

## A Rational Combination Pharmacotherapy in Men with Erectile Dysfunction who Initially Failed to Oral Sildenafil Citrate Alone: A Pilot Study

Rajesh Taneja, MS, MCh

Pushpawati Singhanian Research Institute—Surgical Division, New Delhi, India

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### ABSTRACT

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**Introduction.** Erectile dysfunction (ED) is a complex condition wherein men with minimal organic ED may develop a variable degree of psychogenic component sufficient to reduce the efficacy of medical management. A combination of trazodone with sildenafil has been used to overcome both organic as well as psychogenic components, thus improving the results of medical management.

**Aim.** To evaluate the efficacy of combination of trazodone with sildenafil citrate in treatment of ED in men with initial failure to sildenafil citrate alone.

**Main Outcome Measures.** The symptoms of ED were evaluated using the Erectile Dysfunction Intensity Scale (EDIS) before and after the treatment.

**Methods.** Eighteen men with ED who initially failed to respond to sildenafil citrate alone were enrolled in the study between February 2004 and December 2004. All these men were given a priming dose of trazodone for a 2-week period before giving them sildenafil citrate.

**Results.** Of the 18 men, 12 responded favorably to the above treatment and continued to enjoy good sexual activity while on trazodone and sildenafil. The score on EDIS improved considerably in 12 (66.7%) men, marginally in two (11.1%) men, and did not improve at all in four (22.2%) men.

**Conclusions.** Priming the patients with trazodone appears to be a reasonably good alternative in patients who have initial failure to oral sildenafil citrate and have been found to have no organic cause of ED. However, large double-blind studies are required to potentiate this hypothesis. **Taneja R. A rational combination pharmacotherapy in men with erectile dysfunction who initially failed to oral sildenafil citrate alone: A pilot study. J Sex Med 2007;4:1136–1141.**

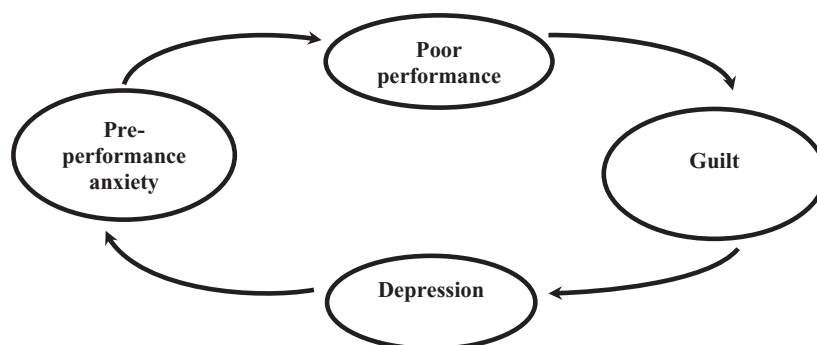
**Key Words.** Erectile Dysfunction; Sildenafil Failure; Combination Pharmacotherapy

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### Introduction

Ever since sildenafil citrate has been approved by the U.S. Food and Drug Administration to be used in patients with erectile dysfunction (ED), men have come forward openly seeking help regarding this hitherto “private” problem. The high response rate approaching 70% of sildenafil when used alone in ED has influenced the algorithm of treatment of this condition [1]. However, this also means that almost 30% of men who are administered this drug do not benefit from it adequately. The causes of failure, as studied by

various researchers have been inadequate patient information, suboptimal dose, and insufficient number of attempts [2,3]. In addition to these factors, performance anxiety, depression, and partner-related factors might have adverse effects on the final outcome of sildenafil therapy. It has been shown that although vascular and endocrine causes of ED are more common in elderly age groups, depression, marital discord, and performance anxiety occur more frequently in younger age groups [4]. The documented improvement in nocturnal penile tumescence with oral sildenafil in men who have initial clinical failure of the same



**Figure 1** Psychological impact of poor performance.

drug emphasizes the role of performance anxiety as a deterrent to the clinical success [5]. The relationship of psychological factors with ED is a complex one. While failure to have successful intercourse leads to depression, the same may in turn be responsible for poor sexual performance (Figure 1). Hence, it is worthwhile to break this cycle by intervening at multiple levels.

