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Safety and efficacy of sildenafil citrate in treating erectile dysfunction in patients with combat-related post-traumatic stress disorder: a double-blind, randomized and placebo-controlled study

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OBJECTIVE

To evaluate the safety and efficacy of sildenafil citrate for treating erectile dysfunction (ED) in patients with combat-related post-traumatic stress disorder (PTSD).

PATIENTS AND METHODS

In all, 266 combat-exposed war veterans with ED (aged 37–59 years) were recruited. They met the Diagnostic and Statistical Manual of Mental Disorders-IV criteria for PTSD according to the Structured Clinical Interview for Patients, Investigator Version. The patients were also evaluated with the Clinician-Administered PTSD Scale, both to establish the diagnosis of PTSD and to measure symptom severity. Only patients with psychogenic ED were included in the study. Patients with comorbid conditions (diabetes mellitus, hypercholesterolaemia, hypertension, Peyronie's disease) and smokers of more than five cigarettes daily were excluded. The patients were randomly divided into a group of 133 who received 100 mg of on-demand sildenafil 0.75–2 h before sexual stimulation, and 133 who received placebo. Patients were asked to use ≥16 doses or attempts at home. The efficacy of the treatments was assessed every four attempts during treatment, and at the end of the study, using responses to the 15-question International Index of Erectile Function (IIEF), Sexual Encounter Profile diary questions 2 and 3, Erectile Dysfunction Inventory of Treatment Satisfaction questionnaire, patients' event logs of sexual activity, and a Global Assessment Question about erections.

RESULTS

Sildenafil did not produce significantly and substantially greater improvement than placebo in each of the primary and secondary outcome measures ($P = 0.08$). A normal EF domain score (≥26) at endpoint was reported by 13 (9.8%), and 11 (8.3%) of patients on the sildenafil and placebo regimens, respectively ($P = 0.09$). Patients treated with sildenafil had no statistically significantly greater improvement in the five sexual function domains of the IIEF questionnaire than those treated with placebo ($P = 0.08$). The incidences of treatment-emergent adverse events were significantly greater in the sildenafil arm than in the placebo group ($P = 0.01$).

CONCLUSIONS

Sildenafil is no better than placebo in treating PTSD-emergent ED. Further randomized clinical trials are warranted in combat veterans and other populations with PTSD to better elucidate the role of phosphodiesterase type 5 inhibitors in treating PTSD-emergent ED.

KEYWORDS

erectile dysfunction, post-traumatic stress disorder, sildenafil, treatment.

INTRODUCTION

Post-traumatic stress disorder (PTSD) was first recognized after the devastating effects that war experiences had on soldiers serving in Vietnam. Of Vietnam veterans, ≈30% developed PTSD during, or at some point after, the Vietnam War [1]. PTSD is listed as an anxiety disorder in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV [2]. The symptoms of PTSD fall into three domains and define PTSD: re-experiencing symptoms, avoidance symptoms, and hyper-arousal symptoms (DSM IV TR) [3]. It has been shown that veterans with chronic PTSD have emotional, social and professional problems [4]. PTSD also results both significant intrapersonal and interpersonal difficulties, including problems with family cohesion, sexual intimacy, and the expression of affection, hostility and aggression [5,6]. The symptoms of PTSD and comorbid conditions among the veterans of wars typically last for more than two decades [7]. There has been very limited investigation of the prevalence of sexual dysfunction (SD) in patients with PTSD. Vietnam combat veterans with PTSD were more likely to report 'low sexual desire' than were subjects without PTSD [8]. Letourneau *et al.* [9] reported that >80% of combat veterans with PTSD experience SD, of whom 69% have erectile dysfunction (ED). The problems of patients with PTSD have a

negative collateral effect on their spouses [10]. It was also shown that partners of veterans reported significantly increased somatic symptoms, as well as significantly less self-esteem and cohesion in their families, than a control group [11]. Therefore the presence of ED can aggravate the problems of couples. Clinical studies show sildenafil to be effective in treating ED of various causes [12–14]. Thus we conducted an extensive randomized placebo-controlled study addressing the safety and efficacy of sildenafil in combat veterans with PTSD-emergent ED.

PATIENTS AND METHODS

Men exposed to combat during the Iran-Iraq war were recruited through referrals and admitted to our clinics for the treatment of ED. Patients were eligible if they had a current diagnosis of PTSD. They met DSM-IV criteria for PTSD [2] according to the Structured Clinical Interview for Patients, Investigator Version [15]. From April 2005 to July 2006, 388 married men (aged 37–59 years) with PTSD, and their wives, were enrolled in the study for screening. The diagnosis of ED was established according to the National Institute of Health statement on ED [16]. All patients had been screened for the standard exclusionary criteria for treatment with sildenafil citrate. Enrolled patients agreed not to use another form of ED treatment during the entire study, including the screening period. After procedures and possible side-effects were explained to patients, all gave their informed consent, and the study was conducted in accordance with the Declaration of Helsinki. The Human Ethics Committee approved the study protocol. We recruited patients free of psychiatric medication use for ≥12 weeks. This study was done without sponsorship, it was not advertised, and no remuneration was offered.

