

The International Index of Erectile Function (IIEF): a state-of-the-science review

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The International Index of Erectile Function (IIEF) is a widely used, multi-dimensional self-report instrument for the evaluation of male sexual function. It is has been recommended as a primary endpoint for clinical trials of erectile dysfunction (ED) and for diagnostic evaluation of ED severity. The IIEF was developed in conjunction with the clinical trial program for sildenafil, and has since been adopted as the 'gold standard' measure for efficacy assessment in clinical trials of ED. It has been linguistically validated in 32 languages and used as a primary endpoint in more than 50 clinical trials. This review summarizes early stages in the psychometric validation of the instrument, its subsequent adoption in randomized clinical trials with sildenafil and other ED therapies, and its use in classifying ED severity and prevalence. The IIEF meets psychometric criteria for test reliability and validity, has a high degree of sensitivity and specificity, and correlates well with other measures of treatment outcome. It has demonstrated consistent and robust treatment responsiveness in studies in USA, Europe and Asia, as well as in a wide range of etiological subgroups. Although only one direct comparator trial has been performed to date, the IIEF is also sensitive to therapeutic effects with treatment agents other than sildenafil. A severity classification for ED has recently been developed, in addition to a brief screening version of the instrument. This review includes the strengths as well as limitations of the IIEF, along with some potential areas for future research.

International Journal of Impotence Research (2002) 14, 226–244. doi:10.1038/sj.ijir.3900857

Keywords: erectile dysfunction; sexual dysfunction; psychometric validation; diagnostic classification; self-report questionnaire

Introduction

The advent of effective oral therapies for erectile dysfunction (ED) has led to significant changes not only in the clinical management of this disorder, but also in the design and conduct of clinical trials. Whereas laboratory-based studies had previously relied on objective or physiological recording techniques, such as penile plethysmography or doppler ultrasonography,^{1–5} these methods are not suitable for use in evaluating efficacy of an oral erectogenic agent, such as sildenafil. Given the mechanism of action of PDE-5 inhibitors, particularly the need for adequate sexual stimulation,^{6–8} it is apparent that less obtrusive, patient-based methods of assessment are required.

Early in the development of sildenafil, Pfizer recognized the need for better efficacy instruments

for erectile and sexual dysfunction. After developing an initial version of the questionnaire that was successfully used in early Phase II trials, the company elicited the help of an international panel of experts to further refine and validate the questionnaire. Accordingly, the International Index of Erectile Function (IIEF) was developed and validated in 1996–1997 as an adjunct to the sildenafil clinical trial program.^{9–11}

The IIEF was designed for availability in multiple languages and cultures, and was intended to meet the needs of regulatory agencies worldwide. Since then, it has been adopted as the 'gold standard' treatment outcome measure for clinical trials in ED, regardless of the type of treatment intervention or study population under investigation. In 1999, the IIEF was recommended by the 1st International Consultation on Erectile Dysfunction,¹² sponsored by the World Health Organization, as the efficacy endpoint of choice for clinical trials in ED.

By any measure, the IIEF has had a significant impact on the field of ED. Since its introduction in 1997, more than 50 clinical trials have been conducted using this instrument with a broad range of treatment agents and study populations.

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Received 5 January 2002; accepted 16 January 2002

Conversely, few clinical trials have been performed since the approval of sildenafil in which the IIEF was not used as a primary efficacy endpoint. The instrument is widely accepted by both the regulatory agencies and scientific journals as a valid and reliable measure of sexual functioning in men. It has been linguistically validated and is currently available in 32 languages world-wide.

Considering the broad adoption and extent of use of the instrument, this review was undertaken to provide a comprehensive assessment of the stages in development and to update readers on the current use of the IIEF in clinical trials of ED. In particular, we considered the reliability or robustness of the measure when used in different geographic populations or etiologic sub-groups, and with different treatment agents or study designs. Our major focus was on randomized clinical trials, although uncontrolled and diagnostic studies were also considered. Search strategies included a review of all Index Medicus and PsychInfo citations between January 1997 and August 2001. Major strengths and limitations of the instrument are considered, along with potential areas of future research.

Stages of development

Item generation and scoring algorithm

The development and validation of the IIEF has been reported elsewhere^{9–11,13} and will be briefly summarized here. Initial items were generated through a review of the literature and in-depth interviews with male patients and their partners. A panel of international experts reviewed the initial item pool and made suggestions for change. Following pilot-testing, a final scale of 15 items was developed and linguistically validated initially in 10 languages. Based upon a principal components analysis and additional expert review, the 15 items were divided into five domains of sexual function: erectile function (six items), orgasmic function (two items), sexual desire (two items), intercourse satisfaction (three items), and overall satisfaction (two items). A scoring key for each of the sexual function domains was developed and validated. Two of the items (Questions 3 and 4) from the erectile function (EF) domain were specifically designed to assess key components of ED—that is, ability to achieve penetration (Question 3) and ability to maintain erection (Question 4) sufficient for satisfactory sexual performance, as defined by the 1993 NIH Consensus Conference on Erectile Dysfunction.¹⁴ These two items were subsequently employed as primary endpoints in the early clinical trials of sildenafil.

Instrument validation

A number of validation tests were performed in three separate studies before the IIEF was adopted for use in clinical trials.^{9,10} These included standard psychometric tests of reliability, validity, and sensitivity (treatment responsiveness). Two aspects of scale reliability—internal consistency and test–retest—were separately examined for the five domains and for the total scale. A high degree of internal consistency (Cronbach's alpha, range=0.73–0.99) and test–retest reliability (r , range=0.64–0.84) across domains was demonstrated in these studies. Discriminant validity was evaluated by comparing the responses of clinically documented ED patients before their treatment intervention with age-matched controls who received no treatment. In that investigation, clear and significant differences ($P < 0.005$) were observed in four of the five domains. Convergent validity was shown by comparison of patient IIEF scores with independent, blinded clinician ratings of sexual function. Finally, divergent validity was demonstrated by comparison of IIEF scores with other scale scores of marital adjustment and social desirability, which measure different constructs.

Tests of responsiveness included sensitivity and specificity analyses of the IIEF to the effects of treatment. Treatment responders were defined as showing global improvements in erectile function after 12 weeks of treatment with sildenafil. A high degree of sensitivity was demonstrated, as treatment responders showed significant changes ($P < 0.0001$) across all five domains. Conversely, no significant changes were observed in any of the IIEF domains in treatment non-responders, showing strong specificity of the IIEF. Hence the instrument was both highly sensitive and specific to the effects of treatment in male patients with ED. Collectively, the validation studies demonstrated strong evidence of the overall validity and reliability of the IIEF.

The IIEF as an efficacy measure in ED trials

The IIEF was developed primarily for use as an efficacy measure in clinical trials of ED. In evaluating its efficacy and utility in this regard, and in attending to the objectives of this paper, we considered the number and range of clinical trials in which the instrument has been used, the relative consistency and reliability of results across trials, and the relationship between results obtained with the IIEF and other measures of outcome. Because the instrument was developed in conjunction with the sildenafil trial program, we began with published studies of sildenafil in which the IIEF was used as a primary efficacy endpoint (see Table 1). Studies in

