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Minimal Clinically Important Differences in the Erectile Function Domain of the International Index of Erectile Function Scale

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Abstract

Background: Despite widespread adoption of the six-item erectile function (EF) domain of the International Index of Erectile Function (IIEF) as a clinical trial end point, there are currently no objective data on what constitutes a minimal clinically important difference (MCID) in the EF domain.
Objective: Estimate the MCID for the IIEF EF domain.
Design, setting, and participants: Anchor-based MCIDs were estimated using data from 17 randomized, double-blind, placebo-controlled, parallel-group clinical trials of the phosphodiesterase type 5 inhibitor (PDE5-I) tadalafil for 3345 patients treated for 12 wk.
Measurements: The anchor for the MCID is the minimal improvement measure calculated using change from baseline to 12 wk on IIEF question 7: "Over the past 4 weeks, when you attempted sexual intercourse how often was it satisfactory for you?" MCIDs were developed using analysis of variance (ANOVA)– and receiver operating characteristic (ROC)–based methods in a subset of studies ($n = 11$) by comparing patients with and without minimal improvement ($n = 863$). MCIDs were validated in the remaining six studies ($n = 377$).
Results and limitations: The ROC-based MCID for the EF domain was 4, with estimated sensitivity and specificity of 0.74 and 0.73, respectively. MCIDs varied significantly ($p < 0.0001$) according to baseline ED severity (mild: 2; moderate: 5; severe: 7). MCIDs consistently distinguished between patients in the validation sample classified as no change or minimally improved overall and by geographic region, ED etiology, and age group. MCIDs did not differ by age group, geographic region, or ED etiology. Current analyses were based on 17 clinical trials of tadalafil. Results need to be replicated in studies using other PDE5-Is or in nonpharmacologic intervention studies.
Conclusions: The contextualization of treatment-related changes in terms of clinically relevant improvement is essential to understanding treatment efficacy, to interpreting results across studies, and to managing patients effectively. This analysis provides, for the first time, anchor-based estimates of MCIDs in the EF domain score of the IIEF.

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1. Introduction

Self-report measures, often referred to as *patient-reported outcomes* (PROs) [1], are widely used in sexual medicine research [2,3]. Among PRO measures used in assessing sexual function, none is more widely used currently than the International Index of Erectile Function (IIEF) [4]. The IIEF was recommended by the International Consultation on Sexual Medicine in 2004 and 2010 as the gold standard self-report questionnaire for measuring erectile function (EF) in clinical trials and observational studies and has been accepted and recommended by regulatory agencies

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worldwide for approval of erectile dysfunction (ED) therapies. A recent PubMed search indicated >1400 citations of the IIEF since its development in 1996. Recently, an abbreviated version of the IIEF [5] has been adopted as a screening tool for clinicians. Multiple validation studies and systematic reviews of the IIEF have been published supporting its use in both clinical and research settings [3,6,7].

The EF domain of the IIEF [4] is the primary measurement domain of the IIEF and is a commonly used primary end point in clinical trials of ED. The psychometric properties of the EF domain have been extensively reported [3–7], but surprisingly, there are no studies in the literature of the minimal amount of change needed in the EF domain to be clinically meaningful to patients. This is commonly referred to as the *minimal clinically important difference* (MCID), which has been defined as the smallest difference in a score in the domain of interest that patients perceive as beneficial and that would mandate, in the absence of side effects and excessive cost, a change in the patient's management [8]. Identifying a clinically meaningful change in the EF domain of the IIEF is critical to understanding efficacy, to interpreting study results, and to managing patients.

The primary objective of this analysis was to estimate the MCID for the EF domain of the IIEF using anchor-based methods (favored by regulatory agencies [1] and clinical investigators) in 17 randomized, double-blind, placebo-controlled, parallel-group clinical trials with virtually identical designs that assessed the efficacy of the phosphodiesterase type 5 inhibitor (PDE5-I), tadalafil for use in men with ED.

2. Methods

2.1. Study design

An integrated post hoc analysis was performed according to a prespecified statistical analysis plan on data collected from 17 randomized, double-blind, placebo-controlled, parallel-group clinical trials with identical designs that were conducted at 148 centers in North and South America, Europe, Asia, and Australia from 1999 to 2004. Details about the general study design, efficacy and safety measures, and statistical analyses have been published in previous integrated analyses of 5 [9] and 11 [10,11] tadalafil trials.