We obtained information about all lifetime traumatic events, including the earliest, most recent and most severe events, and the ages at which these events occurred, using the trauma history questionnaire [17]. The patients completed the Dissociative Experiences Scale [18], the Hamilton Rating Scale for Depression [19], the Hamilton Rating Scale for Anxiety [20], and the Liebowitz Social Anxiety Scale [21]. The patients were also evaluated with the Clinician-administered PTSD Scale (CAPS) [22], both to establish the diagnosis of PTSD and to measure symptom severity. All patients were seen with their wives, and interviewed about their sexual activity and patient's erectile function (EF). To minimize the problem of response bias, patients and their wives were interviewed privately. They had a preliminary assessment, including a medical and sexual history, physical examination, a resting 12-lead electrocardiogram, and structured interview diagnostic of mental and physical disorders. EF was measured using the International Index of EF (IIEF) [23], and Sexual Encounter Profile (SEP) diary questions 2 and 3. The baseline severity of ED was determined using the IIEF EF domain score, with mild ED characterized by a score of 17–25, moderate ED of 11–16, and severe ED of 1–10 [24]. The patterns of attempts at sexual intercourse, by treatment group, were also evaluated, and included the mean number of intercourse attempts per week, percentage of intercourse attempts and percentage of successful intercourse attempts. To be able to exclude organic SD, fasting blood glucose level, urine analysis, complete blood count, sex hormones and prolactin levels were measured. When indicated, other tests were used to establish the diagnosis of vasculogenic and neurogenic ED, including penile colour duplex Doppler ultrasonography before and after intracavernosal injection with 20 μg prostaglandin E_1, pudendal nerve conduction tests and impaired sensory-evoked potential studies.

The enrolled patients had a total score ≥50 on the CAPS and a score ≥4 on the Clinical Global Impression of Severity scale at baseline. The patients had to be in a stable relationship with a partner for at least the previous 6 months. All patients were free of medical illnesses, based on a history, physical examination and laboratory tests, and were medication-free for ≥12 weeks. Patients' reports that they had not been treated with psychotropic medications were verified with their primary-care physicians. All patients had to expect having the same female sexual partner throughout the study, to ensure reliability in recording responses to efficacy endpoints. Patients with any degree of ED severity (mild, moderate or severe) were permitted to enrolment. Only patients with psychogenic ED were included in the study. Patients with comorbid conditions, including diabetes mellitus, hypercholesterolaemia, hypertension, and Peyronie's disease, and smokers of more than five cigarettes daily, were excluded. Due to ambiguous predictions, combat-exposed patients with past but not current PTSD, and a lifetime psychotic disorder, organic brain disorder or substance abuse or dependence, were excluded. Patients were also excluded if they met DSM-IV criteria for a psychotic/affective disorder other than PTSD or non-combat-related PTSD. Other exclusion criteria were: patients with clinically significant penile deformities or penile implants; a primary diagnosis of another sexual disorder, including premature ejaculation or untreated endocrine disease; a history of cardiovascular disease (unstable angina, myocardial infarction or myocardial revascularization); pelvic surgery, stroke or spinal cord injury; systolic blood pressure >170 or <90 mmHg or diastolic blood pressure >100 or <50 mmHg; renal or liver impairment; and those unlikely to be available for follow-up. Use of organic nitrates, other nitric-oxide (NO) donors, or potent CYP3A4 inhibitors (e.g. ritonavir, indinavir, itraconazole, ketoconazole), anticoagulants, and erythromycin were not allowed. Other prohibited concomitant medications included α-blockers (except tamsulosin), androgens, antiandrogens, and trazodone. Of 388 enrolled patients, 266 met the inclusion/exclusion criteria and agreed to proceed with the study protocol.

Eligible patients were randomized to sildenafil 100 mg (133) or indistinguishable placebo (133) tablets using a stratified permuted-block randomization procedure. The clinician prescriber and the patients were all unaware of the treatment conditions. Patients were asked to use at least 16 doses/attempts at home, but not to have more than one attempt per day. All the men were asked not to consume alcoholic drinks within 6 h of sexual activity. All patients were given an instruction sheet before starting the treatment, which emphasized the timing of medication administration (0.75–2 h before sexual stimulation) as well as the absolute need for sexual stimulation. In addition, the instruction sheet stressed that medication should be used 2–3 h after a low fat meal. None of the patients had formal psychosexual counselling.