Table 1 Randomized, placebo-controlled trials with sildenafil

Author	Subjects	Design	IIEF endpoints				Other endpoints	Comments
			Q3	Q4	EF	EF		
Goldstein I, <i>et al</i> ¹⁵ (Study A)	USA; Mixed etiology (n = 532)	Parallel group Fixed-dose (25, 50, 100 mg)	Baseline: Placebo: Sildenafil: (100 mg)	2.0 2.2 4.0	1.5 2.1 3.9	— — —	Event log, GEQ IS,OF,SD,OS Domains	First large-scale clinical trials of sildenafil in the USA Q3 and Q4 used as primary endpoints in both studies. Highly significant treatment effects and strong correlations with other study endpoints
Goldstein I, <i>et al</i> ¹⁵ (Study B)	USA; Mixed etiology (n = 329)	Parallel group Flexible dose (25–100 mg)	Baseline: Placebo: Sildenafil:	2.0 2.3 3.9	1.5 1.8 3.6	11.0 13.0 21.0	Event log, GEQ IS,OF,SD,OS Domains	
Montorsi F, <i>et al</i> ¹⁶	European; Mixed etiology (n = 514)	Parallel group Fixed-dose (25.50,100 mg)	Baseline: Placebo: Sildenafil: (100 mg)	2.1 2.1 3.8	1.9 2.0 3.7	12.5 12.6 22.5	Event Log, GEQ, IS,OF,SD,OS Domains Partner questionnaire	First large-scale European trial of sildenafil. Fixed dose study with similar baseline and post-treatment IIEF scores to USA study. Highly significant treatment effects and strong correlations with other study endpoints again observed
Meuleman E, <i>et al</i> ¹⁷	European; Mixed etiology (n = 315)	Parallel group Flexible-dose (25–100 mg)	Baseline: Placebo: Sildenafil:	1.9 2.2 3.7	1.6 2.1 3.6	11.1 13.3 21.9	Event log, GEQ, Partner questionnaire	Large-scale flexible dose European study with sildenafil. Highly similar baseline and post-treatment scores to USA study (Goldstein <i>et al</i>) ¹⁵ above. Highly significant treatment effects and strong correlations with other study endpoints
Tan HM, <i>et al</i> ¹⁸	Asian; Mixed etiology (n = 254)	Parallel group Flexible-dose (25–100 mg)	Baseline: Placebo: Sildenafil:	2.3 2.6 4.2	1.9 2.4 4.2	13.3 15.5 25.1	Event logs, GEQ IS,OF,SD,OS Domains	First large-scale flexible-dose Asian trial of sildenafil. Highly significant treatment effects and slightly higher post-treatment scores for both sildenafil and placebo than in USA and European studies. Similar pattern of responses observed in other study outcomes
Chen KK, <i>et al</i> ¹⁹	Asian; Mixed etiology (n = 236)	Parallel group Flexible-dose (25–100 mg)	Baseline: Placebo: Sildenafil:	2.3 3.0 4.2	2.0 2.9 4.1	13.5 18.1 24.3	Event log, GEQ IS, OF, SD, OS Domains	Large-scale, flexible dose Taiwanese trial of sildenafil. Similar results to Tan <i>et al</i> . Again, slightly higher post-treatment scores for both sildenafil and placebo than in US and European studies. Same pattern of responses in other study outcomes
Dinsmore W, <i>et al</i> ²⁰	UK; Mixed etiology (n = 111)	Parallel group Flexible-dose (25–100 mg)	Baseline: Placebo: Sildenafil:	1.7 1.7 3.6	1.6 1.6 3.7	10.4 10.1 21.8	Event logs, GEQ IS, OF, SD, OS Domains	Comparison of post-treatment scores in sildenafil-treated patients with non-ED controls. Results show near-normalization of IIEF scores following sildenafil treatment across all IIEF domains

Table 1 (continued)

Rendell MS, <i>et al</i> ²¹	USA; Diabetes (<i>n</i> = 268)	Parallel group Flexible-dose (25–100 mg)	Baseline: Placebo: 1.8 Sildenafil: 3.2	1.5 1.6 2.9	10.6 10.0 18.2	GEQ	Flexible-dose study of sildenafil in diabetics. Highly significant treatment effects, but lower baseline and post-treatment IIEF scores compared to mixed etiology studies above
Giuliano F <i>et al</i> ²²	European; Spinal cord injured (<i>n</i> = 178)	Crossover Flexible-dose (25–100 mg)	Baseline: Placebo: 2.0 Sildenafil: 3.8	1.5 1.7 3.6	— — —	Event logs, GEQ IS, OF, SD, OS Domains	Flexible-dose study of sildenafil in patients with spinal cord injury. Baseline IIEF scores similar to diabetics, but higher post-treatment scores on Q3 and Q4. Highly significant treatment effects
Conti CR, <i>et al</i> ²³	USA; Ischemic heart disease (<i>n</i> = 357)	Parallel group Flexible-dose (5–200 mg)	Baseline: Placebo: 2.0 Sildenafil: 3.3	1.6 1.8 3.2	9.9 10.9 19.7	IS, OF, SD, OS Domains	Combined analysis of IIEF scores from 9, double-blind, randomized studies with ischemic heart disease patients. Highly significant treatment effects, but slightly lower post-treatment scores compared to non-ischemic patients
Olsson AM, Perrson ²⁴	Swedish; ED w/CVD (<i>n</i> = 224)	Parallel group Flexible-dose (25–100 mg)	Baseline: Placebo: 2.2 Sildenafil: 3.7	1.5 1.9 3.3	— — —	IS, OF, SD, OS Domains GEQ	Swedish study of men with mixed CVD on various medications. Highly significant treatment effects on Q3 and Q4, and strong correlations with other study outcome
Seidman SN, <i>et al</i> ²⁵	USA; Depression (<i>n</i> = 152)	Parallel group Flexible-dose (25–100 mg)	Baseline: Placebo: 2.2 Sildenafil: 3.7	1.4 2.0 3.9	9.3 12.4 23.4	HRSQ, CGA, BDI, LSC, GEQ IS, OF, SD, OS Domains	Flexible-dose study of sildenafil in patients with ED and depression. Highly significant treatment effects and post-treatment scores on all IIEF measures. Strong correlations with other study outcomes, including quality of life measures

Baseline (Q3, Q4, EF) = mean baseline response for both groups combined
Placebo (Q3, Q4, EF) = mean post-treatment response for placebo
Sildenafil (Q3, Q4, EF) = mean post-treatment response for sildenafil
Abbreviations: GEQ = Global Efficacy Question; IIEF = International Index of Erectile Functioning; EF = erectile function; IS = intercourse satisfaction; OF = orgasmic function; SD = sexual desire; OS = overall satisfaction; HRSQ = Hamilton Rating Scale for Depression; SCL = spinal cord injured; MOS = medical outcomes study; SF-12 = functional status inventory; PGWBI = psychological well being index; CGA = clinical global assessment; LSC = life satisfaction checklist; BDI = Beck Depression Index.

the USA were compared with those conducted in Europe and Asia (see Figure 1). In this section, we also considered results obtained with selected patient populations, including men with diabetes, heart disease, spinal cord injury, and depression. After reviewing results of clinical trials with sildenafil, we then reported on use of the IIEF in studies with other treatment agents or interventions for ED, as well as in observational and diagnostic studies.

Randomized trials of sildenafil in the USA, Europe and Asia

USA trials

Questions 3 and 4 of the IIEF were used as primary endpoints in the first two large-scale clinical trials of sildenafil in the USA (see Table 1).¹⁵ One of these studies consisted of a double-blind, placebo-controlled, fixed dose trial of 532 men with ED. Patients were randomly assigned to receive placebo, 25, 50, or 100 mg of sildenafil for 24 weeks. The IIEF and event log data were analyzed at 0, 12 and 24 weeks of treatment. Event logs in this and subsequent studies required subjects to report each instance of attempted sexual activity, including the presence or absence of satisfactory erections, and the ability to achieve intercourse. In the second study, 329 men with ED were randomly assigned to receive either double-blind placebo or flexible-dose treatment with sildenafil (25–100 mg) for 12 weeks. Scores on the IIEF and event logs were compared at 0 (baseline) and 12 weeks of treatment. Patients for both studies were aged 20–87 and had ED of mixed organic and psychogenic etiologies.

As shown in Table 1, mean scores on Q3 (ability to achieve penetration) and Q4 (ability to maintain penetration) in the two studies¹⁵ increased from 2.0 (Q3) and 1.5 (Q4) at baseline to 4.0 (Q3) and 3.9 (Q4) at 100 mg in the fixed-dose study, and from 2.0 (Q3) and 1.5 (Q4) at baseline to 3.9 (Q3) and 3.6 (Q4) in the flexible-dose study. Corresponding scores for placebo were 2.2 and 2.1 in the fixed dose study, and 2.3 and 1.8 in the flexible dose study. These differences were all highly significant ($P < 0.001$). Mean scores on the EF domain approximately doubled from 11.0 at baseline to 21.0 for patients taking sildenafil in the flexible-dose study, compared with a treatment score of 13.0 for patients on placebo ($P < 0.001$). Other domains of sexual function and event log data showed a similar pattern of results in both studies: 56, 77 and 84% of men who took 25, 50 and 100 mg of sildenafil, respectively, reported improved erections in the fixed-dose study, while 74% of men reported improved erections in the flexible-dose study. Corresponding placebo rates

were 25% in the fixed dose study and 19% in the flexible-dose study.

European trials

Responses to Q3 and Q4 were similarly used as primary endpoints in the first two, large-scale randomized trials of sildenafil in European men with ED.^{16,17} The first study¹⁶ was conducted in six countries (Denmark, Ireland, Italy, Norway, Sweden, UK). In this study, 514 patients with ED of mixed etiologies were randomly assigned to 12 weeks of treatment with placebo or with a fixed dose of 25, 50 or 100 mg of sildenafil. Mean scores at baseline for both groups combined were 2.1 for Q3 and 1.9 for Q4. After 12 weeks of treatment, mean scores on Q3 and Q4 increased respectively to 3.8 and 3.7 in the 100 mg sildenafil group, compared with 2.1 and 2.0 for placebo. All treatment differences were highly significant ($P < 0.0001$). Similar conclusions were observed for the EF domain scores, event logs, and global assessments of treatment efficacy.

In the second study,¹⁷ conducted in five European countries (Belgium, France, Germany, Netherlands, UK), 315 patients with ED of mixed etiologies were randomly assigned to flexible-dose sildenafil or placebo for 26 weeks. Mean scores of 1.9 for Q3 and 1.6 for Q4 at baseline increased, respectively, to 3.7 and 3.6 following 26 weeks of treatment with sildenafil (vs corresponding scores of 2.2 and 2.1 with placebo). Scores on the EF domain increased from 11.1 at baseline (average for both groups) to 21.9 with sildenafil and 13.3 with placebo ($P < 0.0001$). Again, the pattern of responses observed in the IIEF measures was closely matched by other outcome measures, such as event log and global efficacy ratings.

