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Is Sildenafil Citrate Effective in Treating Erectile Dysfunction Secondary to Upper Motor Neuron Spinal Cord Injury?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For
The Degree of Master of Science
In
Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 14, 2018
ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not “Is sildenafil citrate effective in treating erectile dysfunction secondary to upper motor neuron spinal cord injury?”

STUDY DESIGN: A systematic review of three peer-reviewed primary studies published in English between the years of 2008 and 2010.

DATA SOURCES: Two double-blind, randomized, placebo-controlled trials and one open, before-after study, evaluating if sildenafil citrate is effective in treating erectile dysfunction secondary to upper motor neuron (UMN) spinal cord injury (SCI). Data sources collected using Alt HealthWatch, CINAHL Plus and PubMed.

OUTCOME(S) MEASURED: The clinical outcome of erectile function achieved with sildenafil was measured in these selected studies via the International Index of Erectile Function (IIEF) and the Five-Point Qualitative Scale for Subjective Assessment of Erectile Response.

RESULTS: In each randomized control trial (RCT), statistical significance was determined using a p-value < 0.05. The RCT conducted by Ergin et al. demonstrated a significant improvement in erectile function in patients with erectile dysfunction (ED) secondary to UMN SCI when treated with sildenafil, in comparison to placebo (p= 0.001). In a RCT by Khorrami et al. men with UMN SCI saw a statistically significant increase in erectile function in comparison to placebo when treated with sildenafil citrate (p < 0.05). The open, before-after study by Soler et al. showed statistical improvement in erectile dysfunction, among this population, when treated with sildenafil (change from baseline= 12.8).

CONCLUSIONS: This review concludes that sildenafil citrate is effective in treating ED secondary to UMN SCI. Further studies with standardized patient education and a universal scale for dose titration should be conducted for better generalizability of these results.

KEY WORDS: sildenafil citrate; erectile dysfunction; spinal cord injury
INTRODUCTION

Erectile dysfunction (ED) is defined by the National Institute of Health Consensus Panel as the inability to achieve and/or maintain an erection adequate for penetration.\textsuperscript{1} Spinal cord injuries (SCI) frequently result in organic disorders of sexuality and fertility, thus are a common inciting factor of erectile dysfunction.

There are 300,000 people with SCI in the U.S. with 100,000 cases occurring each year.\textsuperscript{1} Males comprise 82% of this population with the majority being of reproductive age.\textsuperscript{1} Research conducted by Konstantinidis et al. concludes that one month after SCI an estimated 25% of males regain erectile function and one year status post injury, only 80% recovered.\textsuperscript{2} A study by Gomes et al. concludes that among the priorities of rehabilitation in men with SCI, recovery of erectile function was considered the most important aspiration for paraplegic men, followed by overcoming the desire for lower limb motor recovery.\textsuperscript{3} Given this close correlation between satisfaction with sexual life and quality of life, it is a physician assistant’s responsibility to be aware of how to best care for this considerable percentage of the population.\textsuperscript{4}

An exact number of healthcare visits in which erectile dysfunction was addressed as a consequence of SCI is not known. However, a study conducted by French et al. involving 675 patients with SCI, resulted in 27,715 clinic visits annually at the Veterans Health Administration.\textsuperscript{5} Likewise, a precise figure of the healthcare cost for men with erectile dysfunction, secondary to SCI, has not been identified. Although, it is known that paraplegic patients spend an average of $537,271 on medical expenses within the first year of injury, with $71,172 spent each subsequent year.\textsuperscript{5} With such an impressive cost being allocated to medical expenses per year, cost-effectiveness of medications or interventions should be of primary interest to medical providers.
An SCI is characterized by damage to the spinal cord that causes acute or chronic alterations in its ability to function. The impact of SCI on sexual function depends on the location and severity of the injury. UMN and lower motor neuron (LMN) SCI are typically diagnosed by a thorough history and physical exam performed by a neurologist and confirmed with MRI findings. UMN SCIs are defined as injuries that exist above the level of the sacral spinal segments and result in the preservation of sacral reflexes and a spastic type of paralysis. It is important to note then, that any or all of the following may be present in a patient with an UMN SCI: hyperactive bulbocavernosal reflex, deep tendon reflex, or positive Babinski’s sign. The clinical presentation and physiological findings are especially important when considering the mechanism of action of sildenafil citrate and its efficacy in patients with ED secondary to UMN SCI.

