cavernous arteries. Deep erectile tissue arteries (arteria profunda penis) play a decisive role in EF, and blood flow in this tissue is reflected by the peak-flow velocity [9]. Cavernous artery PSV was analyzed using doppler-duplex ultrasound (B&K Doppler-Duplexsonographie, B-K Medical Colour Ultrasound System, Diagnostic Ultrasound System 3535, with a transducer of 7.5 MHz, Copenhagen, Denmark). Measurements were taken before and 5 min after intracavernosal injection of a standardized dose (20 μg) of vasoactive prostaglandin E_1 (with no redosing) [9]. All ultrasound evaluations were performed by a single experienced clinician blinded to both the patient group and baseline examination results. EF and PSV were assessed at baseline (after the 4-week, non-medicated, run-in period) and were re-evaluated: after the 12-month treatment; after the subsequent 4-week, non-medicated, washout period; and (in those patients who had normal EF after the 4-week washout period) after 5 more months without medication. Reports of adverse events were solicited from the patients at the end of the 12-month treatment period.

2.4 Statistical analysis

Assuming a standard deviation of 8 cm/s in PSV, approximately 36 patients per treatment group were required for the trial to have 90% power to detect a response difference of 5 cm/s between the two groups (sildenafil taken nightly at bedtime *vs.* sildenafil taken as needed for anticipated sexual activity). With a projected dropout rate of 25%, the total number of patients required for randomization was determined to be 90 (45 patients in each treatment group).

The goal of assessing long-term efficacy of the 1-year treatment regimen precluded inclusion in the efficacy analysis of those patients who discontinued therapy early. Data are represented as mean ± SD. Multiple factorial analysis of variance (ANOVA) and Newman-Keuls post-hoc test were used to assess differences between the two randomized groups. No formal statistical comparisons were performed between the non-medicated, non-randomized group and the two randomized groups. Significance level was set at $P < 0.05$. Relevant data were fitted to a general linear model with effects for period and treatment by ANOVA. On the basis of the resulting variance estimates, point and 95% confidence interval (CI) estimates of the pair-wise mean treatment differences were calculated for exploratory purposes (without adjustment for multiplicity).

3 Results

3.1 Patients

Between January 2001 and September 2002, men were randomized to treatment with sildenafil nightly (n = 56) or as needed (n = 56) (Table 1). Follow-up

Table 1. Baseline characteristics in men randomized to two sildenafil treatment groups†. BMI, body mass index; ED, erectile dysfunction; EF, erectile function; IIEF, International Index of Erectile Function. †No formal statistical comparisons were made between the medicated groups and the non-medicated group because the latter was not included in the randomization. ‡EF domain score range is 1–30. A score of ≥ 26 was considered normal EF.

	50 mg nightly (n = 56)	50–100 mg as needed (n = 56)
Demographics		
Mean age (years)	44.7	46.1
Mean BMI (kg/m^2)	26.9	27.7
ED		
Duration (years)	4.3	5.5
Severity [IIEF EF domain score]‡ (n [%])		
Severe [6–10]	0	0
Moderate [11–16]	16 (29)	20 (36)
Mild to moderate [17–21]	28 (50)	28 (50)
Mild [22–25]	12 (21)	8 (14)
Peak-flow velocity (mean ± SD, cm/s)	25.8 ± 7.5	23.1 ± 6.9

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continued until April 2004. The nightly and as-needed groups were similar at baseline (Table 1).

After 12 months of treatment, 48 and 49 patients from the nightly and as-needed groups were available for evaluation, respectively. Withdrawal resulted from adverse events in 8 patients (rhinitis [n = 2 in the nightly group], headache [n = 1 in the nightly group and n = 4 in the as-needed group], and flushing [n = 1 in the as-needed group]), and the lack of interest or opportunity for sexual activity in 7 patients (5 in the nightly group and 2 in the as-needed group). None of the men complained of tachyphylaxis. The average number of sildenafil doses in the as-needed group was 1.2 per week; of the 49 patients, 18 used a dose of 50 mg and 31 used a dose of 100 mg.