Asian trials

Consistent results on the IIEF were supported further by results of two randomized controlled trials of sildenafil in Asian men. In the first study by Tan *et al*,¹⁸ 254 ED patients of mixed etiology from three Asian countries (Malaysia, Singapore, the Philippines) were randomly assigned to receive either 12 weeks of flexible-dose treatment with sildenafil or double-blind placebo. Mean scores for Q3 and Q4 at baseline were 2.3 and 1.9, respectively. Each of the Q3 and Q4 scores improved significantly following treatment to a mean of 4.2, and significantly less with placebo (Q3, 2.6; Q4, 2.4). For the EF domain, mean scores improved from 13.3 at baseline to 25.1 with sildenafil treatment, compared to 15.5 with placebo. All treatment differences were

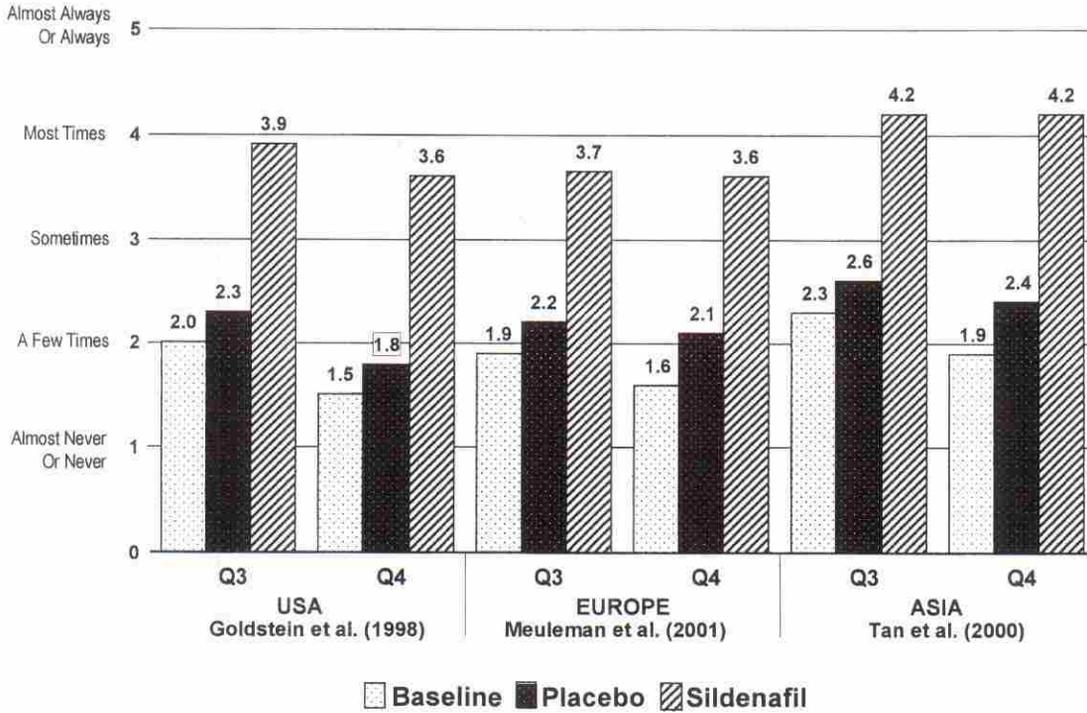


Figure 1 Mean IIEF scores (Q3, Q4) in USA, European and Asian sildenafil trials.

highly significant ($P < 0.001$). Improvements in other domains of sexual function were observed, and treatment changes were corroborated by event log and global efficacy assessments, as in the above studies.

More recently, Chen *et al.*¹⁹ have reported the results of ASSESS-3, a randomized double-blind flexible-dose study of sildenafil in 236 Taiwanese men with ED of mixed etiology. As in previous studies, the primary endpoints were Q3, Q4, and the EF domain. Mean baseline scores for Q3 and Q4 were 2.3 and 2.0, respectively, and 13.5 for the EF domain score. These baseline scores were very similar to the baseline scores observed in the Tan *et al* study.¹⁸ At 3 months of treatment with flexible-dose sildenafil or placebo, mean scores for Q3 and Q4 increased, respectively, to 4.2 and 4.1 for sildenafil vs 3.0 and 2.9 for placebo. The EF domain scores increased to 24.3 for sildenafil and 18.1 for placebo following treatment. Similar improvements were noted in other efficacy endpoints (patient event logs, global efficacy ratings) and the other domains of the IIEF. Similar scores were manifested between this study and the previous Asian study, again demonstrating the reliability and robustness of the measure across studies in different countries and cultures. Event log and global assessment scores in the Asian studies, like the European and US studies, reflected the overall pattern of results obtained with the IIEF.

Comparison of studies

In addition to showing the robust effects of sildenafil treatment across study designs and dosages, these studies demonstrate a highly consistent pattern of responses in IIEF endpoints. Baseline and post-treatment IIEF scores (Q3, Q4, EF domain) were almost identical in the first US and European studies.¹⁵⁻¹⁷ Slightly higher post-treatment scores were observed for both drug and placebo conditions in the two Asian studies,^{18,19} suggesting that Asian men might be slightly more susceptible to the non-specific effects of treatment. However, the drug-placebo differences on Q3, Q4, and the EF domain were highly similar to those observed in both the European^{16,17} and US¹⁵ studies. Strong correlations were noted with other measures of treatment outcome (event logs, global efficacy ratings) in all five studies. Overall, these results strongly support the validity and reliability of the instrument, and its robust sensitivity to treatment across different patient groups, cultures and languages of administration.

Normalization of IIEF scores with sildenafil treatment

How comparable are IIEF scores in patients on sildenafil to normal controls without ED? In a study

conducted in the UK, Dinsmore *et al*²⁰ evaluated the degree to which sildenafil treatment normalizes IIEF responses of ED patients compared with a group of age-matched controls who were not treated. The age-matched controls were without clinically documented ED. Patients with ED of mixed etiologies ($n=111$) were randomly assigned to received 12 weeks of double-blind, flexible-dose treatment with sildenafil or placebo. IIEF responses before and after treatment were compared with those of a sample of age-matched controls without documented ED ($n=109$). For sildenafil-treated patients, mean scores on Q3 increased from 1.7 at baseline to 3.6 at follow-up and Q4 increased from 1.6 at baseline to 3.7 following treatment. The corresponding scores for non-dysfunctional controls on these two items were 4.3 and 4.2, respectively. Based on this, sildenafil restored EF in this study to approximately 85% that of subjects without ED. Of note, control subjects in this study did not achieve the maximum score of '5.0', indicating that a slight diminution of erectile capacity is normal for men in this age range.

Figure 2 shows the sexual function domain scores at baseline and following treatment for the sildenafil group compared with untreated age-matched controls without documented ED. As shown, EF domain

scores following treatment were less than, but approaching scores of age-matched controls. Specifically, the mean EF domain score following treatment was 21.8 for ED patients receiving sildenafil, vs 25.8 for controls. The lower mean scores in the sildenafil group may be at least partly attributed to a relatively small percentage of patients who did not respond to sildenafil treatment, making them statistical outliers and lowering the mean. Similar baseline and post-treatment IIEF scores were observed in the previous European and US studies.¹⁵⁻¹⁷

Four of the five domains of the IIEF (erectile function, orgasmic function, intercourse satisfaction, overall satisfaction) improved significantly following treatment with sildenafil. In contrast, little change was observed in the sexual desire domain. This observation likely stems from two reasons: (i) scores on sexual desire in the patient group before treatment were only marginally less than those in the control group; and (ii) sildenafil acts specifically on the peripheral mechanism of erection and has little or no central effects.^{6,7} This pattern of results has been observed consistently, and it is noteworthy that no study to date has shown clinically significant increases in sexual desire with sildenafil or other erectogenic agents.

