

Sildenafil citrate significantly improves nocturnal penile erections in sildenafil non-responding patients with psychogenic erectile dysfunction

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Effects of sildenafil citrate on nocturnal penile tumescence and rigidity (NPTR) were evaluated among sildenafil non-responding patients with psychogenic erectile dysfunction. All patients ($n = 30$), equally divided into groups I and II, completed four consecutive nights using the RigiScan Plus device. Sildenafil citrate (50 mg) was given in the third night in group I and in the fourth in group II, whereas a placebo was given in the remaining nights. Additional patients ($n = 12$) receiving only a placebo served as a control group. Results of NPTR recordings revealed neither significant differences between the control and non-sildenafil nights of both test groups, nor between the corresponding values of both groups ($P > 0.05$). On the other hand, when sildenafil citrate nights of groups I and II taken together were compared with placebo nights, a significant increase of total events duration ($P < 0.001$), average rigidity of the tip ($P < 0.05$) and base ($P < 0.01$), and rigidity activity unit (RAU) and tumescence activity unit (TAU) of tip and base ($P < 0.001$) was observed. These results suggest that performance anxiety may be responsible for failure of response during awakening.

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Introduction

Sildenafil citrate is widely used as an effective and safe oral treatment for erectile dysfunction of various etiologies.¹ It is a potent and selective inhibitor of phosphodiesterase type 5 enzyme that acts to break down cyclic guanosine monophosphate (cGMP).² Accumulation of cGMP inhibits the degradation of nitric oxide that is responsible for smooth muscle relaxation within the corpora cavernosa. Nitric oxide is released by intracavernous nonadrenergic noncholinergic nerve terminals not only following a central or local erectogenic stimulus but also during rapid eye movement (REM) sleep.³ Psychogenic erectile dysfunction (ED) patients are excellent candidates for sildenafil citrate

therapy due to the intact neurovascular pathway. Nevertheless, the drug has been reported to be effective only in about 78% of patients with psychogenic ED.⁴ It is likely that performance anxiety and sympathetic overtone are the cause of this unresponsiveness to sildenafil citrate during awakening, though data supporting this assumption are lacking.⁵ Therefore, this work is conducted to objectively evaluate the response of those patients to sildenafil citrate during sleep.

Patients and methods

Male patients complaining of psychogenic ED ($n = 30$) and not satisfactorily responding to sildenafil citrate up to 100 mg/dose in more than one occasion within a month time period were included in this study (age 34–58 y). Men having penile anatomical defects, active peptic ulcer, bleeding disorders, retinitis pigmentosa, major hematological, renal or hepatic abnormalities, and history of stroke or recent myocardial infarction, and loss of

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libido were excluded. Patients receiving antihypertensives, nitrates, tranquilizers or drugs known to interfere with sildenafil citrate metabolism, for example, cimetidine and ketoconazol, were also excluded. The cause of ED is confirmed as being psychogenic in origin on the basis of medical and sexual history, physical examination, hormonal studies (including total and bioavailable testosterone, prolactin), blood glucose, cholesterol and lipid levels, intracavernosal pharmacotesting with penile duplex ultrasonography, and psychological evaluation.⁶ Neurological evaluation revealed no signs of depression or other psychoneurological diseases that could interfere with nocturnal penile tumescence and rigidity (NPTR) recordings.

NPTR testing was performed by using the RigiScan Plus device version 5 (Timm Medical Technologies Inc., USA). Number of events, total events duration (in hours), average rigidity of tip and base, and RAU and TAU were determined.⁷ To avoid, or at least minimize the effect of adaptation, patients were randomly divided into two groups, evaluation of NPTR has been extended to four consecutive nights and sildenafil citrate has been administered on a different night in each group.

Group I (n = 15 patients): Sildenafil citrate (50 mg) (Viagra, Pfizer[®]) was given 1 h before bedtime in the third night, whereas a placebo was given in the remaining nights, that is, nights 1, 2, and 4.