3.2 EF

After 12 months of sildenafil treatment, 32 of 48 (66.7%, 95% CI: 51.6–79.6%) evaluable men in the nightly group and 33 of 49 (67.3%, 95% CI: 52.5–80.0%) in the as-needed group had an EF domain score in the normal range, compared with only 1 of 18 (5.6%, 95% CI: 0.1–27.3%) in the non-medicated group (Figure 1A). Following the 4-week post-sildenafil follow-up period, 29 of 48 (60.4%, 95% CI: 45.3–74.2%) men in the nightly group still showed normal EF domain scores, compared with only 4 of 49 (8.2%, 95% CI: 2.3–19.6%) in the as-needed group (Figure 1B).

Of the 29 men who had normal EF domain scores after one year of sildenafil nightly followed by 4 weeks off sildenafil, 28 (97%) maintained this level of EF after an additional 5 months off sildenafil (Figure 1C). All four men who had normal EF domain scores after one year of sildenafil as needed followed by 4 weeks off sildenafil maintained this level of EF after an additional 5 months off sildenafil. Therefore, 28 of 48 (58.3%, 95% CI: 43.2–72.4%) men treated with sildenafil 50 mg nightly for one year compared with 4 of 49 (8.2%, 95% CI: 2.3–19.6%) treated with sildenafil as needed for one year had normal EF domain scores 6 months after completing the course of therapy.

3.3 PSV

In men treated with sildenafil nightly, the mean ± SD PSV of cavernous arteries improved by 11.2 cm/s (95% CI: 4.7–21.4; P = 0.012) from 25.8 ± 7.5 cm/s at baseline to 37.0 ± 10.4 cm/s after the 4-week washout period (Figure 2A). A small but non-significant improvement in PSV was seen in men treated with sildenafil as needed: 3.4 cm/s (95% CI: –5.1–14.7; P = 0.435), from 23.1 ±

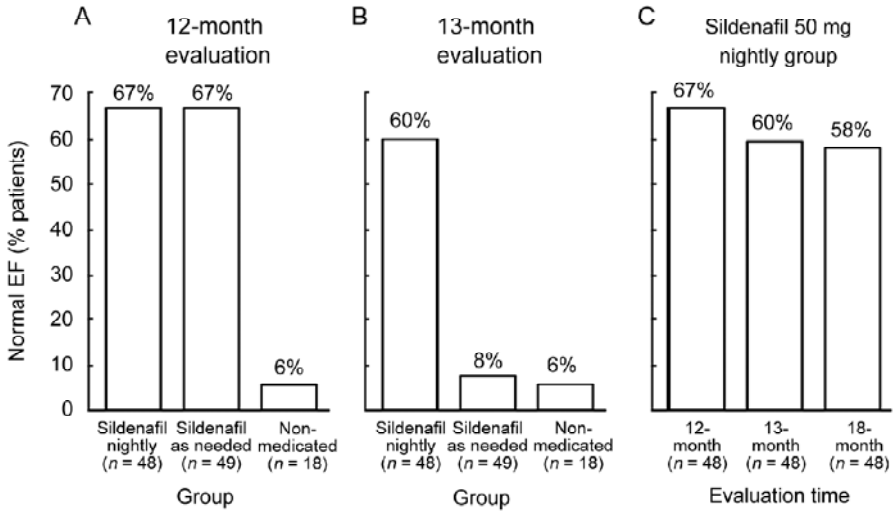

Figure 1. Percentage of men with normal erectile function (EF), defined as a score ≥ 26 on the Erectile Function domain of the International Index of Erectile Function (IIEF EF): (A): by study group after 12 months of sildenafil treatment (nightly or as needed) or no treatment (non-medicated group); (B): by study group at the 13-month evaluation after 4 weeks of no treatment follow-up; and (C) by evaluation time in men treated with sildenafil 50 mg nightly for 12 months, and followed up for an additional 6-month off sildenafil. Percentages rounded to the nearest whole number.

6.9 cm/s to 26.5 ± 8.9 cm/s. In the non-medicated group, PSV declined by 2.1 cm/s (95% CI: –8.6–5.3; P = 0.709) from 21.8 ± 10.1 cm/s to 19.6 ± 11.9 cm/s over the same period (Figure 2A).