In an unaffected male, sexual arousal stimulates the release of nitric oxide at nerve endings in the penis. Phosphodiesterase (PDE) inhibitors, such as sildenafil citrate, potentiate nitric oxide’s effect to enhance erection. Since approximately 93% of SCI patients with UMN lesions maintain the ability to achieve reflexogenic erections, it is reasonable that sildenafil should be considered in the treatment of these patients.

ED diagnosed secondarily to SCI is traditionally treated in the same fashion as primary ED. Intracavernosal injections of vasoactive substances, transurethral suppositories, constrictive rings, vacuum devices and surgically implanted prosthetic devices are all recognized treatments for ED. These methods can be invasive, cumbersome and highly expensive leading to an increased treatment dropout rate. Sildenafil citrate is the first effective oral drug to treat ED and has become the drug of choice in modern practice. Approximately 3.6 million sildenafil prescriptions were written in the U.S. during the first 4 months after its release on the market. In
2017, the estimated drug cost for sildenafil was estimated to be $12,050.\textsuperscript{7} This is proven to be significantly cheaper than the majority of other, less preferred methods of treatment. A standardized, evidence-based treatment plan has not been clinically implemented for males with ED secondary to UMN SCI. For this reason, it is sensible to evaluate the efficacy of sildenafil citrate in treating ED secondary to UMN SCI.

This systematic review evaluates two randomized controlled trials (RCTs) and one open, before-after study comparing the efficacy of sildenafil as an oral medication for treating erectile dysfunction in patients with upper motor neuron (UMN) SCI.

**OBJECTIVE**

The objective of this selective EBM review is to determine whether or not “Is sildenafil citrate effective in treating erectile dysfunction secondary to upper motor neuron spinal cord injury?”

**METHODS**

The population targeted for this review included men of all ages, with ED secondary to UMN SCI. The intervention being investigated for treatment of ED in UMN SCI, is sildenafil citrate in comparison to placebo or other PDE5 inhibitors such as vardenafil or tadalafil. The outcome being measured is the ability to achieve and maintain an erection rigid enough for penetration, determined as per patient. This selective EBM review includes two RCTs and one open, before-after study.

All articles were published in English in peer-reviewed journals between 2008 and 2010. Keywords used include, “sildenafil citrate”, “erectile dysfunction” and “spinal cord injury” to obtain the articles included. Inclusion criteria for the selection of articles were as follows:
published in the English language, published in a peer-reviewed journal in 2008 or later, with no other systematic review, meta-analysis or article in the Cochrane database answering the same question. Inclusion criteria also encompassed articles that were relevant to the clinical question, which measured patient-oriented outcomes. Exclusion criteria included articles that discussed ED without a history of SCI and articles that primarily studied a treatment other than sildenafil.

A summary of statistics reported includes p-value, mean changes from baseline and NNT.

