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Simplified Interpretation of the Erectile Function Domain of the International Index of Erectile Function

Joseph C. Cappelleri, PhD, MPH, MS,[1] Li-Jung Tseng, PhD,[2] Xuemei Luo, PhD,[1] Vera Stecher, PhD,[2] and Tom F. Lue, MD[3]

ABSTRACT

Introduction: This report describes a post hoc analysis of data from a randomized, double-blinded, placebo-controlled, flexible-dose, sildenafil trial in men with erectile dysfunction.

Aims: To simplify interpretation of erectile function (EF) domain scores of the International Index of Erectile Function (IIEF).

Methods: Men at least 18 years old with erectile dysfunction were randomized to receive sildenafil or placebo for 12 weeks. Men taking nitrates or nitric oxide donors were excluded. Responses for each IIEF EF domain question (questions 1−5 and 15) were combined into two broad categories ("success" for responses of the two most favorable categories of a question and "no success" for other responses). Each question was expressed in a logistic regression model (sildenafil and placebo groups combined) as a function of overall EF domain score.

Main Outcome Measures: IIEF EF domain score and items.

Results: A four-point increase in the IIEF EF domain score was associated with an odds ratio of success of 6.1 for getting an erection, 29.2 for having a firm erection, 10.0 for able to penetrate,12.8 for maintaining erection, 4.0 for maintaining erection to completion, and 3.7 for erection confidence. An EF domain score of 22 was associated with a probability of success of 81% for getting an erection, 86% for having a firm erection, 89% for able to penetrate, 67% for maintaining an erection, 70% for maintaining an erection to completion, and 32% for erection confidence. For an EF domain score of 16, the corresponding probabilities of success were 22%, 4%, 20%, 4%, 22%, and 6%, respectively.

Conclusion: These results provide stakeholders with a simplified and meaningful interpretation of IIEF EF domain scores based on six key aspects of EF.

Key Words: Erectile Dysfunction; Sildenafil; Patient-Reported Outcomes; International Index of Erectile Function; Score Interpretation; Questionnaires

INTRODUCTION

Patient-reported outcomes (PROs), defined as any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the response by anyone else, are commonly used to assess various signs and symptoms of health conditions and diseases.[1] A PRO is assessed by patient self-report with responses to a questionnaire or by an interview with the interviewer recording only the patient's response. Given its subjective nature, a PRO measurement must be qualitatively and psychometrically evaluated to confirm its reliability, validity, and ability to detect differences in scores over time in individuals or groups who have changed with respect to the concept of interest that the PRO is intended to measure.[1] In addition, a PRO measurement should aim to provide easy-to-interpret scores or results that make sense to clinicians and their patients and to researchers, health care regulators, and policymakers.[2,3]

The International Index of Erectile Function (IIEF) is a 15-item, 5-domain, psychometrically validated, PRO questionnaire[4] that is widely used for the assessment of male sexual function in clinical trials and clinical practice.[5] The six-item erectile function (EF) domain of the IIEF is a sensitive and specific measurement of treatment-related changes in EF.[4,5] The

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[1]Pfizer Inc, Groton, CT, USA;

[2]Pfizer Inc, New York, NY, USA;

[3]University of California−San Francisco, San Francisco, CA, USA

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EF domain score has been validated as a diagnostic tool that distinguishes between men with and men without erectile dysfunction (ED) with its five ED severity classifications (ie, no ED = EF domain score 26−30; mild ED = score 22−25; mild-to-moderate ED = score 17−21; moderate ED = score 11−16; severe ED = score 6−10 or 1−10 if men are included whose condition is so severe that they did not attempt sexual activity or intercourse).[6] The minimal clinically important difference, the smallest difference in a score that patients perceive as beneficial, for the IIEF EF domain score is four points.[7]

Conveying IIEF EF domain scores in terms of their actual quantitative scores (range = 1−30) remains the primary approach for assessing EF, with ED severity categories based on IIEF EF domain scores providing additional supplementation.[6] To further simplify the interpretation of IIEF EF domain scores (beyond quantitative scores and ED severity categories) for enhanced understanding by patients, clinicians, researchers, regulators, and policymakers, we conducted a post hoc analysis of data from a randomized, double-blinded, placebo-controlled, flexible-dose, sildenafil trial. This analysis is not intended as a substitute for EF domain scores or their associated ED severity categories; rather, the aim is to enhance the meaning on what a given score on the EF domain represents in terms of the likelihood of getting an erection, having a firm erection, being able to penetrate, maintaining an erection, maintaining an erection to completion, and having erection confidence.