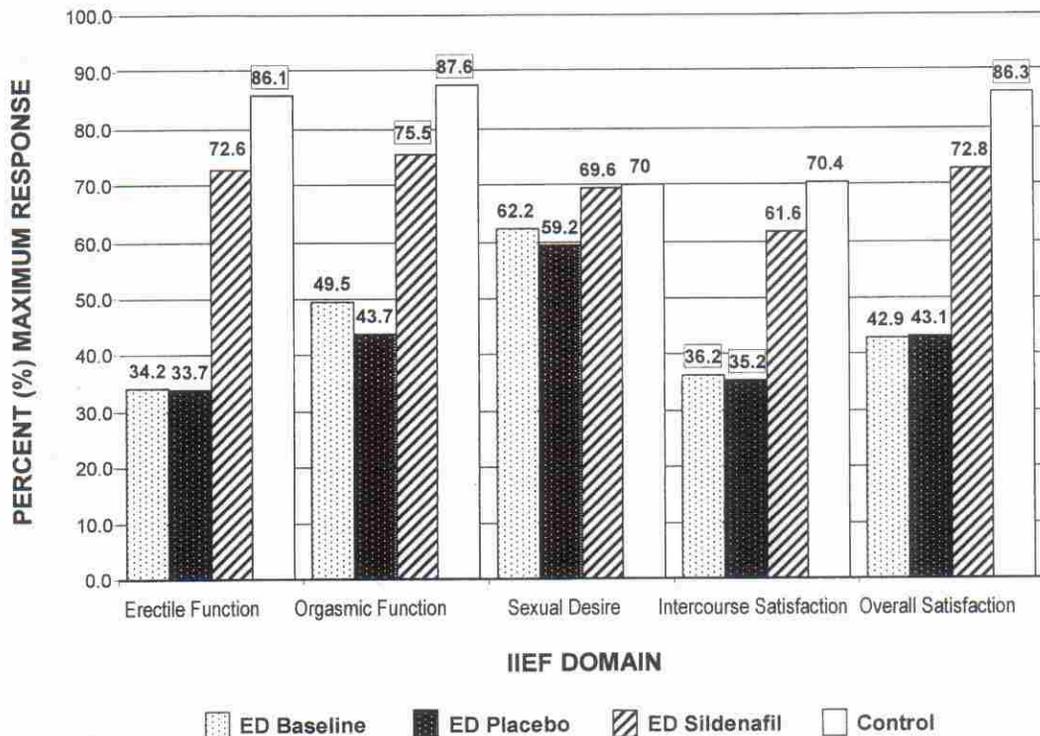


Figure 2 Per cent maximum response on five domains of sexual function for ED patients treated with sildenafil ($n=111$) and age-matched controls ($n=109$). (Per cent maximum response = mean domain score/total domain score \times 100). Adapted from: Dinsmore *et al*.²⁰

Sildenafil trials in specific etiologies

Several studies have evaluated IIEF scores before and after sildenafil treatment in ED patients with specific etiologies. These studies are worth considering, since patients with specific etiologies, such as diabetes and spinal cord injury, might be expected to show lower (that is, more dysfunctional) baseline IIEF scores and differential responsiveness to treatment. In this sense, these studies provided an opportunity for further validation of the IIEF in addition to demonstrating the efficacy of sildenafil in specific patient populations. Figure 3 shows the mean baseline, placebo, and sildenafil values for Q3, Q4, and the EF domain score in patients with diabetes, spinal cord injury, heart disease and depression.

Diabetes

Rendell *et al*²¹ reported the first randomized controlled trial of sildenafil in diabetic men with ED. Patients for this study were 268 men with diabetes and ED who were randomly assigned to receive 12 weeks of flexible-dose treatment with

sildenafil or placebo (see Table 1). Mean scores on Q3 increased from 1.8 at baseline to 3.2 at 12 weeks and Q4 increased from 1.5 at baseline to 2.9 in the sildenafil group at 12 weeks, relative to 2.0 (Q3) and 1.6 (Q4) in the placebo group at 12 weeks. These differences were all highly significant ($P < 0.001$). Event log data showed a similar pattern of results to IIEF scores, with 61% of patients in the active treatment group reporting at least one successful intercourse attempt, vs 22% of patients receiving placebo. A comparison of IIEF scores in these patients with the first two USA studies in patients with mixed etiologies¹⁵ indicates that the baseline scores of patients with diabetes trended lower (that is, more dysfunctional) for both Q3 (1.8 vs 2.0) and Q4 (1.5 vs 1.7). Similarly, although significant treatment effects were observed in all three studies, mean estimates of post-treatment IIEF scores for patients with diabetes were lower on both Q3 (3.9 vs 3.2) and Q4 (3.6 vs 2.9).

Spinal cord injury

Patients with spinal cord injury typically have severe ED due to loss of neural innervation. These patients are likely to have lower baseline scores than

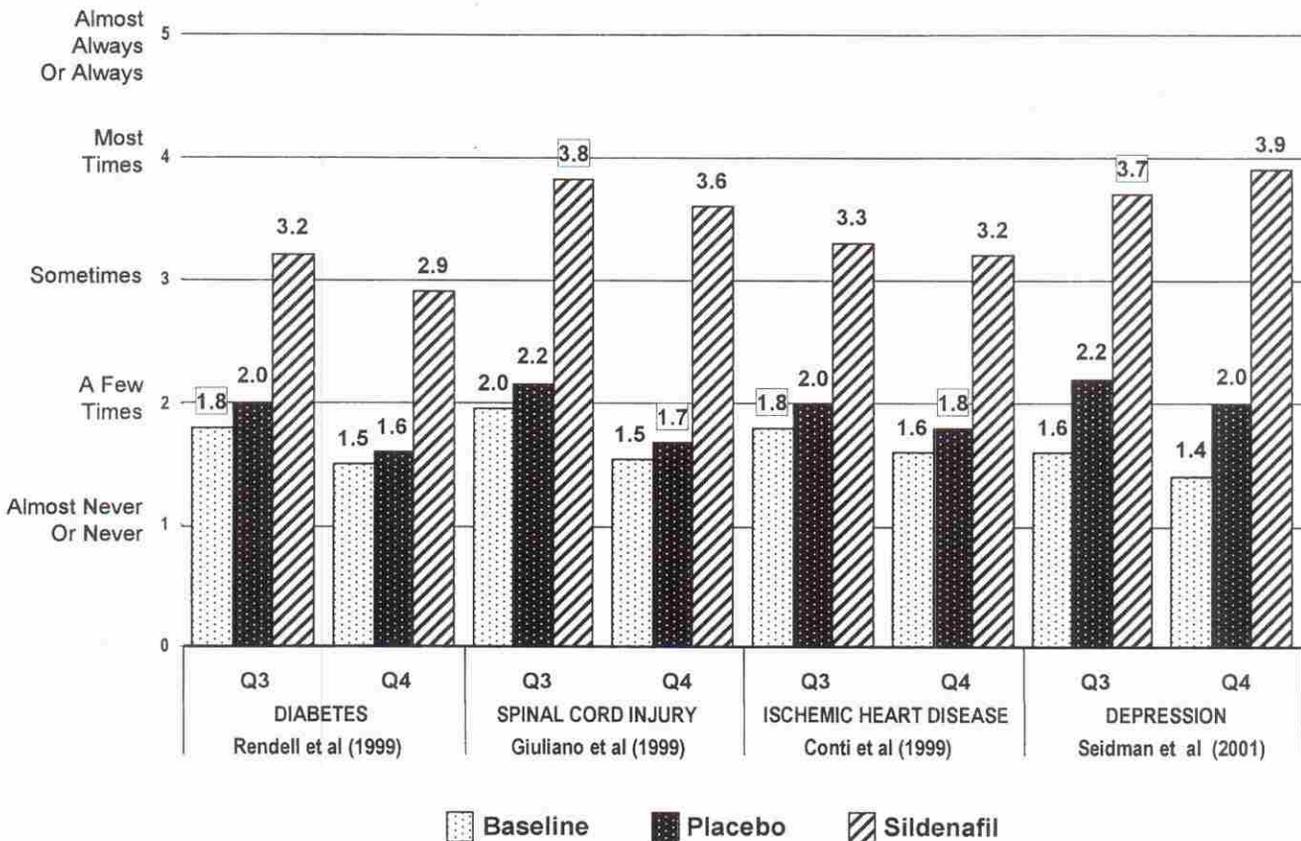


Figure 3 Mean IIEF scores (Q3, Q4) in specific etiological sub-groups.

other etiological sub-groups, but may be more or less responsive to treatment depending on the type and level of injury.

Giuliano *et al*²² conducted a two-way, cross-over design study in 178 European men with spinal-cord injury (see Table 1). Patients were randomly assigned to double-blind, flexible-dose treatment with sildenafil or placebo for 6 weeks; following a 2-week washout period, all patients received the other double-blind treatment. Baseline mean scores for Q3 and Q4 were 2.0 and 1.5, respectively. These scores significantly increased with sildenafil relative to placebo (3.8 vs 2.2 for Q3; 3.6 vs 1.7 for Q4). While the EF domain scores were not calculated, similar changes were observed on other items of the IIEF. Whereas baseline IIEF scores of spinal cord injured patients in this study resembled those of diabetic patients in the Rendell *et al* diabetes study²¹ (2.0 vs 1.8 for Q3; 1.5 vs 1.5 for Q4), post-treatment scores in the spinal-cord injury group more closely resembled those of the USA and European studies with patients of mixed etiology.^{15,16} Event-log data for the spinal cord patients again corroborated the overall pattern of IIEF results obtained. Eighty per cent of patients reported improved intercourse with sildenafil vs 10% with placebo.