**Table 1: Demographic and Characteristics of included studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th># Pts</th>
<th>Age (yrs)</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>W/D</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khorrami(^1) (2010)</td>
<td>Placebo-controlled, double-blind RCT</td>
<td>105</td>
<td>40-55</td>
<td>Male pts. with a diagnosis of ED for &gt;15 years</td>
<td>Anatomic abnormalities of the penis, Severe CVD, Hx of stroke, acute MI, psychologic problems or pelvic surgery, Nitrate use</td>
<td>0</td>
<td>50 mg of sildenafil at least 45 minutes before the start of sexual intercourse</td>
</tr>
<tr>
<td>Ergin(^6) (2008)</td>
<td>Placebo-controlled, double-blind RCT</td>
<td>50</td>
<td>19+</td>
<td>Male pts. &gt;19 y.o. with a diagnosis of SCI ≥ 6 mos.</td>
<td>Diagnosis of ED not attributable to traumatic SCI</td>
<td>0</td>
<td>50-100 mg of sildenafil at least 1 hr before sexual activity</td>
</tr>
<tr>
<td>Soler(^4) (2008)</td>
<td>Open, before-after study</td>
<td>120</td>
<td>18+</td>
<td>Suffered traumatic SCI, Pts. in stable relationship with active sexual life despite ED</td>
<td>BP instability, Known or suspected CVD or neuropathy, Nitrate or anticoagulant use</td>
<td>0</td>
<td>50 mg sildenafil, 10 mg vardenafil or tadalafil at least 30-60 minutes before manual sexual stimulation</td>
</tr>
</tbody>
</table>
OUTCOMES MEASURED

The ability for a man to achieve and maintain an erection was measured by all three studies, using the International Index of Erectile Function (IIEF) survey. The IIEF is a 15-item questionnaire that addresses the pertinent domains of male sexual function. Domain A of this questionnaire is specifically related to erectile function. Questions asked in this portion of the survey require patients to assess their erectile function in the past four weeks by answering the following: How often were you able to get an erection during sexual activity; When you had erections with sexual stimulation, how often were your erections hard enough for penetration; When you attempted sexual intercourse, how often were you able to penetrate your partner; How often were you able to maintain your erection after you had penetrated your partner; During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse; How do you rate your confidence that you can get and keep your erection? Each question may be answered using the following: No sexual activity/stimulation (0); Almost always or always (5); Much more than half the time (4); About half the time (3); Much less than half the time (2); almost never or never (1). A maximum score of 30 can be achieved in this portion of the IIEF, with a score of 15 or greater being considered a positive response to treatment or sufficient erectile function. In each study, participants were required to complete the questionnaire before and after treatment to determine the efficacy of the intervention.

In the before-after study by Soler et al. patients also utilized a six-point quantitative scale to self-assess the quality of the reflexogenic erection; with 0 being no erection at all, to 5 representing full rigidity. A rigidity of 4 or greater was determined hard enough for penetration, and therefore significant erectile function.
RESULTS

This systematic review, consisting of two RCTs and one before-after study, assessed whether or not sildenafil citrate is effective in treating ED, secondary to UMN SCI. Each article analyzed in this review collected and presented data and the statistical significance of the findings in different forms. Demographics and characteristics of participants included in each study are listed in Table 1.

The double-blind, randomized, placebo-controlled trial by Khorrami et al. studied 105 patients suffering from ED secondary to SCI. Out of the 105 participants, 72 people suffered from UMN SCI and 33 had LMN or mixed SCI. Of the 72 patients with UMN SCI, 45 people were given sildenafil (experimental group) and placebo was administered to the remaining 27 participants (control group). Patients were instructed to take 50 mg of sildenafil or a placebo tablet at least 45 minutes before sexual intercourse. The recommended maximum frequency of administration was one dose per day. Throughout the six-month period of the study, patients were visited monthly, during which each participant would complete the IIEF questionnaire. If a participant’s IIEF score was less than 15, the dose of sildenafil was increased to 100mg. In the event that a participant did not experience an improvement in erectile function, regardless of dosage, the patient was marked as “non-responsive”. Of the 45 participants treated with sildenafil, 37 people (82%) achieved and maintained an erection significant enough for sexual intercourse. Eight participants (18%) of the experimental group reported no change with sildenafil treatment and were considered unresponsive. However, in the control group, only 26% of participants reported a significant improvement in erectile function with placebo. The data reported was converted into dichotomous form. A NNT of 2 was extrapolated from the provided data, suggesting that fewer patients needed to be treated with sildenafil to cure one case
of ED, as compared to the control group. A p-value of less than 0.05 is also reported in the study, indicating that is it unlikely these results were obtained by chance alone. These findings are both statistically and clinically significant, given the number of people enrolled in the study and population that it represents. Table 2 details the data concluded from this research.