METHODS

Patients

This post hoc analysis was based on data from a randomized, double-blinded, placebo-controlled, flexible-dose, sildenafil trial,[8] in which men were randomized to receive sildenafil or placebo for 12 weeks. The starting sildenafil dose was 50 mg, taken approximately 1 hour before sexual activity but not more than once daily. At weeks 2, 4, and 8, the dose could be adjusted to 100 or 25 mg based on efficacy and tolerability. Key inclusion criteria included (i) age at least 18 years, (ii) documented clinical diagnosis of ED that was confirmed with a five-item Sexual Health Inventory for Men (also known as IIEF-5)[9] score no higher than 21, (iii) a self-esteem subscale score no higher than 75 from the Self-Esteem And Relationship (SEAR) questionnaire,[10,11] and (iv) being in a stable sexual relationship with a female or male partner. Exclusion criteria included men who had previously taken more than six doses of sildenafil, men who were taking nitrate therapy or nitric oxide donors, and men with significant cardiovascular disease, recent stroke or myocardial infarction, or blood pressure higher than 170/110 mm Hg.

The trial included in the analysis was conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki. The trial protocol was approved by local institutional review boards. All subjects provided written informed consent before enrollment.

Methods

Post hoc analyses included all men with ED who were randomized to treatment, took the study drug (placebo or sildenafil), and had baseline and at least one post-baseline IIEF data. Efficacy variables were assessed at baseline and the end of treatment (week 12 or termination using the last-observation-carried-forward method). In the present analysis, the efficacy variables of interest were the IIEF EF domain (score range = 1−30; recall period = 4 weeks; Table 1) and its six constituent individual questions (Q1 = getting erection; Q2 = having firm erection; Q3 = able to penetrate; Q4 = maintaining erection; Q5 = maintaining erection until completion; Q15 = erection confidence).[4] The multiple response options for each question of the IIEF EF domain (six response options for Q1−Q5; five response options for Q15) were combined into two broad categories ("success" and "no success"), with success defined as being in one of the two most favorable responses of "almost always or always" and "most times" for Q1 to Q4; "not difficult" and "slightly difficult" for Q5; and "very high" and "high" for Q15. Therefore, "success" means being able to perform the activity (Q1−Q5) or achieving erection confidence (Q15). This definition of "success" is agnostic to treatment (as it should be), because the IIEF EF domain is a PRO measurement, which is defined as any report on the status of a patient's health condition that comes directly from the patient, without interpretation of the response by anyone else, including what treatment a patient receives.[1]

Various approaches have been used to aid in the interpretation of PRO scores, including anchor-based approaches, distribution-based approaches, and mediation analysis.[3] The present analysis applied a specific type of anchor-based approach, referred to as a content-based interpretation, which uses a question (item) in the multi-item domain of interest as an anchor that is easier to understand than the multi-item domain itself and sufficiently related to it.[3,12] A binary logistic regression was adopted, with the binary item anchor (success or no success) as the dependent variable expressed as a function of IIEF EF domain scores to augment the interpretation of the scores of the IIEF EF domain based on its constituent questions.

Each IIEF EF domain question was expressed as a function of the sum (overall) score of the six-item EF domain in a logistic regression model[13] (with the sildenafil and placebo groups combined). For each question of the IIEF EF domain, the estimated odds ratios and 95% CIs are reported for one-, three-, four-, and five-point increases in the overall IIEF EF domain score.

In addition, the probability of success for each IIEF EF domain question was calculated and plotted according to IIEF EF domain score. For each question, the assumption of linearity in the logit of success (ie, the natural logarithm of the probability of "success" to the probability of "no success") on the IIEF EF domain score as the continuous predictor was examined descriptively by the following steps: (i) creating a categorical variable (EDCAT) based on the following IIEF EF domain scores: 1 to 5, 6 to 10, 11 to 15, 16 to 20, 21 to 25, and 26 to