The 29 men who had normal EF domain scores after one year of sildenafil nightly followed by 4 weeks of washout were evaluated for PSV again after a total of 6 months off sildenafil. In this subgroup, PSV values improved significantly from 29.1 ± 4.9 cm/s at baseline to 43.9 ± 5.2 cm/s (P = 0.008) after 1 year of sildenafil 50 mg nightly followed by 4 weeks off sildenafil and remained steady at 42.1 ± 5.2 cm/s (P = 0.009) after 6 months off sildenafil (Figure 2B).

3.4 Adverse events

Most adverse events reported by men completing the one-year sildenafil treatment course were mild or moderate in severity. A number of patients reported oversleeping as a side effect of evening medication. One man treated with sildenafil nightly reported rhinitis. In the sildenafil as-needed group, five men reported headache, four flushing, four dyspepsia and two rhinitis. There were no serious adverse events, and the adverse events reported are consistent with the mechanism of action of PDE5 inhibitors.

4 Discussion

This is the first published, randomized trial to show that a long-term course of a PDE5 inhibitor (e.g. sildenafil) taken nightly by men with mild-to-moderate arteriogenic ED responsive to erectogenic treatment can result in normal spontaneous EF persisting after finishing the treatment course. A majority of the men had normal EF domain scores when measured as long as 6 months after completing the 1-year regimen of sildenafil 50 mg nightly. The improvement in EF was associated with improved penile arterial blood flow during pharmacologically-induced erections.

The results contrast with the findings in a group of 25 men with ED who were assessed 4 weeks after finishing a 3-month course of a different PDE5 inhibitor (tadalafil 20 mg given every other day) [10]. In these men, scores for the abridged five-item version of the IIEF (IIEF-5) were normal in only 16% (4/25) and PSV increased by only 4 cm/s, to 36 cm/s. However, compared with our subjects, these men were older (aged 60–70 years, mean 63.6 ± 3.0 years) and had better PSV pretreatment (mean 32 ± 4 cm/s). These men, who had carotid artery media thickness ≥ 1.3 mm (defined as plaque), were part of a larger trial of elderly men with

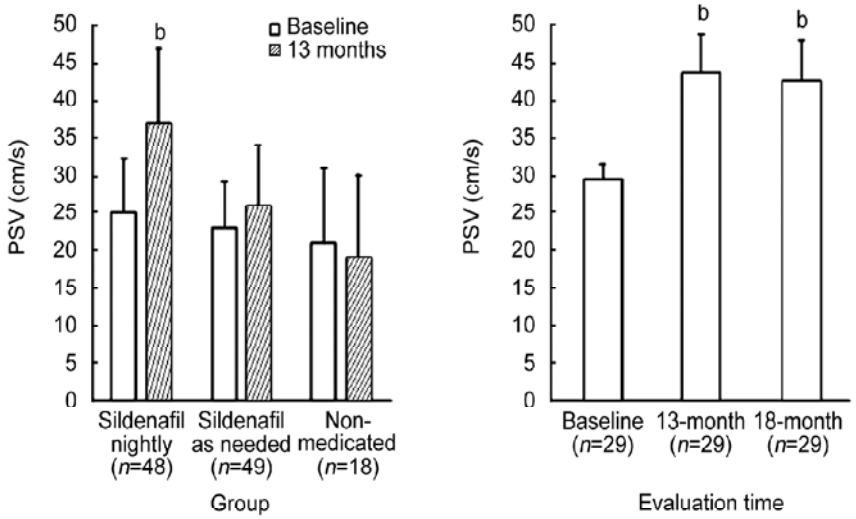

Figure 2. Mean ± SD peak systolic velocity (PSV): (A): by study group after 12 months of sildenafil treatment (nightly or as needed) or no treatment (non-medicated group) followed by 4 weeks of no treatment follow-up (13-month evaluation), compared with baseline and (B): by evaluation time in those men treated with sildenafil nightly and who had normal erectile function (EF) at the 13-month evaluation. $^bP < 0.05$, compared with the baseline.