Patients were screened 4 weeks before the start of treatment, with baseline measurements made 1 day before, and efficacy assessed every four attempts and at the end of the treatment period. The designated primary outcome measures were the changes in IIEF and responses to the questions from the IIEF: question 3, 'When

you attempted sexual intercourse, how often were able to penetrate your partner?' and question 4, 'During sexual intercourse, how often were able to maintain your erection to completion of intercourse?' and SEP diary questions 2 ('Were you able to insert your penis into your partner's vagina?') and 3 ('Did your erection last long enough for you to have successful intercourse?'). Responses to the questions 3 and 4 from the IIEF questionnaire were rated on a scale of 1–5, with five response options: 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); and 5, almost always/always.

Secondary outcome measures included the responses to the remaining 13 IIEF questions. Each patient also responded to a GAQ ('Were your erections rigid, and did they last long enough to have successful intercourse?') and maintained an event log, in which they recorded the date of the medication taken, the presence of sexual stimulation, the hardness of erections on a four-point scale, the number of attempts at sexual intercourse and the number of attempts that were successful. Patient and partner satisfaction was assessed using the patient version of the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) questionnaire, a validated 11-item instrument to assess ED treatment satisfaction, with a final score ranging from 0 (extremely low) to 100 (extremely high) [25]. Other secondary efficacy variables included successful attempts at sexual intercourse, mean intercourse frequency and quality of life (QoL) [26] assessment.

Safety and tolerability were evaluated on the basis of spontaneously reported adverse effects, and physical examination during each patient's visit. Patients were asked to report all treatment-emergent adverse events (TEAEs), which were assessed by the investigator using the Medical Dictionary for Regulatory Activities (version 5.0) for severity and relationship to study drug. TEAEs were defined as any AE that first occurred or worsened after randomization. Patients voluntarily reported AEs throughout the study.

All statistical analyses were based on the intent-to-treat principle. TEAEs were analysed using Fisher's exact test. Changes in symptoms over time were assessed with multivariate repeated-measures ANOVA. To estimate if outcomes were affected by patients who discontinued (who were randomized but discontinued study participation before the fourth attempt), an intent-to-treat analysis using last observation carried forward was done. The responses to the GAQ were analysed using logistic regression. Comparison of sexual satisfaction rates of patients and their wives were tested using the chi-square test with Yates' correction or Fisher's exact test, when necessary. Tests of treatment effects were conducted at a two-sided α of 0.05.

TABLE 1 The demographic characteristics of the patients at baseline; none of the differences were significant

Mean (range) or (SEM) or *n* (%) variable	Sildenafil (133)	Placebo (133)
Age, years	48.4 (38–59)	48.1 (37–59)
Weight, kg	75.6 (55–105)	74.7 (56–106)
Duration of PTSD, years	16.2 (10–22)	16.8 (11–22)
Duration of ED, years	14.4 (8–18)	14.8 (9–18)
ED severity		
Mild	19 (14.3)	18 (13.5)
Moderate	43 (32.3)	41 (30.8)
Severe	71 (53.4)	74 (55.5)
Baseline IIEF domain scores		
EF	12.1 (4.4)	12.3 (4.6)
Orgasmic function	5.5 (1.3)	5.7 (1.5)
Sexual desire	5.2 (1.3)	5.0 (1.5)
Intercourse satisfaction	4.9 (1.5)	4.9 (1.7)
Overall satisfaction with sexual life	4.5 (1.3)	4.3 (1.5)
Education level		
None	0	0
Primary school	7 (5.3)	8 (6.0)
High school	87 (65.4)	84 (63.2)
Graduate	39 (29.3)	41 (30.8)
Occupational status		
Employed	57 (42.9)	55 (41.4)
Unemployed	31 (23.3)	33 (24.8)
Retired	45 (33.9)	45 (33.9)

RESULTS

The baseline characteristics of the patients who completed the study protocol are shown in Table 1. Of 266 randomized patients, 24 failed to complete any scheduled outcome assessment (first four attempts) because of protocol discontinuation. Ten discontinued because of AEs (nine randomized to sildenafil and one to placebo), nine because of a lack of effect (four in the sildenafil and five in the placebo group), and five (two in the sildenafil and three in the placebo group) were lost to follow-up for reasons unknown. The discontinuation rate was 15 (11.3%) and nine (6.8%) in sildenafil and placebo groups, respectively ($P = 0.04$).

In all, 145 (54.5%) patients had severe ED and the mean (SEM) baseline IIEF EF domain score was 12.2 (4.5). The study groups appeared to be well-matched in terms of baseline demographic characteristics, including age, aetiology, ED and PTSD duration, and IIEF domain scores. The distribution of baseline severity was also similar, with similar numbers of mild (19, 14.3% vs 18, 13.5%), moderate (43, 32.3% vs 41, 30.8%), and severe (71, 53.4% vs 74, 55.5%) ED in the sildenafil and placebo groups, respectively.