Group II (n = 15 patients): Sildenafil citrate (50 mg) was given 1 h before bedtime in the fourth night, whereas a placebo was given in the first three nights.

In addition, non-sildenafil-treated psychogenic ED patients (n = 12) with identical clinical findings

and age matched with the test groups received only a placebo in all four nights of NPTR recording and served as a control.

A written consent was signed by all patients of the study, which was also approved by the Ethics and Investigation Committee of Ain Shams University hospital.

Statistical evaluation

Paired Student's *t*-test was used to compare values of a single night with each of the other nights of the same group including control, and values of the corresponding nights between groups I and II. Two samples with equal variance Student's *t*-test was applied to compare values of two or more nights with a single night either in the control group, groups I or II or when values of groups I and II were taken together. Repeated-measures analysis of variance (ANOVA test) was used in evaluating results among the control group and also non-sildenafil nights among each test group. *P*-value <0.05 was considered significant.

Results

In the present study, 30 patients, in addition to 12 control patients, completed the four nights of NPTR monitoring using the RigiScan plus device. The age of patients in group I ranged from 34 to 48 y (mean ± s.d. = 39.8 ± 5.7), while those of group II ranged from 36 to 58 y (mean ± s.d. = 45.1 ± 6.9),

Table 1 Results of RigiScan monitoring in group I and II

Parameter	Night 1		Night 2		Night 3		Night 4	
	Group I	Group II	Group I	Group II	Group I (A)	Group II	Group I	Group II (B)
Number of events ^a	3.8 ± 1.3	2.8 ± 0.7	4.5 ± 0.9	4 ± 0.8	6.7 ± 1.6*	4.9 ± 1** ^b	5.3 ± 1.7* ^c	7 ± 1.2***
Total events duration (h)	1.3 ± 0.2	1.3 ± 0.2	1.3 ± 0.1	1.2 ± 0.1	2.1 ± 0.4***	1.5 ± 0.2	1.5 ± 0.4	2.4 ± 0.2***
<i>Average rigidity</i>								
Tip	39.1 ± 8.8	44.9 ± 11.3	39.6 ± 9.3	44.3 ± 11.6	47.9 ± 10.4*	43.9 ± 9.2	40.4 ± 11	57.6 ± 10.7**
Base	46 ± 10.8	48.8 ± 12.2	44.5 ± 6.7	49.6 ± 10.8	57.3 ± 10.5**	49.8 ± 9.8	44.9 ± 9.5	60.8 ± 11**
<i>RAU</i>								
Tip	35.8 ± 7.9	47.6 ± 11.2	35 ± 10.4	48.8 ± 8.9	56.3 ± 8.5***	49.3 ± 7.6	41 ± 12.6	62.1 ± 7.5***
Base	45.5 ± 9.7	51.9 ± 11.7	40.6 ± 10.6	56.6 ± 9.7	65.5 ± 8.7***	55.1 ± 9.8	44.9 ± 14.6	66 ± 8.6**
<i>TAU</i>								
Tip	31.1 ± 10	38.3 ± 15.1	30.3 ± 10.9	42.3 ± 8.9	49.1 ± 13.2***	39.3 ± 8.2	35 ± 13.5	56.3 ± 7.8**
Base	39.6 ± 10.8	41.4 ± 12.5	33.6 ± 11.8	33.6 ± 11.8	58 ± 15.6***	44.9 ± 10.4	40.6 ± 14.4	59.1 ± 10.9*

P* > 0.05; *P* < 0.01; ****P* < 0.001.

(A) Sildenafil citrate (night 3) in comparison to night 2.

(B) Sildenafil citrate (night 4) in comparison to night 2.

^aRepeated analysis of variance of non-sildenafil citrate nights in groups I and II (*P* < 0.01).

^bSignificant results in comparison with night 1.