ED who were selected for the absence of major cardiovascular risk factors and were stratified by carotid artery media thickness. In most men who had only slight thickening or normal thickness, IIEF-5 scores normalized but mean baseline PSV was much greater (42 ± 6 and 55 ± 8 cm/s, respectively) than in our subjects. Baseline IIEF-5 scores and erectogenic treatment response status were not reported.

The current results offer a new perspective on treatment options for men with ED. In men with ED of psychogenic origin, temporary treatment with sildenafil can help to break the vicious circle of performance anxiety and failure, and can result in a long-term restoration of EF [11]. However, for most men, ED recurs when treatment with sildenafil used as needed is stopped [1]. The treatment regimen presented here offers the possibility of persistent improvement in spontaneous EF for a significant proportion of men with mild-to-moderate arteriogenic ED responsive to erectogenic treatment. It remains to be seen whether this possibility will be sufficient incentive to adhere to a long-term treatment regimen, particularly in those with only mild ED. In studies of short-term regimens (≤ 12 weeks) of another PDE5 inhibitor (tadalafil), a majority of men preferred as-needed administration to a regimen of administration three times weekly in one trial [12] and to a regimen of daily administration in another trial [13].

Improved endothelial function is one of the most interesting of the possible explanations for the results of the current trial. Arteriogenic ED is often the result of a reduced level of NO released from the endothelium [2]. The release of NO from erectile endothelial tissue and the autonomic nervous system increases the level of NO available to support an erection. NO synthesis increases under oxygenated conditions, inducing smooth muscle relaxation through reduced intracellular calcium concentrations and the second messenger cGMP [14]. PDE5 inhibitors have been shown to improve endothelial function in men with increased cardiovascular risk [4, 5, 15] and the effect persists even after termination of treatment [5, 15].

In addition to improving endothelial function, sildenafil nightly might exert persisting improvements in EF by increasing tissue oxygenation through its erectogenic effect. Sildenafil nightly increases nocturnal erections [3, 6, 7]. Nocturnal erections are usually present during approximately 25% of sleep time (associated with REM sleep) [16] and, therefore, represent a significant portion of total erectile tissue activity, but are reduced in patients at risk for erectile disorders [17]. During an erection, blood flow increases 25-fold to 60-fold [18] and the partial oxygen pressure in cavernosal blood increases by 250% to 500% [2]. In arteriogenic ED, a compromized blood supply might result in cavernous hypoxia, promoting synthesis of transforming growth factor-β_1, which is associated with increased collagen synthesis and resultant cavernous fibrosis [19]. Regular increases in blood flow, such as is the case during a normal erection, might hinder the conversion of erectile tissue to fibrous tissue. The normal proportion of smooth muscle to fibrous tissue is 1:1 [2], and any change in this balance in favor of more fibrous tissue might lead to a reduction in EF.

The theory that increased blood flow and oxygenation of erectile tissue can assist in regenerating and maintaining healthy erectile tissue and function is supported by clinical data. First, in men who underwent radical nerve-sparing prostatectomy, spontaneous EF could be restored by early postoperative induction of erections with pharmacological treatment (oral sildenafil [20] or alprostadil intracavernosal injection [21]). Improvements resulting from alprostadil injections cannot be explained by an improvement in endothelial function, because alprostadil exerts its effect directly on vascular smooth muscles in an endothelium-independent manner [22]. Second, disorders that result in reduced tissue oxygenation, such as sleep apnoea, are often associated with ED and, when treated, often show an associated improvement in EF [23]. Moreover, we have shown previously that regular physical activity leads to an increase in pelvic blood flow and an associated improvement in EF [24].

A potential safety advantage is suggested by treatment with sildenafil nightly. Although both regimens were well tolerated, with most adverse events being mild to moderate in severity and no serious adverse events, adverse events (other than for rhinitis) were reported less frequently by men treated nightly at bedtime compared with as needed. These data suggest that, with regular nightly exposure to sildenafil, patients might become accustomed to the minor adverse effects and not report them. However, a more likely explanation is that administration at bedtime results in peak sildenafil concentrations during sleep, when lack of consciousness diminishes awareness of adverse effects. It might be that rhinitis, a local response to temporary nasal vasodilation, persists to be perceived upon awakening.