Keeping this in view, we designed this protocol for treatment of men with ED who had failures with initial treatment by sildenafil. Apart from educating the couples, men were administered a priming dose of trazodone. All antidepressants except for trazodone have an inherent depressive effect on erectile function via sympathetic nervous stimulation. Trazodone is a sedating anxiolytic antidepressant with a specific side effect of altering the penile blood flow in a peculiar, incompletely understood manner which is likely to be related to its antagonistic effect on alpha adrenergic receptors [6]. This has been held responsible for priapism encountered in some of the men taking trazodone over long periods of time. Trazodone has been studied as a single oral agent for treatment of ED with variable results. In addition to the peripheral action on penile blood flow, trazodone is also known to enhance the libido through its effect on brain. However, the dose at which trazodone alone has been shown to be useful is rather high, more than 200 mg per day, with

drowsiness as a major side effect that limits its routine use in cases of ED [7]. The dose of trazodone used in this study is significantly lower than the standard recommendation for use as a single agent in cases of ED in order to reduce the side effects while utilizing its antidepressant property. The combination of trazodone and sildenafil has not been licensed for use in general practice as of now.

#### Aim

The present study is an endeavor to combine the advantages of the two oral agents to overcome the failure of treatment with sildenafil alone.

#### Methods

All men who had initial therapeutic failure with sildenafil and were referred to our tertiary care center for treatment of ED between February 2004 and December 2004 were investigated to exclude other treatable causes of ED. The overall exclusion criteria have been listed in Table 1. Eighteen men were found suitable for inclusion into the study. All these men had followed appropriate instructions regarding medication, tolerated sildenafil citrate well in the dose of 100 mg, and had at least four unsuccessful attempts before being labeled as

**Table 1** Exclusion criteria

1. Active coronary heart disease
2. Continuing nitrate therapy
3. Cavernous artery insufficiency as documented by color Doppler study following intracavernosal injection of vasoactive substance
4. Neurogenic factors such as history of radical prostatectomy or any other known factor affecting neural integrity. Neurological deficits were excluded by detailed clinical examination
5. Obvious severe mental instability so as to require immediate psychiatric help
6. Presence of factors which may adversely affect pharmacodynamics of sildenafil e.g., chronic renal insufficiency, concomitant use of cimetidine, etc.
7. Penile fibrosis
8. Retinitis pigmentosa
9. Hypogonadism

**Table 2** Erectile Dysfunction Intensity Scale

|  | Almost never<br>or never | A few times<br>(much less than<br>half the time) | Sometimes (about<br>half the time) | Most times<br>(much more than<br>half the time) | Almost always<br>or always |
|--|--------------------------|--|------------------------------------|---|----------------------------|
| How often were you able to get an erection during sexual activity?   | 1                        | 2  | 3                                  | 4   | 5                          |
| When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)? | 1                        | 2  | 3                                  | 4   | 5                          |
| When you attempted intercourse, how often were you able to penetrate (enter your partner)?   | 1                        | 2  | 3                                  | 4   | 5                          |
| During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?      | 1                        | 2  | 3                                  | 4   | 5                          |
| During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?                            | Extremely difficult<br>1 | Very difficult<br>2                              | Difficult<br>3                     | Slightly difficult<br>4                         | Not difficult<br>5         |

Adapted from erectile dysfunction (ED) intensity and impact scales, recommendation of the first international consultation on ED, Paris, 1999, as in Campbell's Urology, Eighth Edition [8].

sildenafil failures [1]. After informed consent was obtained, the participants were administered a questionnaire to record their symptoms, duration, and existing comorbidities if any. The symptoms were evaluated using the Erectile Dysfunction Intensity Scale (EDIS) [8] before and after the treatment (Table 2).

The Erectile Dysfunction Intensity Scale has not been reported widely in the literature even though it was recommended by the first international consultation on ED in 1999. If examined closely, this consists of the first five questions of the IIEF15, which pertain directly to erectile function.

All these men were interviewed on the day of induction and on day 14. During the initial consultation, they were explained the importance of appropriate timing of sildenafil in reference to food and sexual activity. They were also encouraged to come forward with their own queries if any regarding the reasons for initial failure of sildenafil. An attempt was made to reassure and explain to the participants in simple language the basis of combination pharmacotherapy. The supportive role of the female partner was also emphasized wherever possible. All men were advised to take trazodone tablets at bed time, 50 mg for first three nights followed by 100 mg for rest of the 11 nights; they were warned about the possibility of drowsiness following medication and were asked to contact the investigator in case of any complaints. The patients were asked to report after 2 weeks. During the second consultation, patients were asked about the side effects, if any, as experienced following oral

trazodone. All the men were then asked to continue trazodone as 100 mg once a day and in addition were given four doses of 100-mg sildenafil and advised to report after an additional period of 2 weeks. They were also allowed to take an additional dose of sildenafil after telephonic discussion, should such a need arise. At the end of this 2-week period, their symptoms were evaluated again using EDIS and the data tabulated.

