Review Article

# A meta-analysis on efficacy and tolerability of sildenafil for erectile dysfunction in patients with diabetes mellitus

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## Abstract

Erectile dysfunction (ED) is a common complication in patients with diabetes mellitus (DM). Sildenafil, a phosphodiesterase-5 inhibitor, is commonly used in patients with ED. This meta-analysis was planned to determine the strength of evidence to assess the efficacy and tolerability of sildenafil in patients with DM-associated ED. Electronic searches were carried out to identify randomized controlled trials (RCTs) which reported clinical efficacy of sildenafil in patients with DM-associated ED. Data were extracted and methodological quality was assessed. Relative Risk (RR) with 95% confidence intervals (CIs) was estimated for the dichotomous outcomes, and the mean difference with 95% CI was estimated for continuous data. Eight randomized controlled trials (RCTs) involving 1172 patients met with our inclusion criteria. In comparison to placebo, sildenafil significantly improved the overall sexual performance in patients of ED associated with DM with relative risk (RR) of answering "yes" to global efficiency question being 3.99 (95% CI: 2.58–6.18) compared to placebo. The rate of discontinuation due to treatment-related adverse reactions was 2.4% in sildenafil arm with RR of 2.67 (95% CI: 0.74–9.62). Sildenafil is an effective and safe medication for the treatment of ED associated with DM.

**Key words:** Diabetes mellitus, erectile dysfunction, sildenafil

## INTRODUCTION

The global prevalence of diabetes among adults over 18 years of age has increased to 8.5%, affecting 422 million people all over the world.[1] It is estimated that 5%–10% of diagnosed cases are of Type I diabetes mellitus (DM), while the remaining 90%–95% are of Type II DM.[2]

Erectile dysfunction (ED) is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual activity and is a common complication of diabetes in men.

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The prevalence of ED of any degree in men aged 40–70 years was estimated to be 52% in the Massachusetts Male Aging Study, with a prevalence of 25% for moderate ED and 10% for complete ED.[3] ED occurs at an earlier age in men with diabetes than in men in the general population,[4] and its frequency has been reported to be higher in people with diabetes compared with those without diabetes in some studies.[5-7] Men with treated diabetes had a 28% age-adjusted prevalence of complete ED (no erections), almost three times higher than the



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prevalence of complete ED observed in the entire sample of men.[3]

ED in diabetes is often complex and caused by several mechanisms including vascular disease, autonomic neuropathy, hormonal imbalance, and psychogenic factors.[8]

The risk of ED increases with duration of diabetes and is directly related to poor glycemic control and the presence of other risk factors such as hypertension, smoking, and hyperlipidemia.[9]

Treatment options for ED include psychological management, vacuum constriction devices, intracavernosal injections, transurethral drug delivery, penile prostheses, vascular surgery, and modification of medication contributing to the problem.[10]

However, many of these treatments have limited acceptability to users. The ideal goal in the treatment of ED is restoration of erectile capacity using a minimally invasive and safe treatment.

Sildenafil is the first oral drug to be marketed specifically for the treatment of ED.

In response to sexual stimulation, locally released nitric oxide (NO) from the endothelial cells stimulates the production of cyclic guanosine monophosphate (cGMP) by guanylate cyclase. In turn, cGMP stimulates smooth muscle relaxation and penile erection. Sildenafil is a potent inhibitor of cGMP-specific phosphodiesterase type 5 (PDE5), the predominant PDE degrading cGMP in the corpus cavernosum.[11] By its inhibition of PDE5, sildenafil has the potential to enhance erectile activity under conditions of sexual stimulation. It does not have a direct effect on libido or smooth muscle.

However, as the endothelial dysfunction is an important factor contributing to the development of ED in diabetic patients, such patients can be resistant to sildenafil therapy. There are reports of lower efficacy of sildenafil in patients of diabetes compared to general population.[7,12] Moreover, there are no reports on relative efficacy of sildenafil in patients of type I and type II diabetes and with varying severities of ED.

Hence, this meta-analysis was conducted to assess the overall efficacy and safety of sildenafil in patients with DM-associated ED of varying severities.

## METHODOLOGY

### Search strategy

Studies were identified using electronic databases – MEDLINE, Cochrane Central Register of Controlled Trials, and Google Scholar in July 2017. The search process was carried out by combining terms "sildenafil," AND "erectile dysfunction" AND "diabetes mellitus."

### Study selection

Only randomized controlled trials (RCTs) comparing sildenafil with placebo or active control for the treatment of ED in patients of DM were included in the study. There were no language restrictions.

Studies comparing sildenafil in combination with other active drugs were excluded from this review.