**Table 2: Khorrami et al- Erectile function with sildenafil citrate in comparison to placebo**

<table>
<thead>
<tr>
<th>NNT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

In the placebo-controlled, double-blind, randomized 2-way crossover study by Ergin et al., 50 participants with ED secondary to SCI were evaluated for response to treatment with sildenafil citrate. Twenty-six people in the study had a previously diagnosed incomplete SCI; which were all primarily UMN in nature. Patients were analyzed for a two week period without treatment to establish baseline data on sexual function. During the first portion of this cross-over study, half of the participants were given 50mg of sildenafil and a placebo pill was dispensed to the other half to be taken one hour before sexual stimulation. Based on an extensive history, physical and laboratory results, there were no differences in the sociodemographics or health status between both groups. After a six week period of the initial treatment, patients underwent another two week “wash-out” period before switching to the alternative treatment method for another 6 weeks. The participants in this study where observed for a total of 16 weeks in which they completed personal logs and the IIEF questionnaire before and after each crossover period. Data detailing the IIEF score of each group or crossover period is not shared in the article. However, the article shares a mean change in baseline of erectile function with sildenafil citrate in patients with incomplete lesions to be 5.0 ± 6. The article also shares a p-value less than 0.05.
for this data, proving these results are unlikely to have occurred by chance alone or, statistically significant. Table 3 summarizes the data collected by this article.

**Table 3: Ergin et al.- Change in mean from baseline in erectile function with sildenafil versus placebo**

<table>
<thead>
<tr>
<th>Sildenafil citrate</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0 ± 6.0</td>
<td>0.2 ± 1.5</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

The open, before-after study conducted by Soler et al. is comprised of a clinical trial and home assessments. Baseline data were obtained during a four-week treatment-free period in which patients used the IIEF questionnaire and six-point scale to rate their erectile function. During the one-week, clinical trial portion of this study, 120 patients were given 50mg sildenafil citrate to take 30-60 minutes before manual stimulation (masturbation). One hundred ten of these participants were previously diagnosed with UMN SCI. Doses were adjusted on a flexible scale from 50-100mg of sildenafil, based upon the efficacy per patient. The patients were asked to report the rigidity of each erection using the six-point scale and to record the duration of each erection in minutes. If responsive to treatment, participants were given the opportunity to continue treatment with sildenafil at home. Fifty-seven people elected to continue treatment at home, where patients were instructed to take the prescribed dose of sildenafil 30-60 minutes before sexual intercourse. The time in which patients were followed varied greatly between three to twenty months. Baseline data showed an average rigidity of 3 or 4 with a mean duration of 2 minutes. During clinical trials, 85% of participants treated with sildenafil reported a rigidity of 4 or 5, with the mean duration increasing to 34 minutes on average. Table 4 condenses the findings gathered from the clinical trial.
Table 4: Soler et al. - Baseline assessment and efficacy outcome in clinical trials with sildenafil citrate

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Sildenafil citrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rigidity</td>
<td>3.7</td>
<td>4.6</td>
</tr>
<tr>
<td>Duration of erection (min)</td>
<td>2.8</td>
<td>33.5</td>
</tr>
</tbody>
</table>

Home assessment data collection showed an IIEF score increase from 14 to 26.8 with treatment. The mean change from baseline is 12.8. During this study, sildenafil was compared to other PDE5 inhibitors, namely vardenafil and tadalafil, which have and identical mechanism of action, and were found to be similar in efficacy in comparison to sildenafil. This mean change from baseline is statistically and clinically significant given the large number of participants included in the study, in relation to the population in which it represents. Table 5 records baseline values to those gathered at home with sildenafil citrate.