All patients were interviewed, with their wives, independently about their sexual activity and patient's EF. Sildenafil did not produce significantly and substantially greater improvement than placebo in each of the primary outcome measures ($P = 0.08$). The percentage of patients who responded to sildenafil treatment (able to attain and maintain an erection sufficient to allow sexual intercourse; 15, 11.3%), was not significantly higher than with placebo (12, 9.0%; $P = 0.08$). The primary endpoint of mean IIEF EF score

TABLE 2 Improvement in EF primary and secondary efficacy measures, and the mean final scores to question 1, 2, and 5–15 of the IIEF, at the end of trial

Mean or % or *n* (%)	Sildenafil (133)	Placebo (133)	*P*
Efficacy measures			
Primary			
IIEF EF	15.8	14.6	0.08
IIEF EF ≥26	13 (9.8)	11 (8.3)	0.09
question 3	1.7	1.6	0.09
question 4	1.4	1.4	0.1
Per-patient, %			
SEP2 'Yes'	18.2	17.3	0.1
SEP3 'Yes'	26.2	24.8	0.08
Secondary			
Per-patient % GAQ 'Yes'	12.8	11.3	0.08
EDITS score (95% CI)	27.7 (23–37)	26.4 (23–36)	0.08
% final EDITS score >50	11.3	12.8	0.08
Sexual attempts per week	1.1	1.0	0.1
IIEF Questions			
1. How often were you able to get an erection during sexual activity?	1.3	1.3	NS
2. When you had erection with sexual stimulation, how were your erections hard enough for penetration?	1.6	1.4	NS
5. During sexual intercourse, how difficult was to maintain your erection to completion of intercourse?	1.9	1.7	NS
6. How many times have you attempted sexual intercourse?	2.0	1.9	NS
7. When you attempted sexual intercourse, how often was it satisfactory for you?	1.8	1.8	NS
8. How much have you enjoyed sexual intercourse?	1.7	1.6	NS
9. When you had sexual intercourse, how often did you ejaculate?	3.1	3.2	NS
10. When you had sexual intercourse, how often did you have the feeling of orgasm or climax?	3.1	3.0	NS
11. How often have you felt sexual	2.2	2.1	NS
12. How would you rate your level of sexual desire?	2.3	2.3	NS
13. How satisfied have you been with your overall sex life?	1.7	1.8	NS
14. How satisfied have you been with your sexual relationship?	1.6	1.7	NS
15. How do you rate your confidence that you could get and keep an erection?	1.6	1.6	NS

NS, not significant.

improved from 12.1 (4.4) and 12.3 (4.6) at baseline to 15.8 (5.6) and 14.6 (5.4) for patients in the sildenafil and placebo groups, respectively ($P = 0.08$). A normal EF domain score (≥26) at endpoint was reported by 13 (9.8%) and 11 (8.3%) of the patients on the sildenafil and placebo regimens, respectively ($P = 0.09$). At the end of trial, the mean score for question 3 was increased from the baseline mean of 1.2 to 1.7, and from 1.2 to 1.6, in sildenafil and placebo groups, respectively; for question 4 the scores increased from 1.1 to 1.4, and from 1.0 to 1.4, respectively. From the ANOVA with multiple comparisons, treatment with sildenafil did not cause a greater increase in mean scores for question 3 and 4 than placebo ($P = 0.1$; Table 2). The number of patients achieving a response of 4 or 5 to IIEF questions 3 and 4 was 13 (9.8%) and 11 (8.3%), and 12 (9.0%) and 11 (8.3%) in the sildenafil and placebo groups, respectively. Treatment with sildenafil and placebo was not associated with significantly higher scores for question 3 and 4 than at baseline ($P = 0.1$). SEP2 is designed to measure the patient's overall ability to penetrate the partner's vagina. The mean per-patient rate changed from 6.5% and 6.4% at baseline, to 18.2% and 17.3% at the end of trial, in the sildenafil and placebo groups, respectively ($P = 0.1$). In response to the SEP3 question, the mean per-patient success rate at baseline was 21.4% and 22.4%, improving to 26.2% and 24.8%, at the end of the trial for patients who received sildenafil and placebo, respectively ($P = 0.08$; Table 2). The per-patient success rates for these variables (SEP2 and SEP3) did not tend to increase over time.

For secondary efficacy measures, differences were similarly not significant between sildenafil and placebo in the intent-to-treat analysis (Table 2). Patients treated with sildenafil had no statistically significantly greater improvement in the five sexual function domains of the IIEF questionnaire than those treated with placebo ($P = 0.08$) (Table 2). The mean (SEM) baseline IIEF domain scores for patients with ED were 12.2 (4.6) for EF, 5.6 (1.4) for orgasmic function, 5.1 (1.8) for sexual desire, 4.9 (1.6) for intercourse satisfaction and 4.4 (1.4) for overall satisfaction with sex life. These were increased to 15.8 (4.8), 6.1 (1.5), 5.9 (1.6), 5.4 (1.6) and 4.8 (1.3) with sildenafil, and 14.6 (4.4), 6.0 (1.4), 5.7 (1.4), 5.7 (1.6) and 4.9 (1.3) with placebo, respectively (all $P = 0.08$).

