Published in final edited form as:

J Sex Med. 2018 June ; 15(6): 866–872. doi:10.1016/j.jsxm.2018.03.089.

Predictors of Erectile Function Normalization in Men With Erectile Dysfunction Treated With Placebo

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Abstract

Background: Clinical study and practice data have shown sildenafil improves sexual function in men with erectile dysfunction (ED). However, some men treated with placebo in double-blind, placebo-controlled sildenafil studies also report improved erectile function as measured by International Index of Erectile Function–Erectile Function Domain (IIEF-EFD) scores.

Aim: This analysis estimated the relationship between postbaseline IIEF-EFD scores and demographic variables, including comorbidities, in men with ED receiving placebo in flexible-dose sildenafil studies.

Methods: Placebo-treated participants in the intent-to-treat population of 42 double-blind, placebo-controlled, flexible-dose, sildenafil studies were included. A participant was classified as a placebo responder if the IIEF-EFD score was ≥ 26 at the last visit.

Outcomes: Variables assessed were age (<45, 45–64, ≥ 65 years), race, body mass index, comorbidities (cardiovascular disease/hypertension, diabetes mellitus, depression), date the last study dose was taken, study completion date, ED etiology (psychogenic, organic, mixed), history of cigarette smoking, ED duration, baseline IIEF-EFD score (≥ 10 , 11–16, ≥ 17), and treatment duration. Stepwise multivariate logistic regression models assessed the odds of being a responder versus a nonresponder for each variable.

Results: A total of 4360 men were included; 13.5% were responders. Odds estimates indicated the largest likelihood of placebo response occurred in men who were black (odds=20.2, $P<0.0001$), were younger than 45 years (odds=7.3, $P<0.0001$), had mild ED (baseline IIEF-EFD ≥ 17 ; odds>100, $P<0.0001$), and did not have diabetes (odds=4.5, $P<0.0001$). The likelihood of a

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Declaration of interest and disclosures

JM was a consultant for Absorption Pharmaceuticals, AMS, Lilly, Meda, Nexmed, Pfizer, and Vivus and has participated in: scientific study/trial for AMS, Pfizer, and Vivus; other for Alliance for Fertility Preservation and Association of Peyronie's Disease Advocates. MC, VS, and L-JT are employees of Pfizer Inc.

All authors participated in the conception and design of the study, the analysis and interpretation of data, and drafting of the article and have provided final approval of the version to be published.

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placebo response decreased as ED duration increased (odds=0.74, $P<0.0001$). The frequency of common adverse events was similar between placebo responders and nonresponders.

Clinical implications: These findings contribute to the improved understanding of predictors of placebo response in sildenafil clinical studies. Elucidation of these factors may contribute to the development of further interventions and treatment strategies and best practices for clinical trials.

Strengths and limitations: Strengths of this analysis include the large and diverse population and the duration of follow-up. Limitations include those associated with retrospective analyses and the inability to ascertain to what extent other demographic factors might have contributed to the placebo responses or how these placebo responses might be related to the natural course of ED.

Conclusion: Certain demographics, comorbidities, and condition characteristics predicted the odds of a placebo response in sildenafil clinical studies of ED. Underlying reasons behind a placebo response warrant further evaluation.

Keywords

erectile dysfunction; sildenafil citrate; placebo effect; men

Introduction

Erectile dysfunction (ED) is a highly prevalent condition that can severely affect quality of life for both the sufferer and his partner [1]. Up to 30% of male adult populations in Western regions are thought to be affected, with older men at higher risk [2–4].

The etiology of ED is multifactorial and can include a combination of organic and psychological factors [1,5]. Individuals with cardiovascular risk factors, including diabetes, hypertension, dyslipidemia, coronary artery disease, and sedentary lifestyle, are at higher risk for ED [2,6,7]. For instance, it is estimated that at least 50% of all men in the United States with diabetes or a history of cardiovascular disease also experience some degree of ED [2]. In men with organic ED, secondary psychological sequelae are common, such as reduced sexual self-esteem and self-confidence [8,9].

