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EFFICACY OF SILDENAFIL CITRATE (VIAGRA™) ON SEXUAL RESPONSES IN NON-DYSFUNCTIONAL YOUNGER-AGED MEN

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ABSTRACT

Sildenafil citrate (Viagra™) is a potent inhibitor of the electrolytic enzyme type V phosphodiesterase (PDE5), in the corpus cavernosum and therefore increases the penile response to sexual stimulation. We evaluated the efficacy of sildenafil, in younger men without erectile dysfunction.

In this study subjects treated with 25 mg oral dose of sildenafil were found to be associated with higher mean scores for the questions of the International Index of Erectile Function (IIEF).

Frequency of penetration and maintenance of erection after sexual penetration and/or during masturbation were found to be enhanced significantly ($p<0.001$) in the sildenafil treated men. Similarly mean domain of erectile function, orgasmic function, intercourse satisfaction and over all satisfaction also showed a significantly positive improvement ($p<0.001$) in the sildenafil group in comparison with their age matched untreated controls. However the sexual-desire domain in sildenafil treated men with respect to their aged matched controls showed a non-significant difference.

Sildenafil citrate may assist an individual or couple in extending/enhancing the excitement phase or prolonging the sexual interaction and may have other sexual effects not recognized in the clinical studies.

Keywords: Non-dysfunctional, younger males, sexual response, sildenafil.

INTRODUCTION

Normal penile erection depends on the relaxation of smooth muscles in the corpora cavernosa. In response to sexual stimuli, cavernous nerves and endothelial cells release nitric oxide, which stimulates the formation of cyclic guanosine monophosphate (GMP) by guanylate cyclase (Rajfer *et al.,* 1992; Barnett 1995). The mechanism by which cyclic GMP stimulates relaxation of the smooth muscles remains to be elucidated. Sildenafil is a selective inhibitor of cyclic-GMP-specific phosphodiesterase type 5, the predominant isozymes metabolizing cyclic GMP in the corpus cavernosum (Boolell *et al.,* 1996). By selectively inhibiting cyclic-GMP catabolism in caversonal smooth-muscle cells (Moralend *et al.,* 1998), sildenafil would be expected to restore the natural erectile response to sexual stimulation but not cause erections in the absence of such stimulation. Sildenafil is rapidly absorbed, with maximum plasma concentrations occurring within one hour after oral administration and a mean terminal half-life of three to five hours (Boolell *et al.,* 1996).

The clinical efficacy of sildenafil has been evaluated by multiple pivotal studies as well as post-marketing studies (Firozzi *et al.,* 2005; Gomez *et al.,* 2005; Brown *et al.,* 2006). These studies which have been carried out over the past 5 years, have demonstrated an excellent efficacy as well as safety profile (Padma-Nathan *et al.,* 2004; Vlachopoulos *et al.,* 2004; Seftel 2005). Comparing sildenafil as an oral

Table-1
Mean scores of responses to Question 3 of The International Index of Erectile Function for the untreated men and the men treated with sildenafil citrate.
Values are Mean ± Standard Errors (SE).

Subjects	Base-Line Score	Final Score	Percent Change from Base Line
UNTREATED GROUP N = 50	2.0 ± 0.1	2.1 ± 0.2	5
SILDENAFIL TREATED GROUP N = 50	1.8 ± 0.2	3.4 ± 0.2	88*

N = Number of the subjects examined. Base line and final scores of untreated and sildenafil treated groups are compared for t-test. * = $p < 0.001$
Question 3 = When you attempted sexual intercourse; how often were you able to penetrate your partner? (Modified with the attempts of successful masturbation in some cases).

Table-2
Mean scores of responses to Question 4 of the International Index of Erectile Function for the untreated men and the men treated with sildenafil citrate.
Values are Mean ± Standard Errors (SE).