Patients on sildenafil treatment also had no statistically significant increase in mean sexual intercourse/week compared with placebo ($P = 0.1$). The benefit of sildenafil compared with placebo was not statistically significant in the treatment of ED as measured by the GAQ. Based on 'yes' responses to the GAQ, 12.8% (sildenafil) and 11.3% (placebo) of men thought that the treatment improved their erections ($P = 0.08$; Table 2). The mean total QoL scores were similar between groups at baseline, and throughout the study changes in QoL were not significantly between the groups ($P = 0.1$). The proportion of attempts at sexual intercourse that were successful also did not increase significantly with sildenafil treatment ($P = 0.1$). Sildenafil also did not increase statistically significant sexual satisfaction scores both in patients and their wives ($P = 0.08$; Table 3). Overall, the proportion of patients satisfied with treatment, defined by Lewis *et al.* [27] as a final EDITS score of >50, was 11.3% for the

sildenafil and 12.8% for the placebo group ($P = 0.08$).

The incidences of TEAEs were significantly greater in the sildenafil than the placebo group ($P = 0.01$; Table 4). AEs were mild, moderate and severe in ≈30%, 35% and 35% of patients reporting them, respectively. Ten AEs led to early discontinuation (nine randomized to sildenafil and one to placebo). Of the nine patients taking sildenafil who discontinued, three had a severe headache after two doses, two had dyspepsia after two doses, two had abdominal pain (with nausea) after one dose, and two developed photophobia after one dose. The most common side-effects of sildenafil were headache (19, 14.3%), flushing (12, 9.0%), nausea (nine, 6.8%), vision disturbances (11, 8.3%), rhinitis (nine, 6.8%), dyspepsia (six, 4.5%) and myalgia (four, 3.0%). Sildenafil was not well tolerated, with side-effects noted in 22.6% of patients, but only 5.9% had to discontinue treatment.

TABLE 3 Treatment satisfaction; none of the differences were statistically significant

EDITS	{*n*} Mean (SEM) score	
	Sildenafil	Placebo
Patient		
Overall score	{132} 29.6 (2.45)	{132} 31.9 (2.46)
Individual items		
1 Overall satisfaction	{132} 0.9 (0.16)	{132} 0.9 (0.13)
2 Expectations	{132} 0.6 (0.14)	{132} 0.6 (0.16)
3 Likelihood of continuing	{132} 1.0 (0.17)	{133} 1.0 (0.17)
4 Confidence	{132} 1.3 (0.18)	{133} 1.4 (0.16)
5 Partner satisfaction	{133} 1.1 (0.17)	{133} 1.0 (0.21)
6 Partner desire to continue treatment	{133} 1.0 (0.16)	{132} 1.1 (0.16)
7 Naturalness of achieving erection	{133} 2.8 (0.16)	{132} 2.7 (0.21)
8 Naturalness of erection hardness	{133} 2.0 (0.14)	{133} 1.8 (0.19)
Partner		
Overall score	{123} 29.0 (3.12)	{125} 30.0 (3.46)
Individual items		
1 Overall satisfaction	{122} 1.1 (0.14)	{126} 1.1 (0.13)
2 Expectations	{124} 0.9 (0.21)	{125} 0.8 (0.24)
3 Sexual desirability	{125} 1.9 (0.12)	{125} 1.8 (0.12)
4 Patient's feelings about continuing treatment	{125} 1.0 (0.18)	{125} 1.1 ± 0.17

TABLE 4 TEAEs listed by decreasing frequency overall

TEAE, *n* (%)	Sildenafil	Placebo	*P*
Headache	19 (14.3)	4 (3.0)	0.01
Flushing	12 (9)	3 (2.3)	0.01
Nausea	9 (6.8)	0	0.001
Rhinitis	9 (6.8)	0	0.001
Nasal congestion	7 (5.3)	0	0.1
Dyspepsia	6 (4.5)	0	0.01
Dizziness	5 (3.8)	1 (0.8)	0.1
Myalgia	4 (3)	0	0.01
Colour vision disturbances	4 (3)	0	0.1
Chromatopsia	3 (2.3)	0	0.1
Photophobia	3 (2.3)	0	0.1
Back pain	3 (2.3)	1 (0.8)	0.03

DISCUSSION

The results of the present study show that oral sildenafil is not effective in restoring the ability to achieve and maintain erections in patients with PTSD-emergent ED. Responses to IIEF questions 3 and 4, which addressed these two aspects of EF, did not significantly differ between the groups. Partner responses to similarly worded questions corroborated the patients' reports. Also, responses to the GAQ showed that 100 mg sildenafil was no better than placebo in improving EF. The present study also evaluated the treatment response to sildenafil by assessing the IIEF domains of male sexual function, i.e. EF, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction with sex life. There were no statistically significant differences between sildenafil and placebo. This shows that all of the sexual aspects of male sexual function are inhibited strongly in patients with PTSD, and peripherally acting vasoactive drugs (such as sildenafil) are ineffective in restoring normal sexual function in these patients.