### Outcome assessment

Four different outcome measures were determined from the pooled data: using the International Index of Erectile Function (IIEF) scoring system, change from baseline to week 12 in score of Question 3 (when you have attempted sexual intercourse, how often were you able to penetrate [enter] your partner?) and Question 4 (during sexual intercourse, how often were you able to maintain your erection after you have penetrated [entered] your partner?), response to global efficacy question (GEQ) ("did treatment improve your erections?"), and event log (patient recorded number of attempts of sexual intercourse and number of attempts that were successful).

### Data extraction

The data were extracted using a prestructured data entry form from the studies that met the above mentioned inclusion and exclusion criteria.

Data were extracted about the name of the author, year of publication, methodological characteristics, treatment arms, duration of the study, sample size in each group, method of assessment of outcome, type of DM, and the outcome data in each of the group.

Data on reported adverse events among the patients receiving sildenafil and placebo were also extracted from the included studies.

### Risk of bias

The quality of the included studies was assessed using Cochrane collaboration assessment's tool for assessing the risk of bias.[13]

## Statistical analysis

Each study was assessed individually by two authors (NT and PC). Data were extracted individually from each published manuscript by both the authors and data were included only if the two authors had independently achieved the same results.

Demographic data are presented as mean ± standard deviation (SD).

Data for dichotomous outcomes, such as response to GEQ, event log, and withdrawal due to adverse drug reactions (ADRs), were extracted by recording the total number of participants randomized, those who experienced these outcomes, and the number analyzed.

For continuous outcomes, for example, change in score of Question 3 and Question 4, data were extracted by the total number of participants analyzed, arithmetic means, and SD. Data on reported adverse events were also extracted.

Meta-analysis was conducted using RevMan version 5.3 (The Nordic Cochrane Centre for The Cochrane Collaboration, Copenhagen, Denmark)[14] with risk ratio (RR) for dichotomous data and mean differences (MDs) for continuous data presented with 95% confidence intervals (CIs). A random effects model (DerSimonian and Laird) was used. The number needed to treat (NNT) was calculated as inverse of absolute risk reduction.

PRISMA guidelines were followed for reporting the study.[15]

# RESULTS

## Study selection and characteristics

A total of eight studies met with the inclusion and exclusion criteria and were included in the present meta-analysis.[2,16-22]

The total number of patients, with varying degrees of ED (of at least 6-month duration) along with DM, was 1172. Of these, 591 patients were treated with sildenafil and 581 were given placebo.

The mean age of patients included in sildenafil arm was 54.18 ± 5.1 years while that of placebo arm was 54.95 ± 5.16 years. The mean duration of ED in sildenafil and placebo treated group was 4.38 ± 1.42 years and 4.98 ± 1.66 years, respectively. The mean duration of DM in sildenafil arm was 11.98 ± 4.20 years while that of placebo arm was 12.15 ± 4.47 years. Of 1172 patients, 24.40% patients were of Type I DM while 75.6% patients were of Type II DM.

The characteristics of the included studies are enumerated in Table 1. Sample size in individual studies varied from 8 to 144. Seven of eight studies were double-blind randomized controlled clinical trials while one study[19] was an open randomized trial.

Four studies[2,16,18,22] used flexible dose of sildenafil (25–100 mg) starting with 50 mg as and when needed. Whereas, the other four studies[17,19,20,21] used fixed dose of sildenafil 50 and 100 mg.

All the studies were placebo controlled except one which compared lifestyle modification as the second arm.[19]

The duration of the study ranged from 10[17] to 16[21] weeks, though most of the studies were of 12-week duration.

## Quality of the studies

Seven studies were randomized double-blind clinical trials; however, only Stuckey *et al*.[22] reported the method of blinding. Four studies[2,19,21,22] described about the method of randomization. Allocation concealment was described by three studies.[2,21,22] Blinding of the outcome assessment was assumed to be present in double-blind RCTs when not specified. Three studies[2,18,21] had conducted intention to treat analysis while others had not. Withdrawal due to treatment-related adverse event accounted for 2.45% of total withdrawal.

## Treatment effectiveness

Treatment with sildenafil produced significant improvement in IIEF Question 3 score with weighted MD (WMD) of 1.14 (95% CI: 0.73–1.50) and IIEF Question 4 WMD of 1.13 (95% CI: 0.85–1.42).

Patients in the sildenafil-treated arm were four times more satisfied with their overall sexual performance compared to placebo-treated arm with RR of 3.99 (95% CI: 2.58–6.18) [Figure 1].

The number of successful events was significantly more in sildenafil-treated group compared to placebo-treated group with RR of 3.34 (95% CI: 2.10–5.31) [Figure 2], with a significantly ($P < 0.00001$) higher number of patients reporting at least one successful attempt of intercourse in the last 4 weeks of treatment with RR of 2.86 (95% CI: 2.25–3.65).