Subjects	Base-Line Score	Final Score	Percent Change From Base Line
UNTREATED GROUP N = 50	1.8 ± 0.1	2.2 ± 0.2	22
SILDENAFIL TREATED GROUP N = 50	1.7 ± 0.1	3.8 ± 0.2	124*

N = Number of the subjects examined. Base line and final scores of untreated and sildenafil treated groups are compared for t-test. * = $p < 0.001$
Question 4 = During the sexual intercourse; how often were you able to maintain your erection after you had penetrated your partner? (Modified with the attempts of successful masturbation in some cases).

treatment for erectile dysfunction, patients prefer this choice to injection therapy, vacuum erection device or penile prostheses because of its efficacy, ease of use and lack of side effects (Karim *et al.,* 2006).

These PDE-5 inhibitors are safe in most patients, with adverse effects limited as previously noted. These adverse effects appear to be of minimal consequence and in placebo-controlled, long-term trials; rates of discontinuation of sildenafil and placebo from side effects are equal throughout (Waldkirch *et al.,* 2005).

There are also reports that sildenafil may improve sexual performance in potent subjects (Aversa *et al.,* 2000).

There is concern, at least in the popular press, that drugs used in the treatment of erectile dysfunction will be misused by non-dysfunctional men. There is no research to document what the consequences of this misuse will be. A review of literature found only one study (Aversa *et al.,* 2000), concerning the effect of these drugs on non-dysfunctional men. The present study investigates the effects of sildenafil citrate on

young-aged men without any history of erectile/sexual dysfunction.

MATERIALS AND METHODS

A total of 68 young men, age ranging from 18 to 25 years (average age of 22 years) with out any history of sexual or erectile dysfunctions were selected for the study. Potential subjects were eliminated for general poor health, nitrate use, any history of sexual dysfunction associated with diabetes mellitus, a history of cigarette smoking, peptic ulcer disease, obesity, hypertension, high blood pressure, or cardiac disease. Men were also excluded if they had penile anatomical defects, a primary diagnosis of another sexual disorder (premature ejaculation) or any psychiatric sexual disorder.

Informed consent was obtained from 50 screened subjects, who were using 25 mg (minimal dose) tablets of Viagra^{TM} (Sildenafil citrate) with standard instruction on its use on regular bases to enhance their sexual performance. Other erectile therapies (if any) were discontinued at the time of screening (four weeks before the subjects received the study medication).

All 50 subjects were instructed to take one tablet of sildenafil citrate (25 mg orally), but not more than once daily for 3 months, one hour before sexual activity, 2-3 hours after a meal. Subject's response to treatment with sildenafil was evaluated using the International Index of Erectile Function (IIEF)-5, a validated, multidimensional, self administered questionnaire (15-questions) used for the clinical assessment of erectile dysfunction and treatment outcomes in clinical studies (Rosen *et al.,* 1997). Based on scores of (IIEF)-5 efficacy was assessed for the five separate response domains of male sexual functions including erectile function (question 1 through 5 and 15), orgasmic function (question 9 and 10), sexual desire (questions 11 and 12), intercourse/masturbation satisfaction (questions 6,7, and 8), and overall satisfaction (questions 13 and 14). The efficacy to the responses of question 3 and 4 was also assessed and rated on a scale of 1 (almost never and never) to 5 (almost always or always).

The mean frequency of response to questions 3 and 4 and the mean domain scores of male sexual functions from IIEF were calculated. An analysis-of-covariance model was fitted for each question and the treatment effects were analyzed with the base line score. A *p*-value of less than 0.05 was considered to indicate statistical significant.

RESULTS

Mean scores of response to question 3 and 4 of the International Index of Erectile Function for the men receiving sildenafil citrate in comparison with their age matched controls are presented in Table-1 and 2. In this study, subjects with the dose of sildenafil were found to be associated with higher mean scores for the questions of the International Index of Erectile Function assessing frequency of penetration (Question-3) and maintenance of erection after sexual penetration or during masturbation (Question-4).

The mean scores for these questions (3 & 4) in respect to achieving erections hard enough for sexual intercourse showed a significantly greater response for sildenafil treated group which was about 88%, and 124% respectively ($p<0.001$).