Sildenafil (Viagra®; Pfizer Inc; New York, NY) was the first phosphodiesterase type 5 inhibitor approved for on-demand treatment of ED [10] and has been shown to be well tolerated and to improve erectile function in double-blind, placebo-controlled studies [10–14]. A systematic review and quantitative meta-analysis of randomized controlled studies found that men treated with sildenafil had a higher percentage of successful intercourse attempts and improved erections compared with placebo recipients [13].

It is well recognized that some men with ED treated with placebo in double-blind, placebo-controlled sildenafil studies also experience improved sexual function, as measured by improvements in International Index of Erectile Function–Erectile Function Domain (IIEF-EFD) scores [11,12]. The etiology of this placebo response has not been elucidated, and a knowledge gap exists in the contemporary literature regarding predictors of placebo response in these studies.

The aim of this analysis was to examine predictors of placebo response in men in sildenafil clinical studies.

Material and methods

Study inclusion

This retrospective analysis included men who received placebo in the intent-to-treat populations of 42 double-blind, placebo-controlled, flexible-dose, sildenafil studies conducted worldwide over a 12-year period (Table S1). Most studies were at least 12 weeks in length. Protocols were standardized across studies and none of the included studies employed a crossover design. All participants in the included studies provided informed consent for inclusion in the individual study.

Variables

The objective of this analysis was to relate IIEF-EFD response with demographic variables in men treated with placebo in the above studies. Within the total population of the included studies, which utilized the intention-to-treat principle, individuals were classified into normalization (placebo responder; defined as an IIEF-EFD score of ≥ 26 at the last visit) and nonresponder (placebo nonresponder; defined as an IIEF-EFD score of <26 at the last visit) cohorts. The 2 cohorts were compared to determine possible predictors of response. Assessed predictor variables were demographic factors, including age (<45 , 45–64, 65 years), race, body mass index, vascular (cardiovascular disease/hypertension, diabetes) and depression comorbidity profiles, and cigarette smoking status. Predictor variables also included ED characteristics, such as duration of ED, duration of prior ED treatment, investigator-assigned etiology (psychogenic, organic, mixed), baseline IIEF-EFD score (≥ 10 , 11–16, 17), and date last study dose taken (ie, the last dosing date for a patient). It was expected that individuals who participated in studies at later times were likely to have access to more information about ED treatment and were more willing to try to remain in the study. As a result, they might be more likely to become responders. Cumulative reports of adverse events from the included studies were determined according to response cohorts (normalization vs nonresponder).

Statistical methodology

All statistical analyses were conducted using SAS[®] Version 9.4. Descriptive summary statistics for predictive variables were determined by applying the Student *t* test on continuous variables and the chi-square test on binary or categorical variables at the 2-sided 5% level of significance. Stepwise multivariate logistic regression models were employed to assess the odds of being a responder versus a nonresponder to placebo with each variable. The large sample size used in this analysis avoided overfitting of the results in relation to the number of predictors and estimated parameters.

The C statistic, which is the area under the receiver operating characteristic (ROC) curve, was used to evaluate the predictive power of the model, with a higher value indicative of higher power. The sensitivity and specificity of the model were determined to evaluate the power of the model to discriminate between those with and without an IIEF-EFD response

to placebo. In addition, the odds estimates for the minimal clinically important difference (MCID) were determined. The MCID is the smallest difference in the variable of interest that is beneficial to the individual being treated and which would also lead to a change in management in the absence of troublesome treatment side effects or prohibitive cost [15].

Results

Baseline characteristics

The analysis included 4360 men who were treated with placebo in the 42 double-blind, placebo-controlled, flexible-dose, sildenafil studies (Table 1). Of these, 589 (13.5%) participants were included in the normalization (ie, placebo responder) cohort. The mean age in the normalization and nonresponder cohorts was 51.7 and 55.3 years, respectively. The majority of individuals in both cohorts were 45 to 64 years of age and white.

The most common comorbidity in both cohorts was cardiovascular disease/hypertension. A lower proportion of participants in the normalization vs nonresponder cohort had cardiovascular disease/hypertension (37.2% vs 48.4%) and diabetes (20.7% vs 29.9%). The proportions of individuals who had never smoked or were former smokers were 75.0% in the normalization cohort and 73.8% in the nonresponder cohort.