PTSD is an anxiety disorder, and has a dramatic impact on patients' well-being and social functioning, with major public health significance in terms of its high prevalence, chronicity and disability [28,29]. In about half of all cases a complete recovery might occur within 3 months. For many others, symptoms persist for >12 months, forming a chronic, debilitating condition [2,29]. Patients with PTSD have reduced sexual drive and interpersonal withdrawal [2]. SD is very common among combat veterans with PTSD. Solursh and Solursh [30] studied the prevalence of SD in Vietnam combat veterans with chronic PTSD, 80% of whom reported premature ejaculation or failure to achieve or maintain an erection.

Since its approval in 1998, oral sildenafil has become a first-line treatment option for men with ED. It has been shown that sildenafil effectively treats ED of various aetiologies, including patients with diabetes [31], treated or untreated hypertension [32], cardiovascular disease [33], ischaemic heart disease [34], spinal cord injuries [35], after radical prostatectomy [36], multiple sclerosis [37], and depression [38]. However, despite its effectiveness, 30–50% of subjects receiving sildenafil do not adequately respond to therapy [39]. In addition, marketing data worldwide showed that discontinuation rates for sildenafil are up to 50% of patients treated [40]. Therefore, sildenafil is not useful and effective in about half of the 150 million men with ED worldwide. This prevalence is projected to more than double by the year 2025 [41,42]. The anticipated increase in the

population of patients seeking treatment for ED, and the consequent requirement for safe and effective therapy, prompted the development of novel therapies for ED, with different mechanisms of action.

Pharmacological approaches to treating ED in patients with PTSD are very rare. Indeed, this very important issue has been neglected. In the only double-blind, placebo-controlled crossover study, conducted on 21 outpatients diagnosed with chronic PTSD accompanied by ED, sildenafil treatment improved ED symptoms and was significantly better than placebo. However, the improvement was marginal, as patients still met the criteria for ED after treatment [43].

In the present series, PTSD persisted despite previous multiple attempts at treatment. The present patients initially had no ED, but developed PTSD-emergent ED. It was reported that sildenafil improved erections in 90% of patients with depression (ED of psychogenic aetiology) [44]. However, sildenafil was no better than placebo in the present patients with PTSD-emergent ED. One possible explanation for this is that patients with PTSD might have be less responsive to sexual situation. If ED is secondary to PTSD,the PTSD should be treated first , and this might result in an improvement of EF. We assessed the severity of PTSD with CAPS and found that the effect of sildenafil did not correlate with the severity of PTSD.

Normal EF relies on the coordination of psychological, neurological, endocrine and vascular factors. The tone and contractility of corporal smooth muscle are determined by a balance of regulatory components such as NO, and sympathetic neurotransmitters such as adrenaline and noradrenaline [45]. Sildenafil enhances the relaxant effect of NO released in response to sexual stimulation by preventing the degradation of cGMP in corporal smooth muscle. Over-activation of the sympathetic nervous system and alterations of the hypothalamus-pituitary-adrenal axis are known to mediate the association between PTSD and adverse health outcomes [46]. Clinical studies suggest that enhanced postsynaptic adrenergic receptor responsiveness to CNS noradrenaline contributes to the pathophysiology of PTSD [47]. Traumatic nightmares and sleep disturbance are among the most treatment-resistant and distressing symptoms of PTSD [48]. Prazosin, an α1-adrenergic receptor antagonist, is an effective and well-tolerated treatment for traumatic nightmares, sleep disturbance and the overall clinical status in veterans with chronic PTSD [49]. Therefore, it is also possible and even likely that prazosin alone or combined with sildenafil might improve EF in patients with PTSD.

Oral sildenafil 100 mg was not well tolerated, with the most common AEs (headache, flushing, and visual disturbances) being bothersome, and moderate to severe. The visual symptoms reported at the 100-mg dose are most likely attributable to inhibition of phosphodiesterase-6 in the retina [50].

Sildenafil is not a panacea, and the group of patients for whom this treatment is either contraindicated or ineffective is still being defined. Sildenafil acts a potentiator of local mediators to maintain smooth muscle relaxation, and thus cannot act in the presence of centrally inhibited different aspects of male sexual function. Combat-related traumatic experience served as a predictor of a poor treatment outcome in the present patients.

While improved EF is the main goal of therapy for ED, QoL is also enhanced as subjects become more satisfied with sexual activity. In the present study the QoL scores were not numerically better throughout the treatment period in both groups.

In conclusion, further placebo-controlled randomized studies in combat veterans and other populations with PTSD are necessary to better determine the role of phosphodiesterase-5 inhibitors in treating PTSD-emergent ED.

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CONFLICT OF INTEREST

None declared.