Briefly, following a screening visit, patients who made at least four attempts at sexual intercourse during a 4-wk treatment-free run-in period were randomly allocated to 12 wk of treatment with placebo (n = 1002) or on-demand tadalafil at fixed doses of 10 mg (n = 527) or 20 mg (n = 1816). Patients were seen at 4-wk intervals until they completed the study or discontinued early for any reason. All 17 studies included IIEF, Sexual Encounter Profile (SEP), and Global Assessment Question (GAQ) as efficacy measures.

Studies were approved by institutional review boards, and each patient gave written informed consent. Studies were conducted in accordance with the Declaration of Helsinki and guidelines for Good Clinical Practice.

2.2. Study population

Men aged >18 yr who had a minimum 3-mo history of mild to severe ED of organic, psychogenic, or mixed etiology (as determined by the investigator) with a steady female partner were eligible to participate in these studies. Patients were excluded if they failed to achieve erection following radical prostatectomy or pelvic surgery, had clinically significant penile deformities or penile implants, had clinically significant renal or hepatic insufficiency, or had a recent history of spinal cord trauma. Patients were also excluded from trials if they had an underlying cardiovascular disorder sufficiently severe or unstable to make sexual intercourse unadvisable (eg, unstable angina, recent myocardial infarction or stroke, recent myocardial revascularization, poorly controlled blood pressure). Men treated with nitrates, antiandrogens, or cancer chemotherapy also were excluded from study.

2.3. Outcomes

The IIEF is a self-administered questionnaire that assesses five domains of male sexual function, including EF, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. The IIEF was administered at baseline and following treatment. Values on the EF domain were set to missing if more than one of the individual items was missing; if the answer to one item was missing, then the average of the remaining items was imputed. Lower EF domain scores indicate more severe ED.

For the purposes of determining the MCID of the EF domain, the change from baseline to week 12 of the EF domain score was used in calculations and models. In the event that the patient discontinued the study prior to week 12 or the week 12 assessment is otherwise missing, the last observed postbaseline value was analyzed.

2.4. Anchor

The clinical anchor is the minimal improvement measure calculated using IIEF question 7 (Q7): "*Over the past 4 weeks*, when you attempted sexual intercourse how often was it satisfactory for *you*?" The following responses are possible: 0, "Did not attempt intercourse"; 1, "Almost never or never"; 2, "A few times (much less than half the time)"; 3, "Sometimes (about half the time)"; 4, "Most times (much more than half the time)"; and 5, "Almost always or always." This item was selected as relevant to the US National Institutes of Health (NIH) definition of ED involving ability to have satisfactory intercourse [12] and its prior use in the development and validation of severity cut points on the EF domain [13]. Minimal improvement in the anchor from baseline to week 12 was defined as a change from little or no satisfactory intercourse at baseline (either 1, "almost never," or 2, "a few times") to satisfactory intercourse sometimes (3, "sometimes"). No change at week 12 was defined as a rating of 1 or 2 at baseline, followed by a similar rating of 1 or 2 at week 12 (see Fig. 1). This measure is later referred to as the *Q7 measure of minimal improvement* (Q7MMI). Patients whose baseline response was 0, "Did not attempt intercourse," were not included in these analyses. Patients with a week 12 score >3 were excluded because these patients would have experienced more than a minimal improvement in intercourse satisfaction.

2.5. Development and validation data sets

Patients were selected for this analysis if, based on the IIEF Q7 responses, they had little or no satisfactory intercourse at baseline (either 1, "almost never," or 2, "a few times") and no more than satisfactory intercourse sometimes at week 12 (3, "sometimes"), regardless of treatment group assignment. A total of 1240 of the 3345 patients in the 17-study data set qualified according to these criteria. Only 93 (2.8%) of the patients in the 17-study data set had missing data for Q7 at either baseline or week 12.

The database of 17 studies was divided into two main groups: the development data set, in which the MCID would be derived, and the validation data set, in which the estimates of the MCID would be evaluated for external validity, convergent validity, and consistency. The development data set was based on 11 of 17 randomly selected studies.