Participants in the normalization cohort had experienced a shorter duration of ED compared with those in the nonresponder cohort (3.3 vs 4.5 years) but had a comparable prior ED treatment duration (72.3 vs 71.6 days). ED etiology was most commonly organic in both the normalization and nonresponder cohorts (40.4% and 48.7%, respectively). Mixed etiology was ascribed to 30.9% and 29.7% of men in the normalization and nonresponder cohorts, respectively, and psychogenic etiology to 20.0% and 14.8%. At baseline, the majority of participants in the normalization cohort had less severe ED compared with the nonresponder cohort (mild, 61.3% vs 25.6%; moderate or severe, 38.5% vs 74.3%).

Testing of multiple logistic regression model

The area under the ROC curve was determined to be >0.90, indicative of the model's high predictive power. In addition, the sensitivity and specificity of the model were determined to be 93.5% and 96.0%, respectively. Thus, the model had high power to discriminate between those with and without an IIEF-EFD response to placebo, with 96% of participants estimated to be correctly classified as placebo responders or nonresponders with the model.

Logistic regression

The verified model was used to determine the odds estimates of a placebo response according to patient and disease demographic variables. The odds estimates indicated that the greatest chance of a placebo response occurred in men who were black (odds=20.2, $P<0.0001$), were younger than 45 years (odds=7.3, $P<0.0001$), had mild to no ED at baseline (odds>100, $P<0.0001$), and did not have diabetes (odds=4.5, $P<0.0001$) at baseline (Table 2).

The odds estimates indicated a significantly increased chance of a placebo response for younger individuals (ie, <45 and 45–64 years) and a significantly decreased likelihood in

those who were older (≥ 65 years; Table 2). In addition, a decreased likelihood of a placebo response was found for participants who were white, Asian, or Hispanic (statistically significant only for participants who were white or Asian). A decreased chance of a placebo response was also determined for participants with diabetes at baseline, although the result was not statistically significant. Participants who did not have comorbid diabetes had a greater likelihood of a placebo response, regardless of age. In addition, the likelihood of a placebo response decreased as duration of ED increased. The chance of a placebo response was notably highest in men with mild ED at baseline (odds >100), with the likelihood of a placebo response decreasing with increasing severity (moderate ED at baseline, odds=2.13; severe ED at baseline, odds <0.01).

The verified model was used in the subgroup of 3387 participants who had moderate to severe ED at baseline (ie, IIEF-EFD <17 at baseline; Table 2). The results of this analysis indicate that the majority of participants with moderate to severe ED at baseline also had a large likelihood of being a nonresponder and, consistent with the analysis in the entire population of participants, shows that those at greatest risk of being placebo responders are those with mild ED at baseline. In addition, the data were assessed with exclusion of the 98 participants with IIEF-EFD scores ≥ 26 at baseline, with the findings remaining consistent with the results in the total population in which participants with mild ED at baseline were most likely to respond to placebo (data not shown).

The verified model was also used to determine the odds estimates of an MCID in placebo response (Table 3) [16]. Consistent with the findings of the overall analysis, the MCID analysis indicated the greatest likelihood of a placebo response was in non-white (odds >100) and younger (ie, <45 years; odds=20.48) men and in those with mild ED at baseline (odds=8.17). In addition, the MCID analysis was assessed in the subgroup of participants with moderate to severe ED at baseline and results were consistent with those for the entire population of participants (Table 3).

Safety

No notable differences were observed in the frequency of the 10 most common adverse events between the normalization and nonresponder cohorts (Table 4). The most common adverse events were headache (4.9% in the normalization cohort, 2.7% in the nonresponder cohort), flushing (1.7%, 1.3%, respectively), and dizziness (0.8%, 0.8%). Most events were mild in both cohorts. The adverse event profile observed in this cumulative analysis is consistent with the known safety profile of sildenafil for the on-demand treatment of ED [17].