REFERENCES

1 **CDC.** Health status of Vietnam veterans. II. Physical Health. Centers for Disease Control, Vietnam Experience Study. *JAMA* 1988; **259**: 2708–14

2 **American Psychiatric Association.** *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. Washington, DC: American Psychiatric Association, 1994

3 **American Psychological Association.** *Diagnostic and Statistical Manual of Mental Disorders; DSM-IV-TR.* Washington, DC: American Psychological Association, 2000

4 **Zatzick DF, Marmar CR, Weiss DS *et al.*** Posttraumatic stress disorder and functioning and quality of life outcomes in a nationally representative sample of male Vietnam veterans. *Am J Psychiatry* 1997; **154**: 1690–5

5 **Jordan BK, Marmar CR, Fairbank JA *et al.*** Problems in families of male Vietnam veterans with posttraumatic stress disorder. *J Consult Clin Psychol* 1992; **60**: 916–26

6 **MacDonald C, Chamberlain K, Long N *et al.*** Posttraumatic stress disorder and interpersonal functioning in Vietnam War veterans: a mediational model. *J Trauma Stress* 1999; **12**: 701–17

7 **Kessler RC.** Post-traumatic stress disorder. The burden to the individual and society. *J Clin Psychiatry* 2000; **61** (Suppl. 5): 4–12

8 **Litz BT, Keane TM, Fisher L *et al.*** Physical health complaints in combat-related post-traumatic stress disorder: a preliminary report. *J Trauma Stress* 1992; **5**: 131–41

9 **Letourneau EJ, Schewe PA, Frueh BC.** Preliminary evaluation of sexual problems in combat veterans with PTSD. *J Trauma Stress* 1997; **10**: 125–32

10 **Glenn DM, Beckham JC, Feldman ME *et al.*** Violence and hostility among families of Vietnam veterans with combat-related posttraumatic stress disorder. *Violence Vict* 2002; **17**: 473–89

11 **Westerink J, Giarratano L.** The impact of posttraumatic stress disorder on partners and children of Australian Vietnam veterans. *Aust N Z J Psychiatry* 1999; **33**: 841–7

12 **Goldstein I, Lue TF, Padma-Nathan H *et al.*** Oral sildenafil in the treatment of