The mean (± SE) scores for domain of the erectile function (five questions; possible total score, 1 to 30) for 50 men in the sildenafil group in comparison with their age matched controls is presented in Figure-1. Sildenafil group showed a highly significant and positive response in erectile function ($p<0.001$) than the control group.

Mean orgasmic function domain score (two questions; possible total score, 0-12) presented in Figure-2 showed a similar

positive response in the sildenafil group when compared with the control subjects ($p<0.001$).

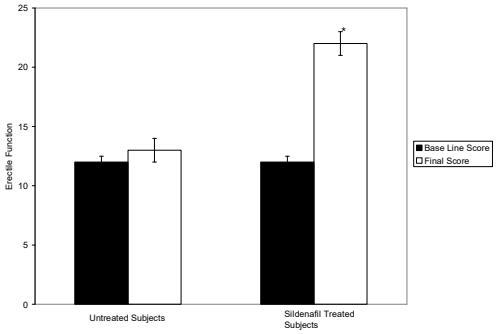

Fig. 1: Mean (±SE) scores for the Erectile-Function Domains of the International Index of Erectile Function for untreated and sildenafil treated men. (Asterisk denotes $p<0.001$)

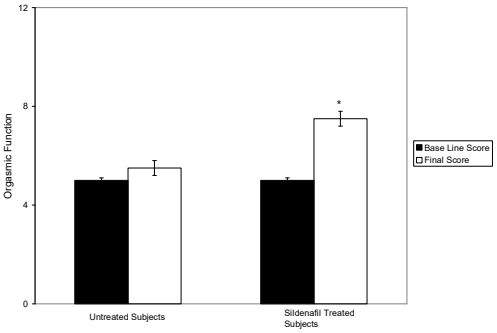

Fig. 2: Mean (±SE) scores for the Orgasmic-Function Domains of the International Index of Erectile Function for untreated and sildenafil treated men. (Asterisk denotes $p<0.001$)

A comparison regarding the sexual-desire domain (two questions; possible total score, 0 to 12); between the sildenafil treated men with respect to their aged matched controls showed a non-significant difference (Figure-3).

The mean domain scores for the intercourse satisfaction (three questions; possible total score, 0 to 12); and overall satisfaction (two questions; possible total score, 0-12) for the sildenafil and the control group is presented in Figures 4 and 5. These results indicated a highly significant and positive response for both the domains in the treated groups ($p<0.001$). All results were tabulated according to the mean (± SE) scores for Domains of the International Index of Erectile Function for men receiving sildenafil citrate in comparison with the age matched control subjects.

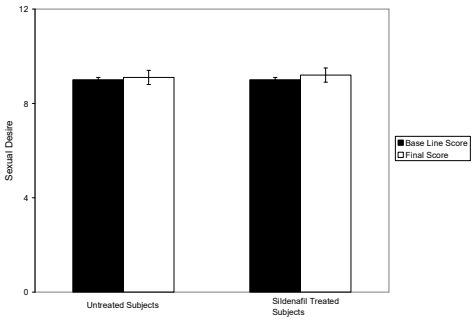

Fig. 3: Mean (±SE) scores for the Sexual-Desire Domains of the International Index of Erectile Function for untreated and sildenafil treated men.

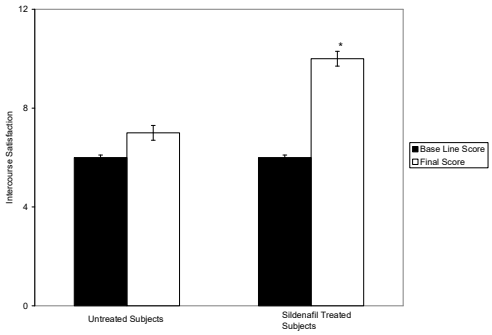

Fig. 4: Mean (±SE) scores for the Intercourse-Satisfaction Domains of the International Index of Erectile Function for untreated and sildenafil treated men. (Asterisk denotes $p<0.001$)

DISCUSSION

The fear of being unable to attain an erection once lost may cause some individuals to truncate the excitement phase of the sexual

interaction. His partner or the sex therapies may interpret this as a goal oriented sex, a phallocentric sex, a failure to consider the partner's level of sexual excitement or a loss of playfulness in the sexual interaction (Feldman *et al.,* 1994).