Discussion

This retrospective analysis of placebo-controlled, flexible-dose, sildenafil studies in men with ED estimated the contemporary relationship between posttreatment IIEF-EFD and demographic and erectile function variables in participants treated with placebo. Our model indicated that the greatest likelihood of a placebo response occurred in participants who were black, were younger, had mild ED, and did not have diabetes. The likelihood of a

placebo response decreased as the duration of ED increased. The frequency of common adverse events was similar between placebo responders and nonresponders.

The notable placebo responses observed in sildenafil studies in participants with ED are not unexpected because pronounced placebo responses have been reported in some therapeutic areas, particularly those using patient-reported outcome measures in clinical investigations [18,19]. In addition, other studies of ED, including studies of other phosphodiesterase type 5 inhibitors, have also reported a response in participants who did not receive active treatment [20–23].

The greatest predictive variable for a high placebo response in our study was mild ED at baseline, which is consistent with other analyses of predictors of placebo response across medical disciplines [24,25]. Similarly, a higher likelihood of a placebo response was observed in men without baseline diabetes, which is indicative of less severe ED in some populations [26,27] and, hence, may be related to the higher likelihood of a placebo response [24,25].

The prevalence of ED can vary by race, with ED reported more commonly in black than in white men [2,3], although conflicting data have been reported regarding the correlation of race with ED severity [3,28]. Differences in the prevalence and potentially the severity of ED in black men are suggested to be related to socioeconomic, family history, genetics, and physiologic factors [3,29]. In addition, although sildenafil has been found to be effective regardless of race, treatment effects from a pooled data set of double-blind, placebo-controlled, flexible-dose studies were significantly greater for white and Asian men compared with black men [30]. In our analysis, black men had the greatest likelihood of a placebo response compared with other races, although the underlying reasons for this observation are unclear and would require a larger dataset to determine any correlations between this effect and contributing variables.

Our analysis also identified a higher chance of a placebo response in men younger than 45 years compared with older men. Organic causes of ED are generally thought to be less common in younger men, with psychogenic factors often thought to be at least contributory in younger populations [31]. A meta-analysis found inconclusive effects of age on the likelihood of a placebo response, with some studies, which were mostly in psychiatric trials, reporting a higher likelihood of a placebo response in younger patients [24]. The underlying causes for the greater likelihood of a placebo response to sildenafil in younger men are unclear and warrant additional consideration.

Despite placebo being an important component of many controlled clinical trials and for evidence-based medicine [20], the reasons for placebo responses in many clinical contexts, including the magnitude, time course, and factors predictive of response, continue to be elucidated [32]. Placebo responses have been postulated to be associated with psychological factors [20], including enhanced behaviors in the clinical study context that may coincide with the patient's expectations for improvement with treatment, such as perceived treatment assignment and expected therapeutic effects [32–35]. Of note, secondary detrimental psychological effects are common in individuals with ED owing to the erosion of confidence

and self-esteem associated with their condition [8,9]. In addition, organic changes, such as changes in levels of hormones, nitric oxide, endogenous opioids, and brain activity, have been associated with placebo responses [20,35], although they are likely secondary to the positive outcome and not the reason for the placebo response. Design limitations of clinical studies, such as a small number of participants and short duration of follow-up, have also been attributed as contributory causes for observed placebo responses in some studies [19,33].

Elucidation of the factors associated with placebo responses in ED and other conditions may contribute to the development of further interventions and treatment strategies and best practices for clinical trials [32,33]. Attempts have been made to isolate placebo responses from the natural disease course and other factors [36], but this has been difficult to achieve in practice [33].

Our analysis included 42 global clinical studies and a combined population of more than 4000 men with a variety of comorbid conditions. In addition, most studies were of at least 12-week duration. One strength of our analysis was the large and diverse population and the duration of follow-up. The logistic regression model included multiple erectile function baseline and comorbidity factors to sufficiently characterize placebo responders. Furthermore, this analysis differentiated the effect from individual factors. The ED efficacy endpoint chosen for our analysis was the erectile function domain of the IIEF, which has been the primary endpoint of all pivotal clinical studies of sildenafil [37]. The IIEF is a robust and valid measurement of sexual function in ED studies, providing consistent findings, regardless of geographic location, patient type, and underlying comorbidity.