^cSignificant results in comparison with nights 1 and 2.

with no significant difference ($P > 0.05$). Age of both groups, that is, the 30 patients, ranged from 34 to 58 (mean \pm s.d. = 42.5 ± 6.7), not significantly different from the control group (age range 35–48 y, mean \pm s.d. = 41.7 ± 5.1) ($P > 0.05$). The final etiological diagnosis of ED according to the complete patients and control group's work-up was indicative of psychogenic rather than organic etiology.

The side effects of sildenafil citrate were carefully monitored, where only two patients (6.7%) reported slight morning headache and one patient (3.3%) slight gastrointestinal upset. No patient developed severe side effects that required test abortion.

NPTR recordings of the control group and non-sildenafil nights of groups I and II revealed values indicative of psychogenic ED, thus confirming the diagnosis set by history, medical examination, and pharmacotesting with penile duplex ultrasonography. Also, no significant difference between control group and non-sildenafil nights of groups I and II, whether separately or when values of both test groups were taken together, was found ($P > 0.05$). On the other hand, patients receiving sildenafil citrate showed improvement in most of the parameters that have been measured by the RigiScan when compared with non-sildenafil citrate nights, as they represent their true control (Table 1).

In group I: The number of events showed significant changes when night 3 was compared with nights 1 or 2 ($P < 0.01$ and $P < 0.05$, respectively), but not with night 4 ($P = 0.2$), though night 4 was significant when compared with nights 1 or 2 ($P < 0.05$). Total events duration (h) was significantly longer when night 3 results were compared with those of nights 1, 2, and 4 ($P < 0.001$). Average rigidity of the tip and base revealed insignificant

changes between nights 1, 2, and 4 ($P > 0.05$). On the other hand, a significant increase in the average rigidity of the tip was noticed when values of sildenafil citrate night (night 3) were compared with either night 1 or 2 ($P < 0.05$), but not with night 4 ($P > 0.05$). The average rigidity of base and RAU and TAU of both tip and base in night 3 were significantly higher in comparison with non-sildenafil nights ($P < 0.01$ – 0.001) (Table 1).

In group II: Significant increase in the number of events was obtained when night 4 results were compared with nights 1 or 2 or 3, and likewise when night 3 results were compared with night 1 ($P < 0.01$ – 0.001). Similarly, total events duration was longer when night 4 results were compared to non-sildenafil nights whether separately or collectively ($P < 0.001$). Average rigidity of the tip and base revealed insignificant changes from night 1 through night 3; however, a significant change was noticed when results of night 4 (sildenafil citrate night) were compared with non-sildenafil citrate nights, whether separately or collectively ($P < 0.01$). RAU and TAU of both the tip and base were significantly higher when night 4 results were compared to the results of the other three nights whether separately or collectively ($P < 0.05$ – 0.001) (Table 1).

Comparing the results of sildenafil citrate night in either group I with the mean values of non-sildenafil citrate nights (including night 1), i.e., basal condition, revealed significant increase in all parameters of NPTR monitoring ($P < 0.01$ – 0.001) except average rigidity of the tip ($P < 0.05$). Excluding night 1 (adaptation night), however, revealed significant improvement in this parameter ($P = 0.02$). In group II, all parameters on sildenafil night were significantly higher when compared with the mean values of non-sildenafil nights ($P < 0.05$ – 0.001) (Table 2).

Table 2 Results of sildenafil citrate night in comparison with basal condition in group I and II

Parameter	Group I		Group II	
	Basal condition (mean of nights 1, 2, 4)	Sildenafil citrate night (night 3)	Basal condition (mean of nights 1, 2, 3)	Sildenafil citrate night (night 4)
Number of events	4.7 \pm 1.4	6.7 \pm 1.6**	3.8 \pm 1.2	7 \pm 1.2***
Total event duration (h)	1.4 \pm 0.2	2.1 \pm 0.4***	1.3 \pm 0.2	2.4 \pm 0.2***
<i>Average rigidity</i>				
Tip	39.7 \pm 9.5	47.8 \pm 10.4	44.3 \pm 10.3	57.6 \pm 10.7**
Base	45.1 \pm 8.8	57.3 \pm 10.5**	49.4 \pm 10.5	60.8 \pm 11*
<i>RAU</i>				
Tip	37.3 \pm 10.4	56.3 \pm 8.5***	48.5 \pm 9	62.1 \pm 7.5***
Base	43.7 \pm 11.5	65.5 \pm 8.7***	54.5 \pm 10.2	66 \pm 8.6**
<i>TAU</i>				
Tip	32.1 \pm 11.3	49.1 \pm 13.2**	39.9 \pm 10.8	56.3 \pm 7.8***
Base	37.9 \pm 12.3	58 \pm 15.6***	45.3 \pm 10.3	59.1 \pm 10.9**