In pooled analysis, the NNT for sildenafil was 2. This means that when compared to placebo, it would require two individuals with DM-associated ED to be treated with sildenafil for one to show the effect ascribed to the medication.

The most common adverse events reported were headache, dyspepsia, and flushing.

The rate of discontinuation due to treatment-related adverse event was higher in sildenafil-treated group (13 out of 529) compared to placebo-treated group (3 out of 520) with RR of 2.67 (95% CI: 0.74–9.62) [Figure 3].

Of 529 patients, 88 reported headache due to sildenafil treatment while only 17 (out of 520) in the placebo-treated arm reported the same, with RR of 4.50 (95% CI: 2.72–7.45).

Flushing and dyspepsia were the other commonly reported ADRs in sildenafil-treated group with

**Table 1: Characteristics of included studies**

| Author | Year | Sample size SIL/placebo | Type of study | Sildenafil (dose mg) | Duration of treatment (weeks) | Assessment of efficacy | DM I/II |
|---|---|---|---|---|---|---|---|
| Rendell *et al.*[2] | 1999 | 136/132 | DBRCT | 25-100 flexible | 12 | IIEF; GEQ; event log | I (18.5%)/II (81.5%) |
| Boulton *et al.*[16] | 2001 | 110/109 | DBRCT | 25-100 flexible | 12 | IIEF; GEQ, event log | II |
| Escobar-Jiménez[18] | 2002 | 44/48 | DBRCT | 25-100 flexible | 12 | IIEF; GEQ; QOL | II |
| Stuckey *et al.*[22] | 2003 | 95/93 | DBRCT | 25-100 flexible | 12 | IIEF; GEQ; event log | I |
| Safarinejad[21] | 2004 | 144/138 | DBRCT | 100 mg | 16 | IIEF; GEQ; event log | I (17%)/II (83%) |
| Morano *et al.*[20] | 2007 | 8/8 | DBRCT | 50 mg | 12 | IIEF | II |
| Deyoung *et al.*[17] | 2012 | 12/12 | DBRCT | 50 mg | 10 | IIEF | II |
| Kirilmaz *et al.*[19] | 2015 | 42/41 | OPEN RCT | 100 mg | 12 | IIEF | II |

DBRCT=Double-blind randomized controlled trial; IIEF=International index Of Erectile Function; GEQ=Global efficacy question; DM=Diabetes mellitus; QOF=Quality of life; RCT=Randomized controlled trials; SIL=Sildenafil

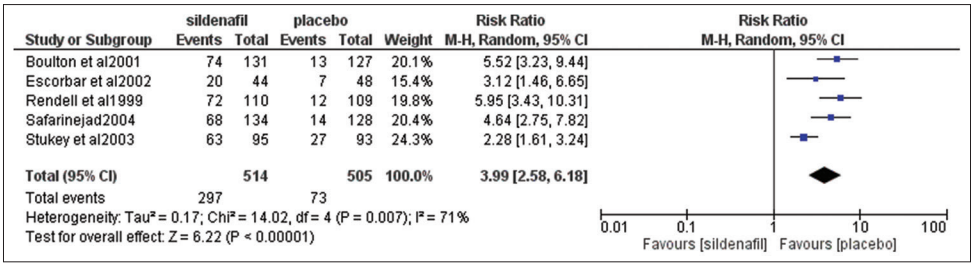


**Figure 1: Forest plot of included studies showing effect of sildenafil on global efficacy question compared to placebo using the random effects model**

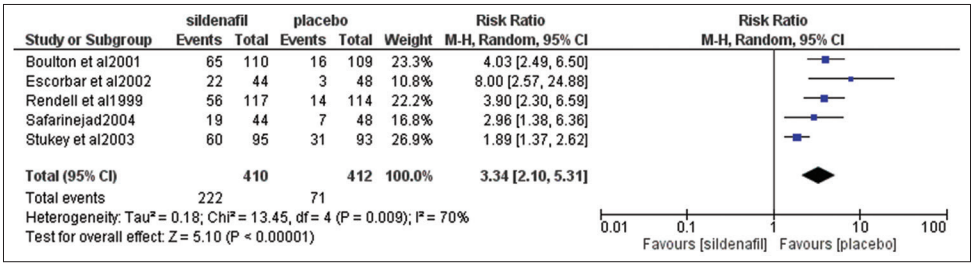


**Figure 2: Forest plot of included studies for proportion of successful attempt in sildenafil-treated group compared to placebo using the random effects model**