Heart disease

Conti *et al*²³ reported results of a sub-analysis of IIEF data from nine double-blind, randomized studies involving 357 patients with ischemic heart disease (Table 1). Most patients were taking concomitant medications for hypertension, hyperlipidemia, or diabetes. Mean scores for Q3 were 1.8 and Q4 were 1.6 at baseline compared with, respectively, 3.3 and 3.2 following sildenafil treatment (vs 2.0 and 1.8 following placebo). Treatment differences were highly significant ($P < 0.0001$). Erectile function domain scores after treatment were also significantly increased on sildenafil vs placebo (19.7 vs 10.9), as were the scores for other sexual function domains. As in previous studies, IIEF scores corresponded well with event-log measures of satisfactory intercourse. Comparison of IIEF data in this study with those previously mentioned suggests that ED patients with ischemic heart disease might be slightly more responsive to sildenafil's effects than those with diabetes, but somewhat less than patients with spinal cord injury. Again, strong consistency in baseline and post-treatment scores was observed across geographic locations.

More recently, Olsson and Persson²⁴ reported results of a double-blind, flexible-dose, 12-week study of sildenafil (25–100 mg) vs placebo in 224 Swedish men with cardiovascular disease and ED (Table 1). In this sample, 80% of patients had hypertension, 20% had ischemic heart disease, and

all patients were receiving one or more cardiovascular drugs. Baseline scores on Q3 and Q4 were, respectively, 2.0 and 1.5, for both groups combined. Following treatment, scores improved to 3.7 (Q3) and 3.3 (Q4) for sildenafil-treated subjects, compared with 2.2 (Q3) and 1.9 (Q4) for placebo-treated subjects. These differences were highly significant ($P < 0.0001$). Baseline and post-treatment scores on Q3 and Q4 in this study were higher (less dysfunctional) than those in the Conti *et al* study,²³ which may reflect the lower percentage of patients with ischemia or more advanced forms of heart disease in the Olsson and Persson study.²⁴ In other respects, the results were highly consistent with the Conti *et al* findings.²³ Erectile function domain scores were not reported in this study.

Depression

A recent study by Seidman *et al*²⁵ reported results of a randomized, controlled trial of 12 weeks of flexible dose sildenafil therapy (25–100 mg) or double-blind placebo in 152 US men with ED and symptoms of depression. Mean baseline scores were 1.6 for Q3, 1.4 for Q4, and 9.3 for the EF domain score. These scores increased to 3.7 (Q3), 3.9 (Q4), and 23.4 (EF domain) following sildenafil compared with 2.2 (Q3), 2.0 (Q4), and 12.4 (EF domain) following placebo. Similar effects were observed on the global assessments of treatment efficacy, as well as other domains of sexual functioning. Of note, improvements in IIEF scores were highly correlated with improvements in mood, regardless of treatment assignment. The pattern of baseline and post-treatment IIEF scores was similar to those observed in the earlier studies with mixed etiological groups,^{15–18} suggesting that the presence of depression in these patients did not diminish the effectiveness of treatment or sensitivity of the IIEF endpoints. In addition, the study showed significant changes in quality-of-life outcomes, which also correlated highly with changes observed in the IIEF.

Summary

In summary, the IIEF has served as a primary endpoint in all of the clinical trials with sildenafil to date. A highly consistent pattern of findings has emerged across these trials, regardless of the types of patients enrolled and geographic location of the trial. Patients with different etiologies of ED, such as diabetes, spinal cord injury, heart disease, and depression, have shown a range of baseline and post-treatment IIEF scores, consistent with clinical prediction and the known mechanism of sildenafil in these different etiological groups. In addition,

scores on the IIEF correlated well with other measures of treatment outcome, including global assessments of treatment efficacy and quality of life. These manifestations further strengthen, above and beyond the original validation study, the robustness of the IIEF for valid measurement of sexual functioning in clinical trials of ED.

Randomized trials with non-sildenafil therapies

Since its initial development in conjunction with the sildenafil trials, the IIEF has been used increasingly as an efficacy measure in treatment studies with other interventions. Comparison of results from these studies can lend further evidence of validity and treatment sensitivity of the IIEF. These non-sildenafil studies also address the potential criticism that, because of its development in conjunction with the sildenafil trials, the IIEF might be uniquely sensitive or responsive to the treatment effects of sildenafil. To the extent that the IIEF shows predictable and reliable treatment sensitivity with other efficacious agents, this potential criticism is addressed.

In recent years, a number of other treatments for ED have been developed including other PDE-5 inhibitors (tadalafil, vardenafil), oral phentolamine (Vasomax), sublingual apomorphine (Uprima), intracavernosal injections (EDEX), and dehydroepiandrosterone (DHEA). Each of these treatments has been evaluated in recent clinical trials with the IIEF as a primary study endpoint. In the absence of direct comparator ('head-to-head') trials, it is not recommended that inferences be made about the efficacy of any of these treatments relative to each other or to sildenafil. Instead, the pattern of IIEF scores observed in these studies is an attempt to seek a corroboration of the robustness and treatment responsiveness of the instrument. These studies are summarized in Table 2.

Tadalafil

Tadalafil (Cialis) is a potent and selective PDE-5 inhibitor with a similar mechanism of action to sildenafil. In the first multi-center, randomized clinical trial of tadalafil in the USA, Padma-Nathan *et al*²⁶ demonstrated efficacy and safety of the drug at doses ranging from 2 to 25 mg. Subjects for this study were 179 men with mild-to-moderate ED of mixed etiology (patients with radical prostatectomy and diabetes were excluded). Patients were randomly assigned to receive one of four doses of the drug (2, 5, 10, 25 mg) or placebo for 3 weeks of treatment. At baseline, mean scores were 2.8, 2.2,

and 13.7 for Q3, Q4, and the EF domain, respectively. Following 3 weeks of treatment, Q3 and Q4 scores ranged, respectively, from 2.5 and 2.4 on placebo to 4.2 and 4.0 on the highest treatment dose (25 mg). Scores on the EF domain at 3 weeks ranged from 14.7 on placebo to 24.2 for the 25 mg dose. Similar changes were noted in the other domains of sexual function. All treatment differences were highly significant ($P < 0.001$).

As in the sildenafil trials, this study included diary measures and global ratings of treatment satisfaction, which corroborated changes in the IIEF. A partner diary measure was included, which provided additional corroboration of IIEF changes. In addition to demonstrating the efficacy of a new PDE-5 inhibitor in the treatment of ED, the results showed a high degree of comparability in the pattern of IIEF scores and other measures of sexual function obtained in the sildenafil trials previously cited. Again, no conclusions about relative efficacy of different interventions should be inferred in view of the differences in study design and lack of direct head-to-head comparisons.

Vardenafil

Porst *et al*²⁷ have reported the first multi-center, randomized double-blind trial of vardenafil, another potent and selective PDE-5 inhibitor, in 580 patients with ED of mixed etiology. This international study was conducted in Belgium, France, Germany, Poland, The Netherlands, South Africa, and the USA. Patients received a fixed dose of 5, 10 or 20 mg of vardenafil or double-blind placebo for 12 weeks. Primary endpoints for the study were Q3, Q4 and the EF domain score of the IIEF. Mean scores at baseline (all subjects combined) for each measure was 2.5 (Q3), 2.1 (Q4) and 14.0 (EF domain).

Higher baseline scores in this study were consistent with the exclusion of patients with diabetes, radical prostatectomy, and those who had previously taken sildenafil without benefit. Significant changes were observed following treatment on each of the primary endpoints ($P < 0.001$), with post-treatment scores at the highest dose being 4.0, 3.8, and 22.8 for Q3, Q4 and the EF domain, respectively, compared with 2.5, 2.0 and 15.6 for placebo. Again, these changes were closely matched by changes in event logs, global efficacy assessments, and other domain scores of the IIEF. As in the tadalafil study, the dose-response pattern in IIEF scores closely mirrored the pattern observed in the earlier sildenafil trials; similar dose-response relations were observed in other study endpoints (eg event logs, global assessment ratings).