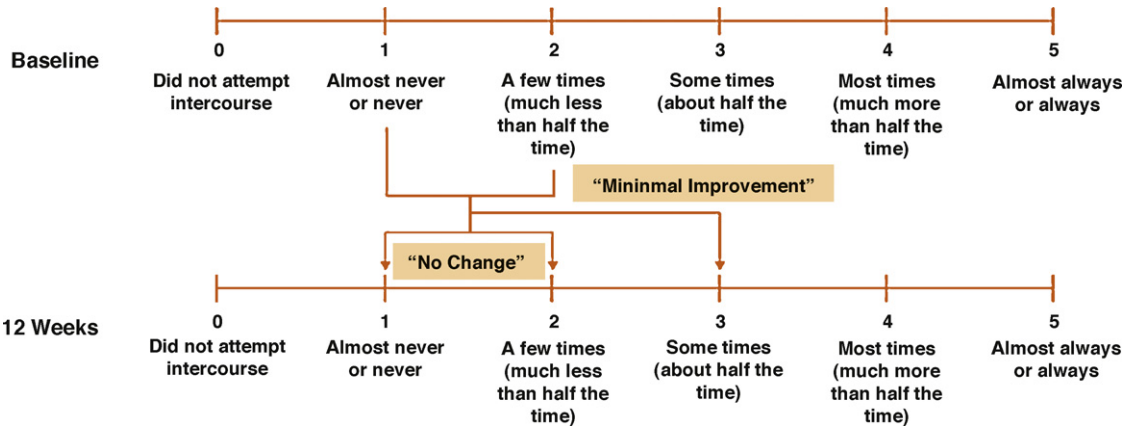

Fig. 1 – The clinical anchor or the measure of minimal improvement in question 7 of the International Index of Erectile Function: "Over the past 4 weeks, when you attempted sexual intercourse how often was it satisfactory for you?".

Of the 1240 patients in the analysis, the development and validation data sets included 863 patients (70%) and 377 patients (30%), respectively.

2.6. *Statistical analyses*

The clinical anchor for developing the MCID was the Q7MMI. The association between minimal important changes in the anchor (independent variable) and change in EF domain score (dependent variable) was assessed preliminarily by two-sample *t* test of the mean EF domain scores among patients with and without minimal important changes in the anchor (later referred to as the analysis of variance [ANOVA] approach) [8,14,15] and analysis of covariance (ANCOVA) models (adjusted for baseline EF domain score [16]), from which MCIDs were estimated. Receiver operating characteristic (ROC) analyses [15,17] were also used to estimate MCIDs, whereby the Q7MMI was regressed on a dichotomized version of the EF domain score, using logistic regression. The MCID was defined as the cut-off value for which the sum of sensitivity and specificity is maximized or, alternatively stated, where the most patients are correctly classified by the cut-off of the IIEF EF domain as having improved versus not having improved.

Convergent validity of the MCID was examined by showing that groups identified by the MCID were consistent with responses in the active treatment and placebo groups. The MCID would show convergent validity if the MCID cut-off discriminated between responses in the placebo versus active treatment groups. A figure displaying box plots of the change from baseline of the EF domain for each treatment group is presented, with reference lines for 0 (no change) and for the IIEF Q7-derived MCIDs using the ANOVA and ROC approaches.

The validation sample was used to replicate and confirm MCID values derived in the development sample. Subpopulations were defined according to (1) geographic region (North America, South America, Europe, Asia, and Australia); (2) age group (<50, 50–64, >65); etiology of ED (organic, psychogenic, mixed); (3) ED duration (3 to <6 mo, 6 mo to <1 yr, ≥1 yr); and (4) ED severity at baseline, defined as severe for EF scores 0–10, moderate for EF scores 11–16, and mild or mild to moderate for EF scores 17–25. Box plots of the change in IIEF EF domain among patients with and without minimal improvement were reviewed for each of the subpopulations.

3. Results

The MCIDs were estimated using the development sample, which was composed of 11 studies from Asia, North America, Europe, South America, and Australia. MCIDs were validated using the validation sample, composed of six studies from Asia, North America, Europe, and Africa. These samples were predicted to be similar but showed statistically significant differences in a few variables at baseline, although the samples were generally similar as middle-aged men, all with ED. Patients in the development sample had lower body mass index, consumed less alcohol, and were more likely to have psychogenic ED (Table 1). Importantly, there was no difference in baseline scores of the IIEF EF domain between the development and validation samples and no difference in the change from baseline to week 12 EF outcome measure. The EF domain values were slightly higher in the validation sample compared with the development sample among patients who had minimal improvement in the Q7MMI (8.1 vs 7.3).