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs basal condition.

Table 3 Results of sildenafil citrate night in all patients (group I±II) ($n=30$) as compared with basal condition and control ($n=12$)

Parameter	Control [†] (first three nights)	Basal condition (non-sildenafil citrate nights)	Sildenafil citrate night
Number of events	4.06 ± 1.5	4.3 ± 1.4	6.9 ± 1.4***
Total event duration (h)	1.3 ± 0.3	1.3 ± 0.2	2.2 ± 0.3***
<i>Average rigidity</i>			
Tip	41.6 ± 10.9	42 ± 10.1	52.7 ± 11.4*
Base	46.7 ± 10.5	47.3 ± 8.7	59 ± 10.6**
<i>RAU</i>			
Tip	41.6 ± 11.9	42.9 ± 11.2	59.2 ± 8.3***
Base	47.9 ± 12.9	49.1 ± 12	65.8 ± 8.4***
<i>TAU</i>			
Tip	35.4 ± 12.8	36 ± 11.6	52.7 ± 11.1***
Base	41 ± 12.7	41.6 ± 11.8	58.6 ± 13***

* $P<0.05$, ** $P<0.01$, *** $P<0.001$ vs basal condition and control group.

[†] $P>0.05$ vs basal condition.

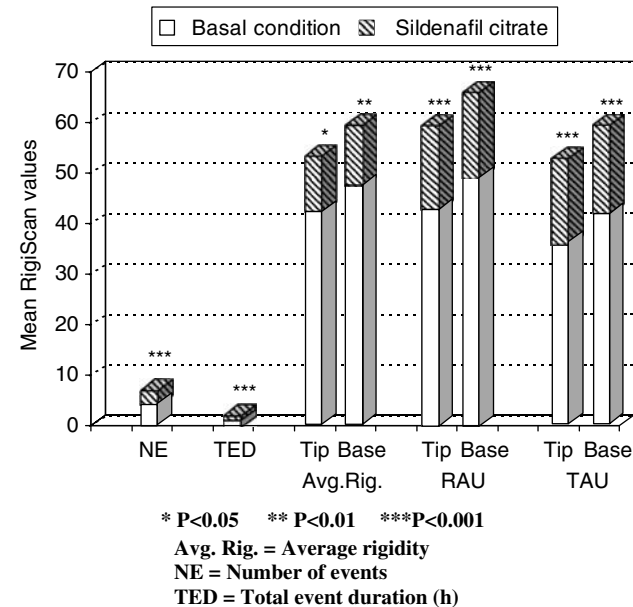


Figure 1 Results of sildenafil citrate night in all patients ($n=30$) in comparison with basal condition.

Nevertheless, as differences between the results of corresponding values of basal condition and sildenafil citrate night were insignificant in both groups ($P>0.05$), it was justifiable to compare sildenafil citrate night with non-sildenafil citrate nights in the whole sample of the study ($n=30$ patients). Table 3 and Figure 1 demonstrate such a comparison which revealed a significant improvement in all parameters

of NPTR recordings ($P<0.05-0.001$). Exclusion of night 1 (adaptation night) or inclusion of control group nights (whether three or four nights) did not significantly change any of the results of the study (Table 3).