Limitations of our study include those associated with retrospective analyses. In addition, we were unable to ascertain to what extent demographic factors other than those identified in our assessment might have contributed to the placebo responses or how these placebo responses might be related to the natural course of ED. Our data set also did not allow assessment of whether patients who received no treatment would have a response similar to those who received placebo.

Conclusions

Our analysis of 42 double-blind, placebo-controlled, flexible-dose studies determined that certain demographics, comorbidities, and ED characteristics predicted the likelihood of a placebo response in sildenafil clinical studies. The underlying reasons behind the placebo response with ED therapies warrant further evaluation. Of note, although response to placebo is not equivalent to response to no treatment, this extensive analysis overall demonstrates that sildenafil treatment has significantly greater effect than placebo. Clinicians should therefore initiate sildenafil treatment without concern about a placebo effect.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Editorial/medical writing support was provided by Janet E. Matsuura, PhD, and Jill E. Kolesar, PhD, of Complete Healthcare Communications, LLC (West Chester, PA), and was funded by Pfizer Inc.

Funding sources

This work was funded by Pfizer Inc.

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Table 1.

Demographic and erectile dysfunction characteristics of study population *

	Normalization cohort [†] (n=589)	Nonresponder cohort [‡] (n=3771)
Demographic characteristics		
Mean (SD) age, y	51.7 (11.3)	55.3 (11.0)
Age group, n (%)		
<45 y	157 (26.7)	626 (16.6)
45–64 y	360 (61.1)	2325 (61.7)
65	72 (12.2)	820 (21.7)
Race, n (%)		
White	295 (50.1)	2142 (56.8)
Black	70 (11.9)	280 (7.4)
Asian	56 (9.5)	570 (15.1)
Hispanic	35 (5.9)	241 (6.4)
Other	77 (13.1)	227 (6.0)
Mean (SD) BMI, kg/m ²	27.9 (4.8)	27.8 (4.8)
Comorbidities, n (%)		
CVD/HTN	219 (37.2)	1825 (48.4)
Depression	76 (12.9)	457 (12.1)
Diabetes	122 (20.7)	1127 (29.9)
Smoking status, n (%)		
Never smoked	252 (42.8)	1282 (34.0)
Current smoker	143 (24.3)	908 (24.1)
Former smoker	190 (32.3)	1502 (39.8)
ED characteristics		
Mean (SD) ED duration, y	3.3 (3.7)	4.5 (4.5)
Mean (SD) ED treatment duration, d	72.3 (23.9)	71.6 (25.7)
ED etiology, n (%)		
Organic	238 (40.4)	1836 (48.7)
Mixed	182 (30.9)	1121 (29.7)
Psychogenic	118 (20.0)	557 (14.8)
IIEF-EFD, n (%)		
17, mild to no ED	361 (61.3)	967 (25.6)
11–16, moderate	139 (23.6)	1113 (29.5)
10, severe	88 (14.9)	1690 (44.8)

BMI=body mass index; CVD=cardiovascular disease; ED=erectile dysfunction; HTN=hypertension; IIEF-EFD=International Index of Erectile Function–Erectile Function Domain.

* Only participants with an IIEF-EFD score at the last study visit are included.

[†] Normalization cohort included participants with a placebo response, defined as an IIEF-EFD score ≥26 at the last study visit.

[‡] Nonresponder cohort included participants without a placebo response, defined as an IIEF-EFD score <26 at the last study visit.

Table 2.