Table 2 Randomized, Placebo Controlled Trials without Sildenafil

Author	Subjects	Design and Treatment		IIEF endpoints			Other endpoints	Comments
				Q3	Q4	EF		
Padma-Nathan, et al ²⁶	USA; Mixed ED (n = 179)	Parallel group Fixed dose Tadalafil	Baseline: Placebo: (5–25 mg):	2.8 2.5 4.1	2.2 2.4 4.0	13.7 14.7 24.2	SEP, GEQ IS, OF, SD, OS Domains	First large-scale study of tadalafil in the US. Highly, significant treatment effects on primary IIEF endpoints. Strong correlations with other study outcomes, including partner ratings
Post H, et al ²⁷	Multi-national mixed ED (n = 601)	Parallel group Fixed dose Vardenafil	Baseline: Placebo: (5–20 mg):	2.5 2.5 4.0	2.1 2.0 3.8	14.0 15.6 22.8	GEQ IS, OF, SD, OS Domains	International study of another PDE-5 inhibitor (vardenafil). Higher baseline scores may be due to exclusion of diabetics, radical prostatectomies and sildenafil non-responders. Highly significant treatment effects and strong correlations with other study endpoints
Goldstein I, et al ²⁸	USA; Mixed etiology (n = 311)	Crossover design Fixed dose Phentolamine (40–80 mg)	Baseline: Placebo:	— —	— —	14.5 —	SEP, GEQ	Large-scale crossover and parallel-design studies of oral phentolamine in mild-moderate ED patients. Relatively small changes in EF domain score for drug vs placebo. <i>Lack of specific IIEF data presented</i>
Goldstein I ²⁸	USA; Mixed etiology (n = 459)	Parallel group fixed dose Phentolamine	Placebo: 40 mg: 80 mg:	Mean change from baseline	—2.3 5.7 6.7	SEP IS, OF, SD, OS Domains	IIEF data presented in the form of mean change from baseline	
Dula E, et al ³⁰	USA; Mixed etiology (n = 569)	Parallel group Flexible dose and fixed dose Apomorphine SL (5, 6 mg)	Baseline: Placebo: Apo:	Significant drug vs placebo effect (P < 0.01) for both doses on EF domain			IS, OF, SD, OS Domains Home-use Questionnaire BSFI	First large-scale US study of apomorphine SL in patients with mild to moderate ED. Parallel group design with placebo, 5 mg, 6 mg. Significant drug effects reported on EF domain scores, but no absolute IIEF values presented. Strong corroboration with event logs, and partner ratings reported
Dula E, et al ³¹	USA; Mixed etiology (n = 296)	Crossover Fixed dose Apomorphine SL (3, 4 mg)	Baseline: Placebo: Apo: (3 mg)	Mean change in EF Domain 30.3% for Apo 4.1% for placebo	— — —	— — —	IS, OF, SD, OS Domains BSFI	Large-scale crossover design studies of sublingual apomorphine in ED patients without significant organic etiology. Relatively small changes in EF domain score for drug vs placebo. Lack of specific IIEF data presented
Reiter WJ, et al ³²	Austrian; Mixed etiology (n = 40)	Parallel group Fixed dose DHEA (50 mg)	Baseline: Placebo: DHEA	— — —	— — —	10.0 8.0 27.0	IS, OF, SD, OS Domains	Austrian study of DHEA replacement in men with ED and low DHEA. Highly, significant changes in EF domain scores, but small n and possible unblinding of treatment effects. first use of IIEF with hormonal treatment for ED
Shabsigh R, et al ³³	USA; Mixed etiology (n = 111)	Crossover Flexible dose EDEX + MUSE (40, 1000 µg)	Baseline: EDEX: MUSE:	1.7 4.4 3.0	1.3 4.2 2.8	9.2 25.3 17.3	IS, OF, SD, OS Domains Buckling Test Physician/ Patient Report	First comparison study of prostaglandin E1 injection compared with intraurethral suppository (MUSE). Significant difference between treatments on all IIEF endpoints. Strong correlation with other study endpoints, including buckling pressure and physicians/patient report

Key:

Baseline (Q3, Q4, EF) = Mean baseline response for both groups combined

Placebo (Q3, Q4, EF) = Mean post-treatment response for placebo

Treatment (Q3, Q4, EF) = Mean post-treatment response for drug treatment

GEQ = Global Efficacy Question; OF = Orgasmic Function; IIEF = International Index of Erectile Functioning; SD = Sexual Desire; EF = Erectile Function; OS = Overall Satisfaction; IS = Intercourse Satisfaction; SEP = Sexual Encounter Profile; OF = Orgasmic Function; IPSS = International Prostate Symptom Score

Oral phentolamine (Vasomax)

Oral phentolamine (Vasomax) is an alpha-1 and alpha-2 adrenergic antagonist, which has been developed as a potential treatment for ED. This drug has previously been used in injectable form in combination with papaverine, but has only recently been evaluated as an oral erectogenic agent. Two large-scale clinical trials with oral phentolamine were recently conducted in the USA,^{28,29} one of which was a cross-over and the other a parallel design. In the cross-over-design study, 311 men with mild-to-moderate degrees of ED were randomized to receive 4 weeks of drug (40 mg phentolamine) or placebo, with a 2-week washout period. In the parallel-design study, 424 patients were randomly assigned to receive placebo, 40 mg, or 80 mg of phentolamine for 4 weeks of treatment. In both studies, the total score on the EF domain was employed as the primary outcome measure. Mean change scores in the EF domain from baseline to the end of treatment in the parallel-design study were -2.3, 5.7 and 6.7 for the placebo, 40 mg, and 80 mg groups, respectively. Specific scores were not reported for the cross-over design study, although both studies observed significant improvements of drug over placebo in IIEF endpoints ($P < 0.001$), which were associated as expected with diary-based and global efficacy assessments.

Sublingual apomorphine (Uprima)

Apomorphine is a centrally-active, dopamine agonist that can be taken in sublingual form (Uprima) and has recently been approved for treatment of ED in some European countries. Two double-blind, randomized trials have recently been reported on the safety and efficacy of apomorphine.^{30,31} In the first study, patients with mixed etiologies were randomly assigned to a flexible dose of apomorphine (2–6 mg), a fixed dose of 5 mg or 6 mg, or placebo for 8 weeks of treatment. A number of efficacy parameters were assessed including diary measures of erection and intercourse, as well as the IIEF. Specific IIEF scores were not reported, although the authors reported a significant ($P < 0.01$) improvement in EF domain scores, intercourse satisfaction, and overall satisfaction between the drug and placebo conditions. This change correlated well with other measures of treatment outcome in the study.

In a second, double-blind cross-over study,³¹ patients with mixed etiologies were randomly assigned to one of two drug sequences: apomorphine 3 mg vs placebo, or apomorphine 3 mg vs apomorphine 4 mg. Each treatment arm was continued for 4 weeks. For the 3 mg vs placebo

comparison, a 4-point improvement in the EF domain scores was observed with 3 mg. This difference was reported to be significant, although no significance level or mean scores were provided. The 3 mg vs 4 mg comparison was reported to be non-significant, although no mean scores or significance levels were reported. Changes in the IIEF appeared to parallel changes in other study outcomes (global assessments, event logs).

DHEA

Reiter *et al*³² reported the first randomized, clinical trial of dehydroepiandrosterone (DHEA) supplementation in the treatment of men with ED and sub-normal levels of DHEA who also responded positively to a pharmacological erection test with prostaglandin E1. Forty patients were recruited from a clinic sample in Vienna, Austria. Subjects were randomly assigned to receive daily oral doses of DHEA (50 mg) or double-blind placebo for 6 months of treatment. Primary endpoints for this study were the IIEF domain scores. Before treatment, the mean EF domain score of both groups combined was 10.0. Scores on the EF domain were increased by 8 weeks to 14.0 in the DHEA group and 10.0 in the placebo group. At 24 weeks of treatment, the mean score in the DHEA group had increased to 27.0, compared with 8.0 for the placebo group. These large between-group treatment differences should be cautiously interpreted, however, because of the small number of patients and relatively high drop-out rate (17/20 patients in the DHEA group; 13/20 patients in the placebo group completed the study). Possible unblinding of treatment may also have occurred during the 6 months of treatment duration. Despite these limitations, the study is noteworthy in showing a high degree of sensitivity of the IIEF to a hormonally-based treatment in men with ED and a specific endocrine deficiency.

Intraurethral and intracavernosal therapies

Local therapies for ED include intracorporal injections (eg EDEX) and intraurethral suppositories (eg MUSE) of prostaglandin E1. In the first randomized, controlled trial to compare these two treatments directly, Shabsigh *et al*³³ evaluated IIEF and other measures of patient and partner satisfaction during 21 days of active treatment. Patients with mixed etiologies were recruited for the study, excluding only those with previous experience with either treatment. Baseline scores for Q3, Q4, and the EF domain were 1.7, 1.3 and 9.2, respectively. Following treatment with EDEX, mean scores increased to 4.4 and 4.2 for Q3 and Q4, respectively, compared

with 3.0 and 2.8 for MUSE. The EF domain score increased to 25.3 for EDEX and 17.3 for MUSE. All between-group treatment differences were highly significant ($P < 0.001$). Similar changes were observed for the other domains of sexual function and subjective measures of treatment satisfaction. This study is noteworthy in demonstrating a high degree of responsiveness of the IIEF endpoints to local therapy with prostaglandin E1, a widely used second line treatment for ED. It is also noteworthy as the first comparator trial to show differences in efficacy between one form of treatment (EDEX) and another (MUSE) via the IIEF. This lends support to the IIEF as a suitable endpoint for further comparator trials.

Summary

In summary, a number of randomized clinical trials have been performed in which the IIEF has been used as a primary endpoint in assessing efficacy associated with various ED therapies. Although developed initially for use in conjunction with the sildenafil trials, the IIEF has demonstrated sensitivity to the effects of treatment with a broad range of ED therapies. Only one comparator trial has been performed to date, and the instrument showed a clear differentiation between two local therapies in this study. IIEF-based measures of treatment efficacy have also been highly correlated with other study outcomes, such as global efficacy and diary-based assessments, across a wide variety of patient populations and treatment interventions. The EF domain score, in particular, has been shown to be a highly sensitive indicator of efficacy across a range of treatment outcome studies. Finally, the broad use of the IIEF across different geographic sites and with patients of varying medical backgrounds attests to the robustness and reliability of the measure in clinical trials of different therapies for ED.