Table 5: Soler et al. – Baseline assessments and efficacy outcome at home with sildenafil citrate

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Home</th>
<th>Change in mean from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erectile function (based upon IIEF values)</td>
<td>14.0</td>
<td>26.8</td>
<td>12.8</td>
</tr>
</tbody>
</table>

All three articles in this systematic review made mention of the side effect profile associated with sildenafil citrate in treating ED secondary to spinal cord injury. The side effects of sildenafil include: mild headache, flushing, dizziness, and dyspepsia. Overall, there were no episodes of symptomatic hypotension, priapism or dysreflexia reported by participants throughout any of the studies. No participants dropped out due to side effects of the treatment in any of the studies. The most significant population reporting mild side effects were in the before-after study conducted by Soler et al. in which 15% of patients on sildenafil reported mild side
effects. In the RCT by Ergin et al., which more closely investigated the safety of sildenafil than all other articles included in this review, the number of adverse effects reported by patients being treated with sildenafil did not differ significantly than placebo groups with a p-value equal to 0.19. Given this data, it can be extrapolated that it is safe to use sildenafil in the treatment of ED secondary to UMN SCI.

**DISCUSSION**

This systematic review is designed to discuss the efficacy of sildenafil in treating ED secondary to UMN SCI. However, sildenafil citrate has a number of alternate uses, including the reduction of angina symptoms in females; which was its initial purpose. Among other popular alternate uses for sildenafil are the treatment of pulmonary arterial hypertension in adults, female sexual arousal disorder, altitude sickness and prostate cancer when combined with other therapies. It is important to note that the FDA has not approved sildenafil citrate for any of the former uses, despite success being noted in smaller studies.

Sildenafil citrate should be used with caution in patients with a medical history significant for coronary artery disease, congestive heart failure, hypertension, stroke, aortic stenosis, hyperlipidemia, diabetes mellitus, hypovolemia, sickle cell anemia or a social history of smoking. The use of sildenafil citrate is contraindicated in patients prescribed any of the following: common HIV medications (atazanavir, darunavir, indinavir, ritonavir, cobicistat, etc.), nitroglycerin, nitroprusside, isosorbide dinitrate/mononitrate and riociguat.

Sildenafil citrate is a familiar and widely available drug in the United States. However, in order to obtain the medication a patient must have the resources to visit a primary care physician, as sildenafil is a prescription-only drug. Traditionally, an added barrier to treatment with sildenafil was the cost. In recent years, GoodRx, a company that tracks drug prices and
distributes coupons, offered retail price of $16.81 for 30 pills of the generic sildenafil. This cost is fiscally reasonable when compared to the financial burden many other treatments for ED in patients with UMN SCI bestow.

While all three articles included in this systematic review have been sufficient in measuring the outcomes studied, some limitations remain present. In the before-after study by Soler et al. the results did not give a specific mean change from baseline in patients with UMN SCI alone. Although 110 participants out of the 120 total suffered from a UMN SCI, it would have been beneficial to see results that excluded the 10 participants who did not pertain to the group being studied in this clinical question. Likewise, while both RCTs examined the efficacy of sildenafil in achieving and maintaining an erection during sexual intercourse, it would be an advantage to also examine its use in manual stimulation as this may lessen the confounding factors that may present in a romantic relationship. Lastly, none of the articles measured compliance among the participants, which could greatly affect the study results.

CONCLUSION

The studies included in this EBM review have provided sufficient evidence to accept that sildenafil citrate is effective in treating ED secondary to UMN SCI. Two RCTs and one before-after study have provided statistically and clinically significant values supporting that sildenafil citrate enhances a patient’s ability to achieve and maintain an erection rigid enough for penetration. This data is specifically tailored to ED secondary to UMN SCI and cannot be used to extrapolate information in regards to ED secondary to LMN SCI or other etiologies. Further research may be warranted to answer those separate clinical questions. This systematic review confirms that sildenafil citrate is an effective and well-tolerated treatment for ED secondary to UMN SCI.
References