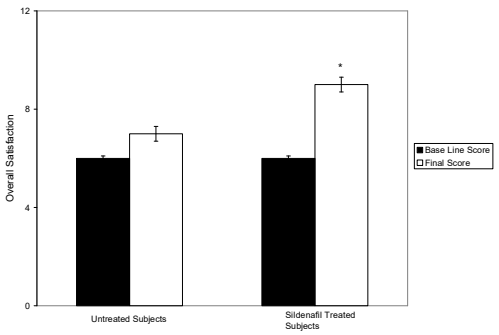

Fig. 5: Mean (±SE) scores for the Overall-Satisfaction Domains of the International Index of Erectile Function for untreated and sildenafil treated men. (Asterisk denotes $p<0.001$)

While there are concerns about the appropriateness of using pharmaceuticals to enhance sexual functioning, data concerning the long-term consequences do not exist. As individuals age it is not uncommon to treat a diminution in bodily function with drugs (e.g. laxative for constipation, antacids for dyspepsia, and analgesics for joint pain). While any drug can be misused and problems ensure, limitations on the use of drug should be based upon known danger.

Sildenafil citrate is the first oral agent for the treatment of erectile dysfunction to be approved by the US FDA, and is marketed widely. Since its introduction in 1998, sildenafil has revolutionized the treatment of erectile dysfunction. This first effective, safe, oral agent for the treatment of erectile dysfunction has been used around the world in all the severities of sexual dysfunction, across age groups, racial groups, ethnicities and erectile dysfunction etiologies (Goldstein *et al.,* 1998; Saftel 2005).

Sildenafil produces relaxation of corpus cavernosum smooth muscle tissue both with and without electric field stimulation in a dose response pattern. This dose response improvement in corpus cavernosum relaxation and subsequent erectile function is like wise seen in clinical efficacy studies. These studies which have been carried out over the past few years have demonstrated an excellent efficacy as well as safety profile (Morals *et al.,* 1998).

The present study relied on self-report, looked at different aspects of male sexual act in response to oral sildenafil administration in younger men (aged 18-25 years) who do not report any sexual dysfunction. In keeping with sildenafil mode of action (i.e. the drug causes erection only in response to sexual stimulation), the studies were performed entirely in a natural environment, which meant that we had to rely on men's own reports of efficacy. However, the self-administered International Index of Erectile Function has a higher degree of sensitivity and specificity for detecting treatment-related changes in men with or without erectile dysfunction (Rosen *et al.,* 1997). The questionnaire provided a comprehensive assessment of erectile function.

We found most recognized improvement with sildenafil citrate in the frequency of penetration and the maintenance of erections after penetration, the mean score for the erectile-function domain of International Index, and the percentage of men reporting better erection. Surprisingly the men treated with sildenafil had a normal level of sexual desire, as might be expected with reference to another study with the men having erectile dysfunction who enter a clinical trial (Akira *et al.,* 2002) and sildenafil did not alter that level.

Sildenafil treatment was found to be well tolerated. Mild adverse effects were headache, flushing, dyspepsia and rare visual disturbances (pharmacological nature of sildenafil as a phosphodiesterase-type-5 inhibitor and as a weak phosphodiesterase-type-6 inhibitor respectively). No men had priapism after sildenafil treatment thus suggesting a

relatively high level of drug tolerability and acceptance in normal healthy men (data not shown).

Overall, the results of the efficacy assessments demonstrated that sildenafil significantly enhanced erectile function, quadrupled the success of intercourse/ masturbation and sexual performance without altering the sex desire in younger men having no erectile dysfunction. Sildenafil citrate may assist an individual or couple in extending the excitement phase or prolonging the sexual interaction. It may restore men's confidence in obtaining an erection and allow the couple to address other concerns in their sexual interactions and may have other sexual effects not recognized in the clinical studies.

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