We performed a preliminary assessment of the association between the Q7MMI and EF domain change using the ANOVA approach. When the model was not controlled for baseline EF domain score (ie, disease severity), the MCID was 7.3 (Table 2); however, the test of the interaction between the baseline EF score (ED severity) and the Q7MMI was significant ($p < 0.001$). MCIDs were highest among patients with more severe ED at baseline (12.4) and lowest among patients with mild ED at baseline (2.8). In the middle range, the mean change was 7.2.

Using the ROC-based approach, the calculated MCID was 4 (Table 2). The MCID using the ROC-based approach was also calculated among patients in each baseline ED severity level (p interaction <0.001); MCIDs were 2, 5, and 7 for patients with mild, moderate, and severe baseline ED, respectively. In a similar analysis evaluating the effect of age group on the choice of MCID, we did not find MCID differences across age groups using either the ANOVA or the ROC approach (p interaction ≥0.64).

The ROC-based MCID showed consistently high sensitivity and specificity in the development and validation samples. The sensitivity and specificity for the ROC-based MCID were 0.74 and 0.73 in the development sample and were similar at 0.78 and 0.69 in the validation sample (Table 2).

Table 1 – Demographic and background characteristics by study sample

	Development (n = 863)	Validation (n = 377)	p value
Therapy, n (%)			0.065
20 mg tadalafil	312 (36.2)	157 (41.6)	
10 mg tadalafil	139 (16.1)	67 (17.8)	
Placebo	412 (47.7)	153 (40.6)	
Age, mean (SD)	55.84 (11.5)	55.68 (11.4)	0.819
Age, median (IQR)	56.86 (16.4)	56.47 (15.8)	
Age, n (%)			0.590
<50	255 (29.6)	126 (33.4)	
50–64	402 (46.6)	168 (44.6)	
65–74	180 (20.9)	73 (19.4)	
≥75	26 (3.0)	10 (2.7)	
BMI, n (%)			<0.0001
<30	740 (85.8)	258 (68.4)	
≥30	123 (14.3)	119 (31.6)	
Smoking status, n (%)			0.302
No	623 (72.4)	283 (75.3)	
Yes	237 (27.6)	93 (24.7)	
Alcohol consumption, n (%)			<0.0001
No	448 (52.1)	138 (36.7)	
Yes	412 (47.9)	238 (63.3)	
Depression, n (%)			0.085
No	842 (97.6)	361 (95.7)	
Yes	21 (2.4)	16 (4.2)	
ED duration, mo, n (%)			0.576
3–6	17 (2.0)	11 (2.9)	
6 to <12	58 (6.7)	24 (6.4)	
≥12	788 (91.3)	342 (90.7)	
ED etiology, n (%)			0.015
Organic	453 (52.5)	216 (57.3)	
Psychogenic	124 (14.4)	32 (8.5)	
Mixed	286 (33.1)	129 (34.2)	
ED severity (three levels), n (%)			0.117
Mild	194 (22.5)	79 (21.0)	
Moderate	260 (30.1)	136 (36.1)	
Severe	409 (47.4)	162 (43.0)	
Baseline EF score, mean (SD)	12.04 (5.38)	12.16 (4.93)	0.393

BMI = body mass index; ED = erectile dysfunction; EF = erectile function; IQR = interquartile range; SD = standard deviation.
Note: The development and the validation samples are compared using two-sample t tests for continuous measures and the chi-square test for categorical measures.

Figure 2 indicates consistent between-group discrimination using either the ANOVA-based method (MCID: 7) or the ROC-based method (MCID: 4). The ROC-based MCID of 4 discriminates well between mean change in EF scores of the placebo group and the active groups in the development sample.

Both methods produced similar results across geographic regions (Fig. 3), ED etiology groups (Fig. 4), and age groups (Fig. 5). The mean improvement in each of the subgroup comparisons was generally consistent with both methods.