Observational and diagnostic studies

Hypertension

Because hypertension is the most prevalent medical risk factor for ED,³⁴ it is of interest to determine whether ED in hypertensive patients can be identified and classified via the IIEF. Burchard *et al.*³⁵ evaluated this hypothesis by administering IIEF and medical history questionnaires to a representative sample of 104 hypertensive patients at an outpatient hypertension center. The mean age was 62.2 (± 10.1 s.d.) y and 91% were white. All patients were being treated with one or more antihypertensive medications. Results indicated that 85% of subjects were sexually active, of

whom 68% had varying degrees of mild, moderate, and severe ED according to their IIEF scores. Specifically, the mean EF domain score for patients with ED was 11.7 ± 9.3 , similar to the 10.7 ± 6.5 for patients in the original validation study.⁹ Relative to previous epidemiological findings,³⁴ a greater degree of severity of ED was also observed in the hypertensive patients in this study.

Diabetes

Male patients with diabetes are at 2–3 times greater risk for developing ED than age-matched controls.³⁶ One recent study³⁷ evaluated sexual function (IIEF items 1–5), presence or absence of peripheral neuropathy, and glycemic control in 78 male patients with type 2 diabetes. The mean EF score (\pm s.d.) was 16.6 ± 5.9 . However, when EF scores were stratified according to baseline hemoglobin A1c levels, a strong inverse relationship was observed (that is, higher HgA1c was associated with markedly lower EF scores). Specifically, patients with HgA1c levels above 9.0 had mean EF scores of 13.4 ± 5.9 , while patients with HgA1c levels less than or equal to 6.0 had mean EF scores of 21.5 ± 2.5 . Moreover, EF was shown to be significantly correlated with the presence or absence of peripheral neuropathy. These findings indicate the applicability of the IIEF in diagnosing ED in these patients and in evaluating the role of specific etiological factors, such as hyperglycemia or peripheral neuropathy.

Prostate cancer

Prostate cancer is highly prevalent in men over 50 and is typically treated with surgery (radical prostatectomy) or radiation therapy. The IIEF has been used in a number of recent studies demonstrating a high prevalence and moderate severity of ED in patients undergoing these treatments. Lowentritt *et al.*³⁸ evaluated 84 male patients with prostate cancer who had received radical prostatectomy surgery. The mean age of patients was 62 ± 7 (s.d.) y and patients were evaluated an average of 2.1 ± 1.9 y following surgery. Mean scores on the IIEF were 1.3 and 1.4 for Q3 and Q4, respectively, and 9.0 for the EF domain. Following open-label treatment with sildenafil, scores improved to 2.3, 2.4 and 14.0 for Q3, Q4 and the EF domain, respectively. Similarly, Zippe *et al.*³⁹ evaluated 91 patients with ED following radical prostatectomy. For both Q3 and Q4 mean scores were 1.2 for patients who had undergone bilateral, nerve-sparing surgery ($n=53$). Mean scores were 1.0 for those with unilateral surgery ($n=12$) and 1.5 for those who

had non-nerve sparing surgery ($n=26$). Similar findings were obtained in studies by Feng *et al*,⁴⁰ Blander *et al*⁴¹ and Jarow.⁴² In each of these studies, scores on the IIEF were noticeably and predictably lower for the prostatectomy patients relative to ED patients with mixed etiologies in the earlier multicenter trials.^{15–18}

External beam radiation therapy is an alternative to surgery for treatment of prostatic cancer. Relatively few studies have evaluated the short- or long-term effects of this treatment on male sexual function. In a Swiss study,⁴³ 35 patients who had received radiation therapy were evaluated for ED using the IIEF. Mean age of the patients was 69 y (range=54–79), and the study was conducted approximately 2 y following treatment. The majority of patients in this study were found to have moderate or severe ED, based upon their EF domain scores. Patients were subsequently treated with sildenafil, and the authors reported an overall improvement rate of 77% by week 6.

Pelvic trauma

Patients who sustain pelvic trauma or fractures are at increased risk for sexual dysfunction following these injuries. In a French study, Malvaud *et al*.⁴⁴ analyzed EF domain scores in 76 consecutive male patients with pelvic ring fractures. Eleven of 37 patients (30%) exhibited various degrees of impaired erection (EF score ≤ 25). Severity of ED was based on a published classification system on the EF domain, described later.⁴⁵ In contrast to diabetic and hypertensive patients in the previous studies, most patients with ED in this study had mild or mild-to-moderate ED, according to baseline IIEF scores. However, patients in this study were also significantly younger (mean age=39.9 y) than those in either of the previous two studies; this may have partially accounted for the difference in IIEF scores. The authors concluded that the IIEF diagnostic classification might help at the time of rehabilitation to identify those patients that could benefit from supportive treatments.

Renal transplantation

Malvaud *et al*⁴⁶ also evaluated IIEF scores in 212 patients (mean age=48.5 y) receiving kidney transplants for renal failure who were sexually active at the time of study. Of these patients, 56% were diagnosed as having ED, which was found in turn to be significantly related to age, duration of dialysis, and number of transplants. Although detailed information on the EF domain scores was not provided, comparison of the mean IIEF scores from

the whole transplant sample, including sexually active and inactive patients ($n=271$), showed discernable differences in EF and intercourse satisfaction scores between renal transplant patients and the normative control group in the original validation study.⁹ These differences occurred despite the older age of patients in the original normative sample (mean age = 56.2 y).

Aortic aneurysm

Surgical repair of an abdominal aortic aneurysm has been associated with an increased risk of ED in a number of studies.^{47,48} One recent study in a Veteran's Administration hospital in the USA assessed IIEF scores in a sample of 68 male patients following aortic surgery.⁴⁹ To evaluate the effects of surgery retrospectively, investigators asked patients to complete each question on the basis of their recall of performance prior to surgery compared with their current performance. Based on this analysis, EF domain scores were found to be decreased in 67 of 68 patients, with a mean retrospective EF domain score of about 18.0 prior to surgery, compared with about 6.0 after surgical repair of the aortic aneurysm ($P < 0.0001$). No differences were found in the type of surgery performed (tube vs bifurcated graft). Other potential predictors of outcome were not examined. An unanticipated outcome of the study was a large influx of requests for ED treatment in these patients following completion of the questionnaires.

Spinal cord injury

Patients with spinal cord injury are typically younger, but often present with more severe ED than other patient groups. Schmid *et al*⁵⁰ evaluated sexual function by means of IIEF questionnaires in 41 spinal cord injured patients in a Swiss clinic. The mean age of patients in this study was 36.5 y (range=20–63); the mean duration since injury was 5.9 y (range=0.5–26). Most patients in the study ($n=23$) had incomplete paraplegias with lower motor neuron injuries. Although individual item scores were not reported, the mean EF domain score at baseline was 9.2 ± 4.4 (s.d.). This mean resembles the mean EF domain scores for the spinal cord injured samples in double-blind studies by Giuliano *et al*²² and Hutling *et al*.⁵¹

Summary

In summary, the IIEF has been used in several observational studies to characterize the degree or

severity of ED in patients with different etiologies. These studies were performed in a variety of clinical settings and geographic locations. Results demonstrate that the IIEF provided sensitive and reliable information regarding the presence and severity of ED across a wide range of etiologies and disease states. Accordingly, it can also be recommended for initial screening or baseline assessment of patients with ED prior to treatment with oral agents or other treatment interventions.

The IIEF as a diagnostic measure

The NIH Consensus Panel on ED outlined several goals for basic and clinical research on ED.¹⁴ One of these goals was to create a staging system for the quantitative and qualitative classification of ED. Such a system would assist research and patient management by: (1) quantifying the specific type of patient population to include in a clinical trial; (2) determining and comparing responder rates associated with different treatments; (3) improving clinical decision-making and patient care; (4) fostering educational initiatives; and (5) supporting claims for reimbursement. The EF domain of the IIEF was considered for such a purpose. This subscale in particular showed a high degree of reliability, as well as excellent sensitivity and specificity to treatment effects in the main validation studies.⁹ Accordingly, the ability of the EF domain to serve as a diagnostic tool to discriminate between men with and without ED, as well as to classify the degree of severity of the disorder, was investigated.^{10,52}

For this analysis, baseline patient data from four separate sildenafil trials were pooled for comparison with an age-matched control sample. A total of 1035 patients and 116 controls from the USA and UK were included in the analysis. A receiver operating characteristic (ROC) curve was constructed to assess the diagnostic precision of the EF domain in distinguishing men with ED from age-matched controls (see Figure 4a). The resulting ROC curve supported the EF domain as an excellent diagnostic tool, with high sensitivity and specificity. Based upon a classification-tree analysis, the optimal cut-off score was found to be 25, with men scoring less than or equal to 25 classified as having ED and those scoring above 25 as not having ED (sensitivity = 0.97; specificity = 0.88). Subsequently, among men in a stable relationship who attempted sexual activity and intercourse, severity of ED was classified into five diagnostic categories: no ED (EF score = 26–30); mild ED (EF score = 22–25); mild to moderate (EF score = 17–21); moderate (EF score = 11–16); and severe (EF score = 6–10).⁵²

The validity of this diagnostic classification was evaluated in a separate, independent study compar-

ing severity classification according to EF domain scores with a single-item self-assessment of ED severity before and after treatment.¹¹ The single self-assessment question of ED severity was adapted from the Massachusetts Male Aging Study⁵³ and, like the IIEF, was administered at baseline and at the end of treatment (week 12). An erection problem was defined as 'not being able to get and/or keep an erection that is hard enough for satisfactory sexual intercourse/activity.' Response options (and their definitions) included the following: no erection problem ('always able' to get and keep an erection hard enough for sexual intercourse/activity); minimal/mild erection problem ('usually able'); moderate erection problem ('sometimes able'); and severe erection problem ('never able'). Patients were asked to choose the response option that best suited their condition during the past 4 weeks.