## Results

All the 18 men were available for compilation of data. The mean age of the patients enrolled was 39.83 years (range 22–72 years). The duration of symptoms ranged from 2 months to 48 months (mean 14.61 months). The coexisting medical disorders included diabetes mellitus in three patients, hypertension in three and bronchial asthma in one (Table 3).

The only side effects reported were sedation in eight (44.4%), dizziness in three (16.6%), and fatigue in one (5.5%) cases. These were never so severe as to warrant discontinuation of treatment.

The analysis of EDIS feedback prior to the treatment revealed the total score to be a minimal 5/25 in 11 (61.1%) patients, 6/25 in five (27.7%) cases, and 7/25 in two (11.1%) cases. At the end of 4 weeks, the score improved considerably in 12 (66.6%) patients, ranging between 14 and 21. Couples in this group had successful intercourse more than once during the 2-week period following the second counseling session. Four of these men

**Table 3** Patient profile

| Serial no. | Age (years) | Comorbidities     | Duration of ED (in months) |
|------------|-------------|-------------------|----------------------------|
| 1.         | 28          | None              | 4                          |
| 2.         | 30          | None              | 2                          |
| 3.         | 31          | Bronchial asthma  | 6                          |
| 4.         | 55          | None              | 48                         |
| 5.         | 40          | Diabetes mellitus | 6                          |
| 6.         | 48          | None              | 12                         |
| 7.         | 38          | Diabetes mellitus | 8                          |
| 8.         | 28          | None              | 6                          |
| 9.         | 46          | Hypertension      | 24                         |
| 10.        | 60          | Diabetes mellitus | 24                         |
| 11.        | 22          | None              | 4                          |
| 12.        | 29          | None              | 12                         |
| 13.        | 50          | Hypertension      | 6                          |
| 14.        | 46          | None              | 3                          |
| 15.        | 58          | Hypertension      | 42                         |
| 16.        | 48          | None              | 6                          |
| 17.        | 36          | None              | 2                          |
| 18.        | 72          | None              | 48                         |

ED = erectile dysfunction.

asked by telephone for more doses of sildenafil for additional sexual activities.

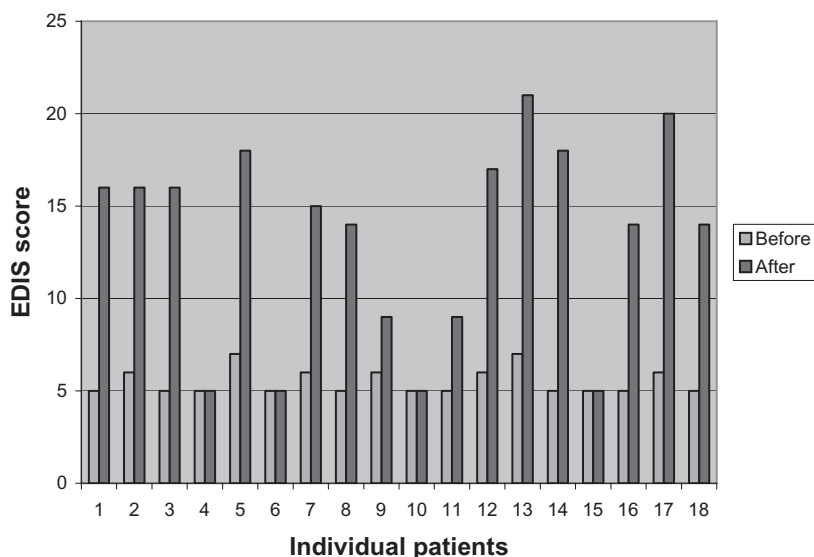
However, the total EDIS score improved marginally in two (11.1%) cases and became 9/25. These two men reported definite improvement in the quality of erections, which were ill-sustained. Though their erections were sufficient enough for penetration, they could not achieve orgasm because of early detumescence. In four (22.2%) cases, it did not change at all and remained at the baseline 5/25 (Figure 2).