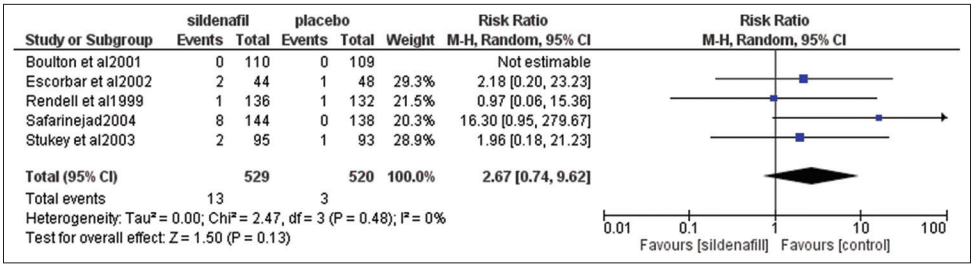


**Figure 3: Forest plot of included studies using the random effects model showing rate of discontinuation due to adverse drug reaction in patients treated with sildenafil in comparison to placebo**

RR of 11.53 (95% CI: 4.24–31.39) and 8.34 (95% CI: 1.93–39.01), respectively.

## DISCUSSION

ED is reported to occur in 50% of men with diabetes worldwide.[23,24] In the Massachusetts Male Aging Study,[3] diabetic men showed a 3-fold probability of having ED when compared to men without diabetes; moreover, the age-adjusted risk of ED had doubled in diabetic men when compared to those without diabetes.[25] The occurrence of ED is 10–15 years earlier in men with diabetes;[3] moreover, diabetes-associated ED is more severe[3] and less responsive to oral drugs,[3,26] leading to reduced quality of life.[3] Advancing age, duration of diabetes, poor glycemic control, hypertension, hyperlipidemia, sedentary lifestyle, smoking, and presence of other diabetic complications have been associated with an increased risk of ED in diabetic patients.[9] Both microvascular and macrovascular diabetic complications also increase the risk of ED in diabetic men.

The use of concomitant medications such as antihypertensive drugs (β-blockers, thiazide diuretics, and spironolactone), psychotropic drugs (antidepressants), and antihyperlipidemic drugs (statins and fibrates) for the comorbidities frequently associated with diabetes, have also been known to have an additive deleterious effect on diabetic ED[27,28].

The present meta-analysis suggests that sildenafil, a PDE5 inhibitor, is effective in the treatment of ED in patients of DM. With an overall response rate of 57.7%, the results of the present study correlate well with that observed by Balhara *et al*.[29] However, the overall percentage of improvement reported in the present study is lower than that reported in the nondiabetic patients with ED, which is reported to be 69%–88%.[22,29-31]

The possible reason for lower efficacy of sildenafil in diabetic patients is thought to be due to the multifactorial nature of the disease. Sildenafil promotes NO-mediated relaxation of vasculature and smooth muscle of corpus cavernosum. However, in patients of ED with DM, there is a reduced production of NO and cGMP in the corpus cavernosum as a result of advanced glycosylation product accumulation.[32] Moreover, there is a poor vascular blood supply to the penile arteries as a result of macrovascular disease, atherosclerotic lesions,[33] and impaired neurogenic and endothelium-dependent relaxation of penile arteries.[34] All of these contribute to the poor responsiveness to sildenafil in diabetes-associated ED.

Moreover, concomitant medications frequently used in diabetic patients, such as antihypertensive agents (β-blockers, thiazide diuretics, and spironolactone), psychotropic drugs (antidepressants), and antihyperlipidemic drugs (statins and fibrates) can contribute to a reduced efficacy of sildenafil.[35]

In the present meta-analysis, headache, dyspepsia, and flushing were the most commonly reported adverse reactions by almost all studies. The development of event rate for the sildenafil-treated group was 4–5 times higher compared to that receiving placebo. However, most of the adverse reactions were mild to moderate in nature with rate of discontinuation due to ADR being 2.4% in sildenafil-treated group compared to 0.57% in placebo-treated group.

The present meta-analysis should be contextualized in the presence of some limitations. Only peer-reviewed published material was included in this review, and unpublished material was not sought. This could have resulted in omission of some of the studies, which might have influenced the outcome data.

Moreover, subgroup analysis of comparative effectiveness with varying severities could not be conducted as many studies did not report sub group efficacy details and focused only on overall outcome data. However, study by Stuckey *et al*.[22] reported that, though improvements in sexual function were seen irrespective of the degree of ED severity, men with mild/moderate ED achieved a higher overall score compared with men with severe ED.

Moreover, in the present meta-analysis, we could not attempt to isolate the subgroups based on comorbidities and concomitant medications, which could have possible influence on the outcome of treatment.

## CONCLUSIONS

The study suggests that sildenafil is effective in patients with DM with ED, but with slightly lower efficacy than in nondiabetic population.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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