erectile dysfunction. *N Engl J Med* 1998; **338**: 1397–404
13 **Boolell M, Gepi-Attee S, Gingell JC *et al.*** Sildenafil, a novel effective oral therapy for male erectile dysfunction. *Br J Urol* 1996; **78**: 257–61
14 **Morales A, Gingell C, Collins M *et al.*** Clinical safety of oral sildenafil citrate (Viagra™) in the treatment of erectile dysfunction. *Int J Impot Res* 1998; **10**: 69–74
15 **First MB, Spitzer RL, Gibbon M *et al.*** *Structured Clinical Interview for DSM-IV Axis I Disorders (SCIDI).* Washington, DC: American Psychiatric Press, 1997
16 **NIH Consensus Conference.** Impotence. NIH Consensus Development Panel on Impotence. *JAMA* 1993; **7**: 270–83
17 **Green BL, Stamm BH eds.** *Measurement of Stress, Trauma, and Adaptation.* Lutherville, MD. Sidran, 1996: 366–9
18 **Bernstein-Carlson E, Putnam FW.** An update on the Disssociative Experiences Scale. *Dissociation* 1993; **6**: 16–27
19 **Hamilton M.** A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; **23**: 56–61
20 **Hamilton M.** The assessment of anxiety states by rating. *Br J Med Psychol* 1956; **32**: 50–5
21 **Heimberg RG, Horner KJ, Juster HR *et al.*** Psychometric properties of the Liebowitz Social Anxiety Scale. *Psychol Med* 1999; **29**: 199–212
22 **Blake DD, Weathers FW, Nagy LM *et al.*** The development of a clinician-administered PTSD scale. *J Trauma Stress* 1995; **8**: 75–90
23 **Rosen RC, Riley A, Wagner G *et al.*** The International Index of Erectile Function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997; **49**: 822–30
24 **Cappelleri JC, Rosen RC, Smith MD *et al.*** Diagnostic evaluation of the Erectile Function domain of the International Index of Erectile Function. *Urology* 1999; **54**: 346–51
25 **Althof SE, Corty EW, Levine SB *et al.*** EDITS: development of questionnaires for evaluating satisfaction with treatments for erectile dysfunction. *Urology* 1999; **53**: 793–9
26 **Fugl-Meyer AR, Lodnert G, Bränholm IB *et al.*** On life satisfaction in male erectile dysfunction. *Int J Impot Res* 1997; **9**: 141–8
27 **Lewis R, Bennett CJ, Borkon WD *et al.*** Patient and partner satisfaction with Viagra (sildenafil citrate) treatment as determined by the erectile dysfunction inventory of treatment satisfaction questionnaire. *Urology* 2001; **57**: 960–5
28 **Cuthbert BN.** Social anxiety disorder: trends and translational research. *Biol Psychiatry* 2002; **51**: 4–10
29 **Yehuda R.** Post-traumatic stress disorder. *N Engl J Med* 2002; **346**: 108–14
30 **Solursh LP, Solursh DS.** Male erectile disorders in Vietnam combat veterans with chronic post-traumatic stress disorder. Special Issue. Sexuality and disability in adolescence and beyond. *Int J Adolescent Med Health* 1994; **7**: 119–24
31 **Rendell MS, Rajfer J, Wicker PA *et al.*** Sildenafil for treatment of erectile dysfunction in men with diabetes. *JAMA* 1999; **281**: 421–6
32 **Kloner RA, Brown M, Prisant LM *et al.*** Effect of sildenafil in patients with erectile dysfunction taking antihypertensive therapy. Sildenafil Study Group. *Am J Hypertens* 2001; **14**: 70–3
33 **Olsson AM, Persson CA.** Efficacy and safety of sildenafil citrate for the treatment of erectile dysfunction in men with cardiovascular disease. *Int J Clin Pract* 2001; **55**: 171–6
34 **Conti CR, Pepine CJ, Sweeney M.** Efficacy and safety of sildenafil citrate in the treatment of erectile dysfunction in patients with ischemic heart disease. *Am J Cardiol* 1999; **83** (Suppl.): 29C–34C
35 **Hultling C, Giuliano F, Quirk F *et al.*** Quality of life in patients with spinal cord injury receiving Viagra (sildenafil citrate) for the treatment of erectile dysfunction. *Spinal Cord* 2000; **38**: 363–70
36 **Zagaja GP, Mhoon DA, Aikens JE *et al.*** Sildenafil in the treatment of erectile dysfunction after radical prostatectomy. *Urology* 2000; **56**: 631–4
37 **Fowler C, Miller J, Sharief M.** Viagra (sildenafil citrate) for the treatment of erectile dysfunction in men with multiple sclerosis. *Ann Neurol* 1999; **46**: 497
38 **Nurnberg HG, Gelenberg A, Hargreave TB *et al.*** Efficacy of sildenafil citrate for the treatment of erectile dysfunction in men taking serotonin reuptake inhibitors. *Am J Psychiatry* 2001; **158**: 1926–8
39 **Salonia A, Rigatti P, Montorsi F.** Sildenafil in erectile dysfunction: a critical review. *Curr Med Res Opin* 2003; **19**: 241–62
40 **Souverein PC, Egberts AC, Meuleman EJ *et al.*** Incidence and determinants of sildenafil (dis) continuation: the Dutch cohort of sildenafil users. *Int J Impot Res* 2002; **14**: 259–65
41 **Aytac IA, McKinlay JB, Krane RJ.** The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. *BJU Int* 1999; **84**: 50–6
42 **McKinlay JB.** The worldwide prevalence and epidemiology of erectile dysfunction. *Int J Impot Res* 2000; **12** (Suppl. 4): S6–11
43 **Orr G, Weiser M, Polliack M *et al.*** Effectiveness of sildenafil in treating erectile dysfunction in PTSD patients: a double-blind, placebo-controlled crossover study. *J Clin Psychopharmacol* 2006; **26**: 426–30
44 **Seidman SN, Roose SP, Menza MA *et al.*** Treatment of erectile dysfunction in men with depressive symptoms: results of a placebo-controlled trial with sildenafil citrate. *Am J Psychiatry* 2001; **158**: 1623–30
45 **Andersson KE.** Pharmacology of penile erection. *Pharmacol Rev* 2001; **53**: 417–50
46 **Schnurr PP, Green BL.** *Trauma and Health: Physical Health Consequences of Exposure to Extreme Stress.* Washington, DC: American Psychological Association, 2004
47 **Southwick SM, Krystal JH, Morgan CA *et al.*** Abnormal noradrenergic function in post-traumatic stress disorder. *Arch Gen Psychiatry* 1993; **50**: 266–74
48 **Neylan TC, Marmar CR, Metzler TJ *et al.*** Sleep disturbances in the Vietnam generation. Findings from a nationally representative sample of male Vietnam veterans. *Am J Psychiatry* 1998; **155**: 929–33
49 **Raskind MA, Peskind ER, Hoff DJ *et al.*** A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. *Biol Psychiatry* 2007; **61**: 928–34
50 **Gillespie PG, Beavo JA.** Characterization of a bovine cone photoreceptor phosphodiesterase purified by cyclic GMP-sepharose chromatography. *J Biol Chem* 1988; **263**: 8133–41

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Abbreviations: **ED**, erectile dysfunction; **PTSD**, post-traumatic stress disorder; **IIEF**, International Index of Erectile Function; **SEP**, Sexual Encounter Profile; **EDITS**, Erectile Dysfunction Inventory of Treatment Satisfaction; **GAQ**, Global Assessment Question; **SD**, sexual dysfunction; **DSM**, Diagnostic and Statistical Manual of Mental Disorders; **CAPS**, Clinician-administered PTSD Scale; **NO**, nitric oxide; **QoL**, quality of life; **TEAE**, treatment-emergent adverse event.