4. Discussion

Despite widespread use of the IIEF in clinical research and practice, no published data are available concerning MCID of the EF domain. In this study, we estimated anchor-based

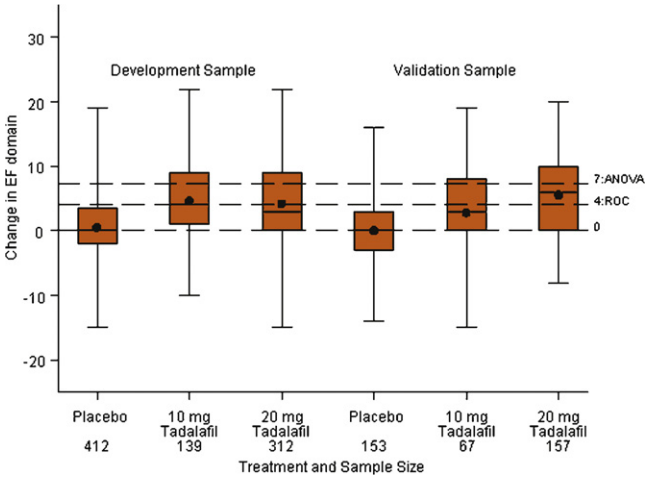

Fig. 2 – Distribution of the change in erectile function domain by treatment group in the development and validation samples. ANOVA = analysis of variance; EF = erectile function; MCID = minimal clinically important difference; ROC = receiver operating characteristic.

MCIDs based on a combination of methods. After showing a statistically significant association between EF domain scores and our selected clinical anchor (ie, IIEF Q7) by means of ANOVA, we then identified optimal cut points for MCID using a traditional ROC approach. Notably, estimated MCIDs varied according to baseline ED severity, with MCIDs increasing in magnitude with increasing ED severity. Regardless of the analytic method used to estimate the MCID, estimates generated from the development samples were generally replicable and were confirmed in the validation samples. Additionally, across geographic regions, ED etiology, and age groups, we found consistent support for the ROC-based MCID in the EF domain.

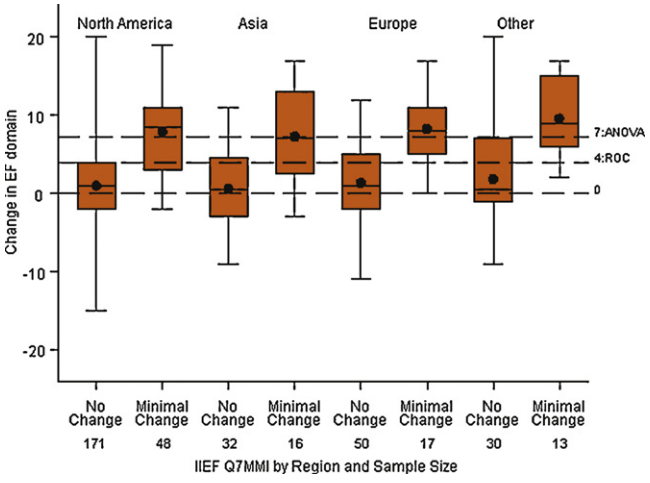

Fig. 3 – Distribution of the change in erectile function domain by question 7 measure of minimal improvement and region: validation sample. ANOVA = analysis of variance; EF = erectile function; IIEF = International Index of Erectile Function; MCID = minimal clinically important difference; Q7MMI = question 7 measure of minimal improvement; ROC = receiver operating characteristic.

Table 2 – Minimal clinically important differences of the change in International Index of Erectile Function erectile function domain

	Development sample (n = 863)				Validation sample (n = 377)			
	Mean (SD)	Minimum	Median	Maximum	Mean (SD)	Minimum	Median	Maximum
Change from baseline to week 12 IIEF EF domain								
No change in Q7MMI (n = 679)	1.27 (5.46)	−15	0	22	1.12 (5.72)	−15	1	20
Minimal improvement in Q7MMI (n = 184)	7.27 (5.93)	−7	7	22	8.13 (5.24)	−3	8	19
	MCID (95% CI)	p value	Sensitivity	Specificity		Sensitivity	Specificity	
ANOVA-based MCID [1]	7.27 (6.46–8.07)	<0.001	–	–	–	–	–	
ED severity level interaction [2]		<0.001	–	–	–	–	–	
Mild	2.79 (1.53–4.05)				3.45			
Moderate	7.21 (6.00–8.42)				8.11			
Severe	12.38 (11.04–13.72)				11.96			
ROC-based MCID [3]	4	<0.001	0.74	0.73	–	0.78	0.69	
ROC-based MCID by ED severity level [3]								
Mild	2	<0.001	0.65	0.70	–	0.68	0.77	
Moderate	5	<0.001	0.79	0.77	–	0.76	0.71	
Severe	7	<0.001	0.91	0.81	–	0.81	0.77	

