The Role of Initial Success Rates and Other Factors in Determining Reliability of Outcomes of Phosphodiesterase Inhibitor Therapy for Erectile Dysfunction: A Pooled Analysis of 17 Placebo-Controlled Trials of Tadalafil for Use as Needed

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ABSTRACT

Introduction. Reliability of successful outcomes in men with erectile dysfunction (ED) on phosphodiesterase type 5 inhibitors is an important aspect of patient management.

Aims. We examined reliability of successful outcomes in a large integrated dataset of randomized tadalafil trials.

Main Outcome Measures. Success rates, time to success, subsequent success after first success, and probability of success were analyzed based on Sexual Encounter Profile questions 2 and 3.

Methods. Data from 3,254 ED patients treated with tadalafil 10 mg (N = 510), 20 mg (N = 1,772), or placebo (N = 972) were pooled from 17 placebo-controlled studies.

Results. Tadalafil patients had significantly higher first-attempt success rates vs. placebo. This effect was consistent across most subgroups; however, patients with severe ED experienced a greater response to tadalafil than patients with mild–moderate ED. Approximately 80% of patients achieved successful penile insertion within two attempts with either tadalafil dose and successful intercourse within eight attempts for tadalafil 10 mg and four attempts for tadalafil 20 mg. However, approximately 70% of tadalafil-treated patients achieved successful intercourse even by the second attempt. Subsequent success rates were higher for patients with first-attempt success (81.5% for 10 mg and 86.1% for 20 mg vs. 66.2% for placebo, $P < 0.001$) vs. patients with later initial success (53.2% for 10 mg and 56.4% for 20 mg vs. 39.9% for placebo, $P < 0.001$). Among patients treated with tadalafil, intercourse success rates at early attempts were similar to rates at later attempts (i.e., attempts 5 and 10 vs. 25), although insertion success rates were significantly lower earlier in treatment.

Conclusions. The findings affirm the reliability of successful outcomes with tadalafil treatment and that first-attempt success is a critical factor affecting subsequent outcomes. The results further show that even among men who did not succeed on first attempt, a substantial proportion will have successful outcomes if treatment is maintained. **Sontag A, Rosen RC, Litman HJ, Ni X, and Araujo AB. The role of initial success rates and other factors in determining reliability of outcomes of phosphodiesterase inhibitor therapy for erectile dysfunction: A pooled analysis of 17 placebo-controlled trials of tadalafil for use as needed. J Sex Med 2013;10:541–550.**

Key Words. Erectile Dysfunction; Phosphodiesterase Type 5 Inhibitors; PDE5; Tadalafil; Reliability of Efficacy; Pooled Analysis

Introduction

Erectile dysfunction (ED) is a widespread health problem estimated to affect approximately 300 million men worldwide by 2025 [1]. Phosphodiesterase type 5 (PDE5) inhibitors are safe and effective treatments and are recommended as a first line of therapy for treatment of ED [2]. Yet, despite the broad efficacy and safety of these agents, discontinuation of PDE5 inhibitor treatment is relatively high [3]. One reason postulated for the discontinuation of PDE5 therapy in

some patients is related to a lack of early success, which may affect patient satisfaction, and in turn, affect treatment continuation [3,4].

With this potential relationship in mind, it is important for clinicians to have in-depth knowledge of both initial success and subsequent reliability of success with PDE5 inhibitors in men with a broad spectrum of ED. In particular, it is important to understand the extent to which early success and reliability of success may be a predictor of long-term continuation with treatment and thus ultimate treatment efficacy. As PDE5 inhibitor effectiveness could be influenced by comorbid health issues [5,6], concomitant medications [7], patient demographics, and ED clinical characteristics [8,9], and these factors can be expected to affect treatment outcomes [10,11], the potential differences in treatment effectiveness among these subgroups need further exploration. Thus, the rates of initial treatment success, maintenance of success with continued treatment, and the potential influence of patient characteristics on overall treatment effectiveness are important elements for clinicians to understand as they evaluate therapies and counsel patients on appropriate expectations with their ED treatment.

Aims

Previous studies have evaluated first-attempt success rates for PDE5 inhibitor treatments as well as reliability of success over time [10–13]. Among the patient characteristics identified in these studies that contributed to both short-term and long-term success rates were ED severity, age, and comorbid illness [10–13]. The current analysis expands upon previous research regarding success rates and reliability of success with PDE5 inhibitors by utilizing a large, placebo-controlled clinical trial database of tadalafil. In addition to confirming previous research using a larger cohort of patients selected from multiple clinical trials, novel statistical analyses of reliability of success are presented.

Methods

Studies and Patients

Data from 17 parallel, double-blind, placebo-controlled trials of 10 and 20 mg tadalafil were pooled for this analysis (N = 3,345). The studies were conducted by Eli Lilly and Company between 1999 and 2004 in North America, South America, Europe, Asia, and Australia. Studies were similar in design, duration, and inclusion and exclusion criteria, including the requirement that subjects were to make at least four attempts at sexual intercourse during a 4-week treatment-free run-in period. Subjects were randomly allocated to treatment with as-needed tadalafil (doses ranging from 2.5 to 20 mg; only the patients treated with 10 or 20 mg were included in this analysis) or placebo. The double-blind treatment period was 12 weeks for 16 studies and 20 weeks for one study; the cutoff for this analysis was the 12th week of treatment.

Patients were men ≥18 years of age with a history of mild-to-severe ED of organic, psychogenic, or mixed etiology for at least 3 months prior to randomization. Patients were required to have a stable female partner and were excluded from the studies if they failed to achieve an erection following radical prostatectomy or pelvic surgery. Patients were also excluded if they had clinically significant penile deformities or penile implants, a recent history of stroke or spinal cord trauma, cardiovascular diseases (including unstable angina, recent myocardial infarction, recent myocardial revascularization, or poorly controlled blood pressure), or clinically significant renal or hepatic insufficiency. The majority of the studies (14 of 17) also excluded men who, in the opinion of the investigator, did not respond to previous use of other PDE5 inhibitors.

Main Outcome Measures

All studies utilized the Sexual Encounter Profile (SEP) diary, an immediate recall instrument that subjects used to document the outcome of each sexual attempt made during the course of the study [14]. Successful insertion was defined as a "yes" response to SEP question 2 (SEP2) "were you able to insert your penis into your partner's vagina"; successful intercourse was defined as a "yes" response to SEP question 3 (SEP3) "did your erection last long enough to have successful intercourse."

"First attempt" was defined as the first attempt at sexual intercourse following the first dose after randomization. "First-attempt success" for insertion and intercourse was defined as a "yes" response on SEP2 and SEP3 on the first attempt. "Initial success" was defined as the first "yes" response to SEP2 or SEP3, regardless of number of attempts prior to that success. "Reliability of success" was evaluated in two ways: (i) as the overall subsequent success rate after an initial