Discussion

Results of the present study clearly demonstrate that sildenafil citrate taken at bedtime significantly improves almost all NPTR parameters, despite repeated failure of response during sexual act in psychogenic ED patients. The psychogenic etiology of ED was objectively confirmed in the present study by pharmacotesting with duplex ultrasonography and interestingly by NPTR monitoring itself. Several studies have shown improvement in almost all parameters of NPTR monitoring among patients with organic ED.^{8,9} Regarding the impact of sildenafil citrate on NPTR in potent men, controversial results were obtained. Montorsi *et al*⁹ showed that sildenafil citrate did not significantly improve nocturnal penile activity, whereas Yaman *et al*,¹⁰ conducting a similar study with a larger sample, concluded that sildenafil citrate can improve nocturnal erectile quality not only in patients with ED, but also in potent men. Psychogenic ED has a complex background. In a recent study on 23 men with psychogenic ED, there was no significant correlation between anxiety scores or peripheral/cavernous catecholamines and erection rigidity.¹¹ This controversy and the fact that sildenafil citrate is effective in about 78% of cases of psychogenic ED were the trigger for the present study. In this study, 30 psychogenic ED patients not responding to repeated trials of sildenafil citrate completed the four consecutive nights study. Interestingly, all cases showed significant improvement in nocturnal erectile activity in the sildenafil citrate night when compared with either the control group or non-sildenafil nights of the test group.

Dividing patients into two groups aimed at lending validity to the recorded changes under the effect of sildenafil citrate. This fact was verified by the significant improvement of NPTR parameters in the sildenafil citrate night, namely night 3 in group I and night 4 in group II. This was also the rationale for conducting the NPTR monitoring along four nights and including night 1, usually excluded in previous reports, in the evaluation.^{9,10,12}

Previous studies of NPTR in psychogenic ED have shown improvement of RAU and TAU of the tip and base of the penis after sildenafil citrate. The duration of tip rigidity ($>60\%$) was also longer during the sildenafil citrate night. In the present study, however, no improvement of average rigidity of the tip in group I was recorded. This could be attributed to the small sample size and to the wide

variations between individual RigiScan recordings.^{8,9,13} In contrast to these studies, however, the number of events was significantly improved, not only in the sildenafil citrate night, but also in night 4 in group I and in night 3 in group II. In group I, the improvement in night 4 when compared with that of night 3 (sildenafil citrate night) was insignificant. Likewise, in group II, no significant difference was noted between nights 3 and 4. Therefore, this improvement is likely due to the effect of increased adaptation from night 1 to night 4, rather than to persistent sildenafil citrate effect till night 4, as its effect declines after 4 h of administration.¹⁴ This argument has also been verified in the control group of this study (data not shown).

To further support the role of sildenafil citrate and eliminate that of adaptation, mean values between the three non-sildenafil citrate nights were used as a basal condition to be compared with the mean results of sildenafil citrate night. Apart from the average rigidity of the tip of group I, all other parameters of NPTR were significantly greater in the sildenafil night. Nevertheless, excluding night 1 revealed significant improvement of average rigidity of tip in group I as well. Comparing the corresponding results of both groups was insignificant, denoting that sildenafil citrate had the same effects, no matter whether administered on the third or fourth nights, which was a justification for considering both groups as a single group of 30 patients. On repeating statistical analysis for the 30 patients and taking control group into consideration, significant changes were present in all parameters of NPTR recordings. This change from the results of group I and II could be attributed to the larger sample size.

Therefore, it is justifiable to assume that performance anxiety and sympathetic overtone are the causes of this non-responsiveness to sildenafil citrate during awakening.¹⁵ Indeed, psychogenic influences and anxiety about performance may result in inhibitory sympathetic nervous activity, and the anticipatory anxiety can make the condition self-perpetuating.¹⁶

To conclude, our study showed that, in patients with psychogenic ED, sildenafil citrate administered at bedtime significantly improves the average rigidity of the tip and base, total events duration, RAU of the tip and base and TAU of the tip and base. Failure

of response to sildenafil citrate during awakening is most likely due to performance anxiety and sympathetic overtone.

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