ANOVA = analysis of variance; ED = erectile dysfunction; EF = erectile function; IIEF = International Index of Erectile Function; MCID = minimal clinically important difference; Q7MMI = question 7 measure of minimal improvement; ROC = receiver operating characteristic; SD = standard deviation.
[1] The p value tests the significance of the effect of the IIEF Q7MMI in predicting the change from baseline to week 12 of the IIEF EF domain. Change in EF = 1.3 + 6.0 × Q7MMI.
[2] The p value tests the interaction of the ED severity level by Q7MMI in predicting the change from baseline to week 12 of the IIEF EF domain of the analysis of covariance model.
[3] The p value tests the significance of the association between the IIEF Q7MMI and the dichotomy of the EF domain and was calculated using logistic regression.

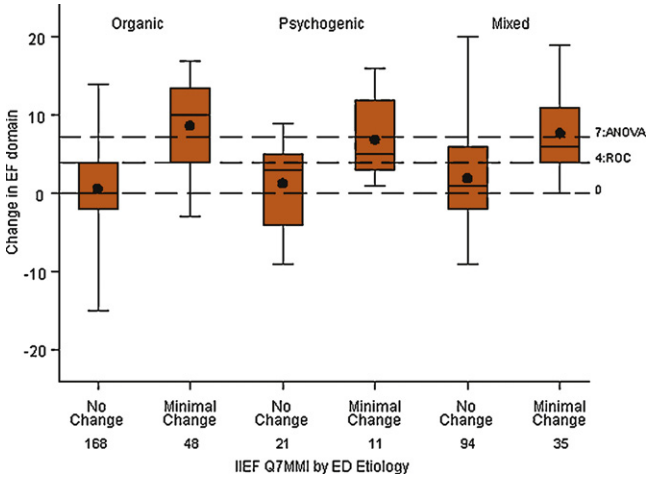

Fig. 4 – Distribution of the change in erectile function domain by question 7 measure of minimal improvement and etiology of erectile dysfunction: validation sample.
ANOVA = analysis of variance; ED = erectile dysfunction; EF = erectile function; IIEF = International Index of Erectile Function; MCID = minimal clinically important difference; Q7MMI = question 7 measure of minimal improvement; ROC = receiver operating characteristic.

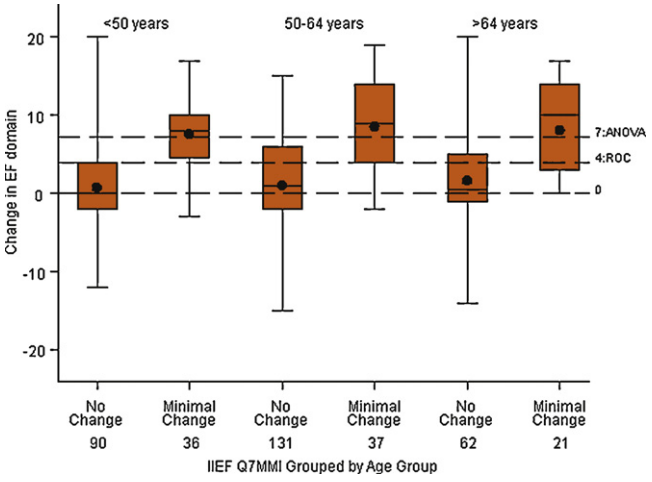

Fig. 5 – Distribution of the change in erectile function domain by question 7 measure of minimal improvement and age group: validation sample.
ANOVA = analysis of variance; EF = erectile function; MCID = minimal clinically important difference; Q7MMI = question 7 measure of minimal improvement; ROC = receiver operating characteristic.

4.1. Variation in minimal clinically important differences according to baseline erectile dysfunction severity

Estimated MCIDs of the IIEF EF domain varied according to baseline ED severity, with MCIDs increasing in size with increasing baseline ED severity. Depending on the proposed use of the MCID estimate, clinicians or researchers would be advised based on these findings to consider setting an expected change for a given individual patient based on baseline severity of ED. If the patient has a baseline EF score in the severe dysfunction range (6–10), for example, he would need to increase his EF score almost twice as much to achieve a noticeable improvement in satisfactory intercourse attempts compared with a man in the moderate ED range. Conversely, patients with mild ED (EF score: 22–25) would need to show only a 2–3 point change in EF domain score to

meet or exceed the MCID. Published reports in the literature have similarly shown greater relative improvements in patients with lower initial values in EF domain scores [9,18,19]. In contrast, no differences in MCID were observed across age groups, etiology, or geographic regions.

