SEXUAL MEDICINE REVIEWS

Efficacy and Safety of Sildenafil in Men With Sexual Dysfunction and Spinal Cord Injury

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ABSTRACT

Introduction: Spinal cord injury (SCI) is estimated to affect approximately 276,000 individuals in the United States. Since 2010, the mean age of individuals at the time of the SCI has been 42 years, with nearly 80% of cases involving men. This means that individuals with SCI generally are young men who typically place a great deal of importance on normal sexual and reproductive function.

Aim: To assess the effect of sildenafil treatment on erectile function and the frequency of ejaculation in men with SCI.

Methods: This study was a post hoc analysis of pooled data from two randomized, double-blinded, placebo-controlled, flexible-dose, crossover sildenafil trials conducted in Europe, Australia, and Turkey. Two hundred forty-eight men at least 18 years old with traumatic SCI of at least 6 months' duration, with erectile dysfunction solely attributed to SCI, and in a stable heterosexual relationship were treated sequentially with sildenafil and placebo. Exclusion criteria included taking nitrate therapy, severe cardiac failure, and recent stroke or myocardial infarction. The starting sildenafil dose was 50 mg, taken approximately 1 hour before sexual activity, with subsequent dose adjustment to 100 or 25 mg based on efficacy and safety during treatment. There was a 2-week washout between 6-week treatments.

Main Outcome Measures: Change from baseline in International Index of Erectile Function question 3 (frequency of penetration), question 4 (maintaining erection after penetration), question 9 (frequency of ejaculation), and erectile function domain scores; intercourse success; and treatment preference.

Results: All International Index of Erectile Function outcomes, including achieving and maintaining erections and ejaculation frequency, were statistically significantly greater with sildenafil vs placebo, including the subgroup with complete SCI ($P < .01$ for all comparisons). The percentage of successful intercourse attempts with sildenafil (53% vs 12%) and preference for sildenafil (96% vs 4%) vs placebo were significant ($P < .001$), including the subgroup with complete SCI. The most common all-cause adverse events with sildenafil were headache (16.1%) and urinary tract infection (11.6%).

Conclusion: Sildenafil significantly improves erections, intercourse success, and ejaculation frequency vs placebo, including in men with complete SCI. Sildenafil is an effective and well-tolerated treatment for sexual dysfunction in men with SCI. The increase in frequency of ejaculation could allow the possibility of having children without medical intervention in this patient population. **Ohl DA, Carlsson M, Stecher VJ, Rippon GA. Efficacy and Safety of Sildenafil in Men With Sexual Dysfunction and Spinal Cord Injury. Sex Med Rev 2017;X:XX-XX.**

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Key Words: Ejaculation; Erectile Dysfunction; Randomized Controlled Trials; Sildenafil; Spinal Cord Injury

INTRODUCTION

Spinal cord injury (SCI) is estimated to affect approximately 276,000 individuals (range = 240,000–337,000) in the United States, with 12,500 new surviving cases occurring each year.[1] The most common causes of SCI are vehicular accidents (36%) and falls (30%). Since 2010, the mean age of individuals at the time of the SCI has been 42 years, with nearly 80% of cases involving men. This means that individuals with SCI generally are young men who typically place a great deal of importance on normal sexual and reproductive function.

Erectile dysfunction (ED), defined as the persistent inability to achieve and maintain an erection sufficient for satisfactory sexual performance,[2] and anejaculation are common complications in men with SCI.[3] After SCI, ED occurs in 54% to 95% of cases, with coitus possible in 5% to 75%.[4] These widely varying results

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are due to lack of standardization of methodologies for defining success and to the varying neurologic attributes of patients. Reflex erections are more common in patients with higher lesions and with an intact sacral reflex arc. Psychogenic erections generated by higher neurologic centers are more common with very low lesions and generated by the thoracolumbar cord. Schmid et al[5] found that loss of reflex erections was more likely when the bladder was areflexic and when the bulbocavernosus reflex was absent. They also noted that psychogenic erections were impaired when there was loss of perineal sympathetic skin responses. Unfortunately, despite the possibility of some degree of preserved erectile function (EF), erections in men with SCI tend to be unreliable and short-lived, thereby leading to unsatisfactory outcomes.