### Discussion

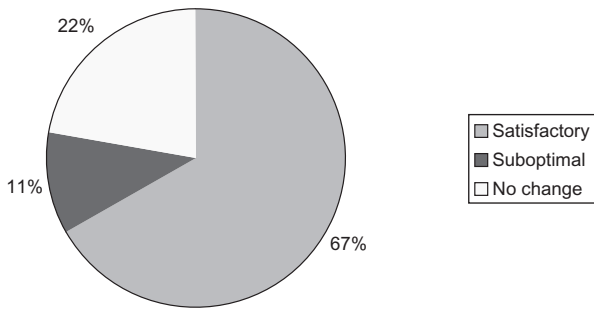
Sildenafil has become the first-line treatment for ED as used by primary care physicians [9]. There

are a substantial number of such patients, almost 30% of the total number, who have an initially poor response to sildenafil alone leading to discouragement and an adverse impact on their psyche [10]. Patient education regarding sildenafil usage alone has been shown to salvage around 40–58% of initial sildenafil failures [1,9].

There exists a documented need for more research in the pharmacotherapeutic development of various oral agents for safe and effective treatment of ED [11]. In search of improvement in the clinical results of sildenafil, various combinations have been reported. Testosterone supplements in late onset hypogonadal men have been used to improve the clinical outcome of treatment of ED with sildenafil [12]. Another study has shown that



**Figure 2** Erectile Dysfunction Intensity Scale (EDIS) score before and after treatment.



**Figure 3** Overall improvement in erectile function.

the addition of atorvastatin improves the efficacy of sildenafil in treatment of ED [13].

The present study has indicated encouraging results of a combination pharmacotherapy protocol to improve the overall results of treatment of patients with ED in cases of initial failures (Figure 3). Patient education regarding proper dosing schedule, adequate number of attempts, the need for sexual stimulation, and realistic expectations go a long way in improving the efficacy of treatment.

The mean age of the present cohort is very young as compared with the standard ED population as documented in other series. This is perhaps because in India young men have a lot of performance anxiety, as they are amenable to suggestion by cheap and misleading literature, which is freely available while authentic sex education is scanty.

Sociodemographic conditions have been documented to be risk factors in a study of epidemiology of sexual dysfunction [14].

The exact role and the extent of contribution of trazodone is difficult to assess. It may, however, be presumed that the antidepressant action of trazodone along with its complex effect on penile hemodynamics has a bearing on the overall result by breaking the vicious cycle as follows:

Poor performance → Guilt → Depression → Pre-performance anxiety → Poor performance.

It may be appreciated that in order to conclusively prove this hypothesis, a large-scale, randomized, double-blind, placebo-controlled study is required. The delicate and highly vulnerable psychological state of these individuals may make this kind of study difficult to be carried out by further accentuating their anxiety levels.

In the present series, use of trazodone and sildenafil has been shown to convert initial non-responders to successful responders in almost 67% of cases. However, no separate attempt was made to quantify the amount of satisfaction of

the female partners. None of the patients needed to discontinue the treatment because of the minimal side effects which were encountered during the study.

An inverse relationship has been found between the duration of symptoms and response to treatment as illustrated by cases 4, 6, 10, 15. All these patients were much older than the mean age of the study group, i.e., 55, 48, 60, and 58 years against mean 39.83 years. The longer duration of symptoms i.e., 48, 12, 24, and 42 months also points toward some form of organic/endothelial defect. If one is inclined to consider psychogenic factors in this group, then it might be assumed that the repeated inability to perform over a long period of time might have had a deep impact on their psyche, resulting in lack of confidence in addition to underlying organic condition, if any. Lance et al. have reported similar observations in another study. They have found that the duration of ED was inversely related to the response to trazodone [15].

Encouraged by the results of this study, one may be inclined to use the above combination in selected de novo cases of ED as primary therapy especially in men with significant anxiety at the time of initial presentation.

In rural Indian society, where much misleading cheap literature is the prime source of sex education, many unscientific myths prevail that are detrimental to the sexual health of young men. Many such young men develop performance anxiety and seek medical help. Simply prescribing sildenafil to such individuals is expected to result in higher failure rates. Appropriate use of combination pharmacotherapy in such situations may be rewarding.

## Conclusions

Combining trazodone with sildenafil has been shown to have encouraging initial results in cases of primary sildenafil failures with no organic cause of ED. However, larger, preferably placebo-controlled studies are required to conclusively prove the efficacy and advantage of this combination therapy.

**Corresponding Author:** Rajesh Taneja, MS (General Surgery), MCh (Urology), Surgical Division, Pushpawati Singhania Research Institute, Press Enclave Road, Sheikh Sarai, Phase II, New Delhi-110017, India. Tel: (+91) 11 29252516; Fax: (+91) 11 29250548; E-mail: rajeshjtanejad@rediffmail.com

*Conflict of Interest:* None declared.

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