4.2. Variation in minimal clinically important differences according to analysis method

Not surprisingly, results differed somewhat across statistical methods used. The ANOVA-based approach is more conservative in estimating the MCID using the mean change in the EF domain for all patients who showed improvement. In contrast, the ROC-based approach is used to identify an MCID that provides optimal classification of responders and nonresponders regardless of treatment condition. Accordingly, using the ROC approach, 73% of patients were correctly classified as having improved, whereas the ANOVA approach resulted in only 47% of the patients being correctly classified as having improved. In keeping with regulatory guidelines that suggest a responder criterion be developed, we chose to emphasize the ROC-based approach as offering evidence-based cut points for classifying ED patients in clinical trials as responders or nonresponders [1].

4.3. Replication

We observed that regardless of the analytic method used to estimate the MCID, estimates generated from the development samples were generally replicable in the validation samples. The large sample size and multiple clinical trials included were major strengths of the current study and allowed cross-sample replication of the main findings.

4.4. Consistency of estimated minimal clinically important differences across subpopulations

Another strength of this analysis is the diversity of the patient base with regard to geographic region, ED etiology and duration, and age. MCIDs performed equally well across a broad range of geographic regions, ED etiology, and, importantly, age group.

4.5. Limitations

Data for the current analyses were based solely on 17 studies of tadalafil (10 mg, 20 mg) and placebo in men enrolled in ED clinical trials. These results need to be replicated in studies using other PDE5-Is or in nonpharmacologic intervention studies (eg, weight loss) [20]. All patients were heterosexual and engaged in regular sexual activity with a partner as an inclusion criterion in the studies, and this profile limits generalizability. Additional studies are also needed in special medical or surgical populations, such as men with ED secondary to radical prostatectomy, spinal cord injury, pelvic trauma, or Peyronie's disease. There were insufficient numbers of patients with these conditions in our integrated analyses for adequate replication.

Another potential limitation is our selection of the clinical anchor for our analyses (ie, IIEF Q7). Anchor-based approaches to defining MCIDs should ideally use patient ratings of change administered at different periods of time or on exit from a clinical trial [1]. This anchor was selected as the best of the available options. Of the items available in the integrated data set, Q7 of the IIEF represented the clinical intent and spirit of MCID analyses by allowing us to select an item that could quantify the minimally important difference and that was directly relevant to the NIH definition of ED (ie, inability to perform satisfactory intercourse) [12]. Other items were less optimal. GAQ, which required patients to rate the overall success of treatment, was administered in all randomized clinical trials with tadalafil; however, this item was asked in a simple "yes/no" (binary) response format in each case, limiting its utility as a sensitive anchor or index of minimal improvement. The SEP measure has a similar binary rating of intercourse success and is rated on every intercourse event rather than for the overall treatment period. For these and other reasons, we selected IIEF Q7, which we noted has been used previously as an anchor item in the development and validation of severity cut points on the EF domain of the IIEF [3,13].

5. Conclusions

This analysis considered the estimation of MCIDs using anchor-based approaches for an end point (the EF domain of the IIEF) that is commonly used in ED efficacy trials. The anchoring of changes in the scoring of the EF domain of the IIEF in clinically meaningful terms is critical to understanding efficacy, to interpreting study results, and to managing patients. This analysis provides, for the first time, anchor-based estimates of MCIDs in IIEF. Based on these results, responder rates can be calculated more accurately and used as study end points in terms of normalization of function, as traditionally defined (ie, EF score >25) [4], or as the percent of subjects who achieve MCID, correcting for baseline severity of ED. This evidence-based end point is recommended for future studies of ED.

***Author contributions*:** Raymond C. Rosen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Rosen, Allen, Ni, Araujo.
Acquisition of data: Rosen, Allen, Ni, Araujo.
Analysis and interpretation of data: Rosen, Allen, Ni, Araujo.
Drafting of the manuscript: Rosen, Allen, Araujo.
Critical revision of the manuscript for important intellectual content: Rosen, Allen, Ni, Araujo.
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