Odds estimates

	All Subjects			Subjects with IIEF-EFD <17 at Baseline		
	Odds	95% CI	P value	Odds	95% CI	P value
Age group						
<45 y	7.27	4.73–11.17	<0.0001	0.96	0.54–1.68	0.872
45–64 y	2.72	2.08–3.57	<0.0001	<0.10	<0.10	<0.0001
65 y	0.41	0.27–0.60	0.0041	<0.10	<0.10	<0.0001
Race						
White	0.15	0.11–0.20	<0.0001	<0.10	<0.10	<0.0001
Black	20.18	11.06–36.83	<0.0001	1.38	0.67–2.84	0.386
Asian	0.07	0.05–0.12	<0.0001	<0.10	<0.10	<0.0001
Hispanic	0.79	0.46–1.34	0.3763	<0.10	<0.10	<0.0001
Other	>100	>100	<0.0001	14.80	5.87–37.32	<0.0001
Diabetes						
No	4.45	3.38–5.87	<0.0001	0.07	0.04–0.12	<0.0001
Yes	0.90	0.63–1.28	0.5590	<0.10	<0.10	<0.0001
ED duration	0.74	0.70–0.77	<0.0001	0.58	0.53–0.65	<0.0001
ED treatment duration	1.08	1.07–1.09	<0.0001	1.08	1.07–1.09	<0.0001
IIEF-EFD						
17, mild to no ED	>100	>100	<0.0001	NA	NA	NA
11–16, moderate	2.13	1.55–2.92	<0.0001	0.27	0.17–0.44	<0.0001
10, severe	<0.01	<0.01–0.01	<0.0001	<0.10	<0.10	<0.0001
Date last study dose taken	1.00	1.00–1.00	<0.0001	1.01	1.00–1.01	<0.0001

ED=erectile dysfunction; IIEF-EFD=International Index of Erectile Function–Erectile Function Domain; NA=not applicable.

Table 3.

Odds estimates for MCID analysis

	All Subjects			Subjects with IIEF-EFD <17 at Baseline		
	Odds	95% CI	P value	Odds	95% CI	P value
Age group						
<45 y	20.48	12.75–32.87	<0.001	0.65	0.38–1.11	0.116
45–64 y	0.78	0.62–0.98	0.0325	<0.10	<0.10	<0.0001
65 y	<0.10	0.05–0.12	<0.0001	<0.10	<0.10	<0.0001
Race						
White	<0.01	<0.01–0.01	<0.0001	<0.10	<0.10	<0.0001
Non-white	>100	>100	<0.0001	41.37	24.73–69.20	<0.0001
ED duration	0.53	0.50–0.57	<0.0001	0.49	0.45–0.54	<0.0001
ED treatment duration	1.20	1.18–1.22	<0.0001	1.16	1.13–1.18	<0.0001
IIEF-EFD						
17, mild to no ED	8.17	5.48–12.18	<0.0001	NA	NA	NA
11–16, moderate	1.24	0.91–1.68	0.1735	0.07	0.04–0.12	<0.0001
10, severe	0.13	0.09–0.18	<0.0001	<0.10	<0.10	<0.0001
Date last study dose taken	1.01	1.01–1.01	<0.0001	1.01	1.01–1.01	<0.0001
Overall satisfaction	0.75	0.68–0.82	<0.0001	0.66	0.58–0.74	<0.0001

Cutoff values for a MCID response were 2, 5, and 7 for mild, moderate, and severe ED, respectively, as described previously [16].

ED=erectile dysfunction; IIEF-EFD=International Index of Erectile Function–Erectile Function Domain; MCID=minimal clinically important difference; NA=not applicable.

Table 4.

Most common adverse events*

Event, n (%)	Normalization cohort [†] (n=589)	Nonresponder cohort [‡] (n=3771)
Headache	29 (4.9)	101 (2.7)
Flushing	10 (1.7)	48 (1.3)
Dizziness	5 (0.8)	30 (0.8)
Feeling hot	4 (0.7)	6 (0.2)
Back pain	3 (0.5)	8 (0.2)
Dry mouth	3 (0.5)	10 (0.3)
Dyspepsia	2 (0.3)	11 (0.3)
Nasal congestion	1 (0.2)	10 (0.3)
Vision blurred	1 (0.2)	8 (0.2)
Nausea	0	8 (0.2)

IIEF-EFD=International Index of Erectile Function–Erectile Function Domain.

* Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.

[†] Normalization cohort included participants with a placebo response, defined as an IIEF-EFD score ≥26 at the last study visit.[‡] Nonresponder cohort included participants without a placebo response, defined as an IIEF-EFD score <26 at the last study visit.