Although patient selection was randomized, a source

of potential bias in the current trial is the lack of blinding. A hindrance to the interpretation of the results is the absence of a placebo control; the non-medicated group was not included in the randomization, so no statistical comparison was made with the medicated groups and no clinical significance can be implied from the results in this group. The requirement that patients pay for their medication might have affected compliance. The goal of assessing long-term efficacy of the one-year treatment regimen precluded inclusion in the efficacy analysis those men who discontinued therapy early, which might have introduced imprecision in the results. However, given that no patient discontinued early because of lack of treatment efficacy, this effect is likely to have been minor. The results of this trial are generalizable only to men with arteriogenic ED of mild to moderate severity responsive to erectogenic treatment. Nonresponse to erectogenic treatment is characterized by the presence of severe vascular lesions and substantial (> 35%) reduction of cavernous smooth muscle [12].

The use of sildenafil 50 mg nightly as a therapeutic regimen for the improvement in spontaneous EF in men with arteriogenic ED is promising but requires further investigation. One of the important unanswered questions is the potential for response within each of the examined severity groups (mild, mild to moderate, and moderate), in more difficult-to-treat patient groups (e.g. those with severe ED), and within subgroups defined by age and comorbidities. Another unanswered question is whether arterial structure is normalized and whether normalized arterial structure is maintained. Additionally, the optimal treatment period requires determination, and longer follow-up is needed to determine the duration of response. It would be valuable to compare the effect of sildenafil with that of intracavernosal vascular endothelial growth factor, which has been shown to restore smooth muscle integrity and improve EF in aged rats [25]. Lastly, it would be worthwhile to determine whether a similar effect to that of a sildenafil therapeutic regimen is achievable with a regular regimen of mechanical stimulation or whether the beneficial effect is dependent upon a unique pharmacological effect of sildenafil on the endothelium.

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References

1 Christiansen E, Guirguis WR, Cox D, Osterloh IH. Long-term efficacy and safety of oral Viagra (sildenafil citrate) in men with erectile dysfunction and the effect of randomised treatment withdrawal. Int J Impot Res 2000; 12: 177–82.
2 Saenz de Tejada I, Gonzales Cadavid N, Heaton J, Hedlund H, Nehra A, Prickard RS, *et al*. Anatomy, physiology and pathophysiology of erectile dysfunction. In: Jardin A, Wagner G, Khoury AE, Giuliano F, Padma-Nathan H, Rosen RC, editors. Erectile Dysfunction. Plymouth: Health Publications 2000; 65–102.
3 Terradas C, Levalle O, Nagelberg A, Mormandi E. Sildenafil improves nocturnal penile erections in organic impotence. Int J Impot Res 2001; 13: 125–9.
4 Katz SD, Balidemaj K, Homma S, Wu H, Wang J, Maybaum S. Acute type 5 phosphodiesterase inhibition with sildenafil enhances flow-mediated vasodilation in patients with chronic heart failure. J Am Coll Cardiol 2000; 36: 845–51.
5 Desouza C, Parulkar A, Lumpkin D, Akers D, Fonseca VA. Acute and prolonged effects of sildenafil on brachial artery flow-mediated dilatation in type 2 diabetes. Diabetes Care 2002; 25: 1336–9.
6 Montorsi F, Maga T, Strambi LF, Salonia A, Barbieri L, Scattoni V, *et al*. Sildenafil taken at bedtime significantly increases nocturnal erections: results of a placebo-controlled study. Urology 2000; 56: 906–11.
7 Rochira V, Granata AR, Balestrieri A, Madeo B, Carani C. Effects of sildenafil on nocturnal penile tumescence and rigidity in normal men: randomized, placebo-controlled, crossover study. J Androl 2002; 23: 566–71.
8 Cappelleri JC, Rosen RC, Smith MD, Mishra A, Osterloh IH. Diagnostic evaluation of the erectile function domain of the International Index of Erectile Function. Urology 1999; 54: 346–51.
9 Jünemann KP, Weiske WH. Duplex-und Farbduplexsonographie der penilen Gefäße S. In: von Jünemann KP, Weiske WH, editors. Dopplersonographie in der Urologie. New York, NY: Medizin, VCH, 1991; 48–72.
10 Caretta N, Palego P, Ferlin A, Garolla A, Bettella A, Selice R, *et al*. Resumption of spontaneous erections in selected patients affected by erectile dysfunction and various degrees of carotid wall alteration: role of tadalafil. Eur Urol 2005; 48: 326–32.
11 van Lankveld JJ, van den Hout MA, Spigt MG, van Koeveringe GA. Cognitive changes predict continued recovery of erectile functioning versus relapse after discontinuation of sildenafil treatment for male erectile dysfunction. Psychosom Med 2003; 65: 709–18.
12 Mirone V, Costa P, Damber JE, Holmes S, Moncada I, Van Ahlen H, *et al*. An evaluation of an alternative dosing regimen with tadalafil, 3 times/week, for men with erectile dysfunction: SURE study in 14 European countries. Eur Urol 2005; 47:

846–54.
13 McMahon C. Comparison of efficacy, safety, and tolerability of on-demand tadalafil and daily dosed tadalafil for the treatment of erectile dysfunction. J Sex Med 2005; 2: 415–27.
14 Kim N, Vardi Y, Padma-Nathan H, Daley J, Goldstein I, Saenz de Tejada I. Oxygen tension regulates the nitric oxide pathway. Physiological role in penile erection. J Clin Invest 1993; 91: 437–42.
15 Rosano GM, Aversa A, Vitale C, Fabbri A, Fini M, Spera G. Chronic treatment with tadalafil improves endothelial function in men with increased cardiovascular risk. Eur Urol 2005; 47: 214–20.
16 Fisher C, Gorss J, Zuch J. Cycle of penile erection synchronous with dreaming (REM) sleep. Preliminary report. Arch Gen Psychiatry 1965; 12: 29–45.
17 Karacan I, Hursch CJ, Williams RL. Some characteristics of nocturnal penile tumescence in elderly males. J Gerontol 1972; 27: 39–45.
18 Wagner G. Erection: Anatomy. In: Wagner G, Green R, editors. Impotence: physiological, psychological, surgical diagnosis and treatment. New York: Plenum, 1981; 7–24.
19 Ryu JK, Song SU, Choi HK, Seong DH, Yoon SM, Kim SJ, *et al.* Plasma transforming growth factor-beta1 levels in patients with erectile dysfunction. Asian J Androl. 2004; 6: 349–53.
20 Padma-Nathan H, McCullough AR, Giuliano F, Toler SM, Wohlhuter C, Shpilsky AB. Postoperative nightly administration of sildenafil citrate significantly improves the return of normal spontaneous erectile function after bilateral nerve-sparing radical prostatectomy. J Urol 2003; 169 (Suppl): 375–6.
21 Montorsi F, Guazzoni G, Strambi LF, Da Pozzo LF, Nava L, Barbieri L, *et al.* Recovery of spontaneous erectile function after nerve-sparing radical retropubic prostatectomy with and without early intracavernous injections of alprostadil: results of a prospective, randomized trial. J Urol 1997; 158: 1408–10.
22 Sinzinger H, Fitscha P, Kritz H. Antimitotic actions of vasodilatory prostaglandins-clinical aspects. Agents Actions Suppl 1997; 48: 92–106.
23 Karacan I, Karatas M. Erectile dysfunction in sleep apnea and response to CPAP. J Sex Marital Ther 1995; 21: 239–47.
24 Sommer F, Peters C, Klotz T, Michna H, Schoenenberger A, Engelmann U. [Sport und Bewegund in der Pravention Urologischer Erkrankugen]. Urologe [B] 2002; 42: 297–305.
25 Park K, Ahn KY, Kim MK, Lee SE, Kang TW, Ryu SB. Intracavernosal injection of vascular endothelial growth factor improves erectile function in aged rats. Eur Urol 2004; 46: 403–7.

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