Ejaculatory dysfunction in this patient population remains the largest impediment to spontaneous procreation. Biering-Sorensen and Sonksen[4,6] indicated that the rate of ejaculation during sexual stimulation or masturbation in men with SCI ranged from 0% to 55% (median = 15%). Brackett et al[3] reported that only approximately 9% of men with SCI could ejaculate with masturbation or sexual intercourse. A recent large literature review and meta-analysis of 45 studies reported that ejaculation with coitus or masturbation occurred in 11.8% of men with complete SCI and 33.2% of men with incomplete SCI, but that these rates could be augmented with additional medical interventions.[7] Because of ejaculatory dysfunction, Guttmann and Walsh[8] estimated many years ago that the possibility of procreation without medical intervention was less than 5%.

Medical treatments for ED include oral phosphodiesterase type 5 inhibitors, intracavernosal injections with vasoactive agents,[9] vacuum constriction devices, and penile implants. Sildenafil is an oral phosphodiesterase type 5 inhibitor that was approved by the US Food and Drug Administration for the treatment of ED in 1998. With its peripheral mechanism of action, sildenafil has a beneficial effect on reflexogenic erections caused by penile stimulation and psychogenic erections occurring through central activation of pro-erectile pathways.

Various procedures have been developed to induce ejaculation, such as rectal probe electroejaculation and penile vibratory stimulation (PVS), but these procedures can be uncomfortable, carry some risks, and require that artificial insemination or in vitro fertilization be performed. In some selected men with SCI, it might be possible to perform PVS in the home setting with vaginal insemination.[10] However, many will require attempting pregnancy in the clinic setting because of autonomic dysreflexia or other factors, thereby increasing the costs and "medicalizing" what should be a normal process of life—that is, creating a pregnancy within a normal sexual relationship in the privacy of the home. Men with SCI yearn to regain any function that has been lost because of the injury, including sexual function and natural procreation.[11]

Two double-blinded, placebo-controlled, flexible-dose, two-way crossover trials have demonstrated the efficacy and safety of oral sildenafil in men with ED and SCI.[12,13] We conducted a post hoc analysis of pooled data from these two placebo-controlled, two-way crossover trials to further evaluate the efficacy and safety of sildenafil in men with sexual dysfunction and SCI.

METHODS

In this post hoc analysis of pooled data from two randomized, double-blinded, placebo-controlled, flexible-dose, two-way crossover trials (NCT00654082),[12,13] men were randomized to receive sildenafil or placebo for 6 weeks. After a 2-week washout period, participants received the alternative treatment for 6 weeks. Men were enrolled in the two studies from 1996 to 2003. The starting sildenafil dose was 50 mg, taken approximately 1 hour before sexual activity but not more than once daily. At week 2 of treatment, the response of each patient was evaluated by the investigator to consider dose adjustment to 100 or 25 mg based on efficacy and safety. Men who experienced no adverse events with the 50-mg dose of sildenafil or placebo, but whose ED was not sufficiently improved, had their dose increased to 100 mg. Men who responded well at the 50-mg dose were not allowed to receive a higher dose. Men taking the 50-mg dose were allowed to decrease the dose to 25 mg if they were experiencing an intolerable or serious adverse event. Men taking the 100-mg dose were discontinued from the study if they experienced an intolerable or serious adverse event. Inclusion criteria included men with SCI of at least 6 months' duration whose ED was due solely to the SCI based on patient history (eg, no ED before SCI) and who were in a stable heterosexual relationship for at least 6 months. Men with some psychogenic or reflexogenic erectile function and men with complete ED (ie, no reflexogenic or psychogenic erections present) after an SCI were eligible for enrollment. Exclusion criteria included men taking nitrate therapy or nitric oxide donors and men with significant cardiovascular disease or recent stroke or myocardial infarction. Men with diabetes mellitus were excluded from enrollment in one of the two studies. The two studies included in the analyses were conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki. All trial protocols were approved by appropriate local ethics committees or institutional review boards. All men were required to provide written informed consent before enrollment. Men who met study enrollment criteria and provided written informed consent underwent a full physical examination, including genital assessment, hematology and biochemistry laboratory tests, and sitting blood pressure and pulse rate measurements, before entering the study.

Efficacy analyses included all men with SCI and ED who were randomized to treatment, took study drug, and had baseline and at least one post-baseline evaluation of the efficacy variable. Safety analyses included all randomized men who received any study medication. Efficacy variables assessed were the International Index of Erectile Function (IIEF) question 3 (frequency of