Patient self-assessments of ED severity and disease grades from the EF domain score were obtained from about 247 men enrolled in a clinical trial of sildenafil. Results showed a moderate-to-high degree of correlation between the two diagnostic measures, with a high correlation at 12 weeks of treatment ($r = 0.86$).

Brief screening version

An abridged 5-item version of the IIEF, also known as the Sexual Health Inventory for Men (SHIM), was developed and separately validated as a brief, easily administered diagnostic tool.⁵⁴ The SHIM is widely used as a screening measure in clinical practice settings in the USA and elsewhere. Like the IIEF itself, the SHIM has been translated into 32 languages. In addition, the SHIM has been adopted as a standard diagnostic aid for office screening of ED. The SHIM includes four of six items from the original 6-item EF domain, in addition to a single item on intercourse satisfaction domain (IIEF item numbers 2, 4, 5, 7, 15). Of the 15 items on the IIEF, these five items were found to discriminate most highly between men with and without ED.

Validity and sensitivity of the abridged scale were evaluated by analyses of patients with ED ($n = 932$) from four placebo-controlled trials of sildenafil, as well as with a control group of men without ED ($n = 115$). The set of analyses and its results were similar to those found with the EF domain. The ROC curves showed a high degree of sensitivity and specificity of the SHIM in distinguishing between men with and without ED (Figure 4b). A classification-tree analysis suggested an optimal cut-off score of 21 or less for diagnosis of ED (sensitivity = 0.98; specificity = 0.88) for this clinical trial population of patients from the USA and UK. Among men in a stable relationship who attempted sexual activity and intercourse, classification of ED was partitioned

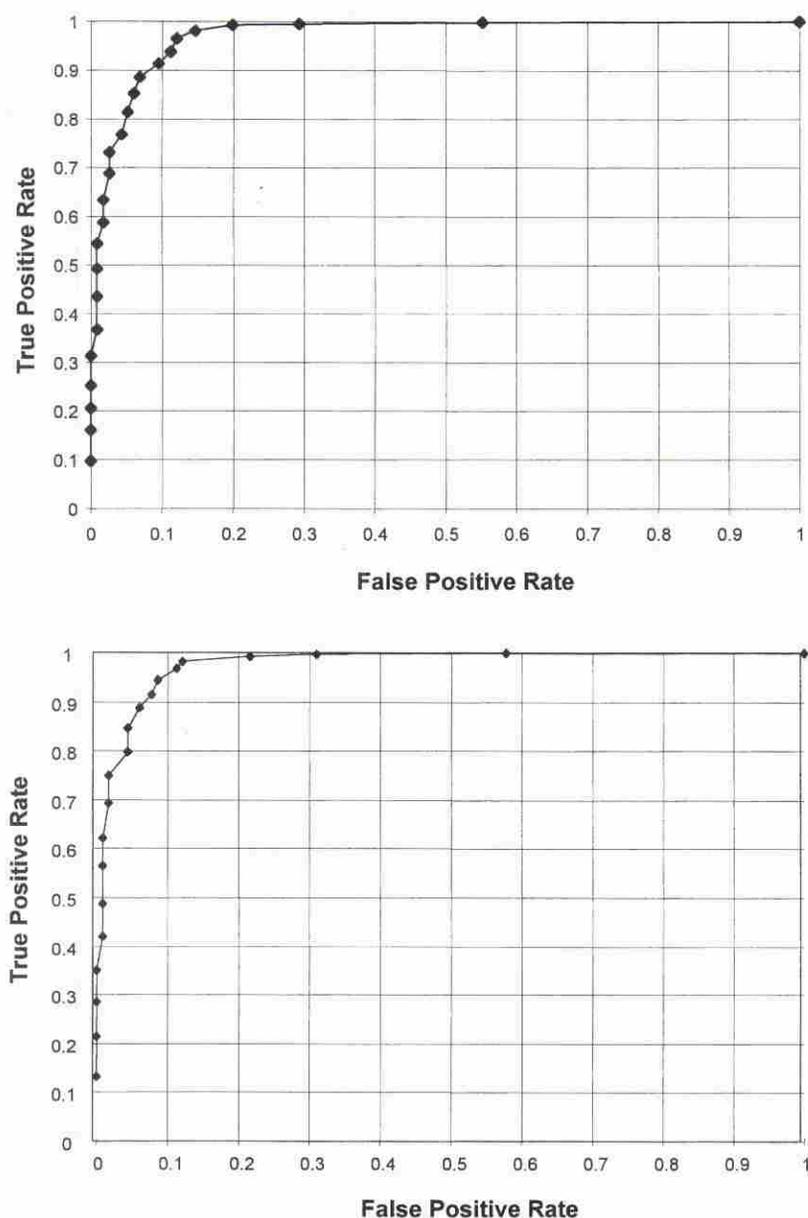


Figure 4 (A) Receiver operating characteristic (ROC) curve of the erectile function (EF) domain. (B) Receiver operating characteristic (ROC) curve of the Sexual Health Inventory for Men (SHIM).

into five severity grades: no ED (SHIM total score, 22–25), mild ED (17–21), mild to moderate (12–16), moderate (8–11), and severe ED (5–7).

Like the EF domain score, the SHIM showed a moderate-to-high degree of correlation with patient self-assessment of ED severity at baseline, at end of treatment, and change from baseline.⁵⁵ Agreement between the SHIM and the one-item self-assessment, measured by the weighted kappa statistic, mirrored the correlations at baseline and after treatment. Furthermore, both measures correlated moderately, as expected, with improvement in erections and

with treatment satisfaction from both patient and partner.⁵⁵ In a recent analysis of more than 30 000 SHIM questionnaires administered in over 600 physicians' offices, the predicted relationship between ED, age and other medical risk factors (hypertension, diabetes, ischemic heart disease) was observed.⁵⁶ Additionally, this study reported a high sensitivity (81.8%) and moderate specificity (57.7%) for detection of ED in patients scoring below 21 on the test. Based on these findings, the authors concluded that the SHIM provides a convenient method for rapidly identifying patients

at high risk for ED who require further clinical assessment.

Limitations of the IIEF

Despite its strong psychometric properties and wide adoption, the IIEF has limitations or weaknesses in specific areas. Some of these limitations pertain to the inherent design and construction of the instrument, while others are intrinsic to the use of brief questionnaires of this type in general. As noted in the original report,^{9,10} the IIEF focuses only on current sexual functioning and provides superficial assessment of domains of sexual functioning other than erection. It does not provide any specific information about the partner relationship or sexual functioning of the partner. It could be argued that these are important areas for assessment in clinical practice. Similarly, the IIEF provides a limited assessment of the domains of sexual desire and orgasmic dysfunction. The instrument is not expected to differentiate between different types of sexual desire disorders (eg primary vs secondary) or to distinguish between premature ejaculation and other types of male orgasmic disorders. The IIEF, therefore, may not be as suitable for use as the primary endpoint in clinical trials of these latter disorders. Although designed as a multi-dimensional instrument, the major focus of the instrument is first and foremost on erectile function. For this reason, it is only recommended for use in clinical or research contexts in which assessing erectile function is the primary goal.

The IIEF focuses on heterosexual activity, including vaginal intercourse. This focus is based on the requirement of regulatory agencies that new treatments for ED be effective in restoring erections sufficient for intercourse. In fact, the IIEF is highly predictive of patients' ability to achieve satisfactory intercourse, as indicated by strong correlations with other measures of intercourse ability, such as the event log. On the other hand, the IIEF may be less suitable in assessing treatment outcome for individuals whose primary sexual activity is not heterosexual intercourse.

The instrument provides accurate and reliable information as a quantitative index of ED severity,^{9–11} which may be of value to clinicians in diagnosing the disorder or evaluating the patient's response to treatment. However, two important clinical limitations of the IIEF are its sole focus on current sexual function and lack of information provided about etiology of the disorder. In assessing sexual function over the 4-week period prior to completing the questionnaire, the IIEF provides researchers or clinicians with a reliable baseline measure against which to compare future responses to treatment. The 4-week time period was selected as a relatively

standard period of assessment in sexual function studies.¹³ Nevertheless, this should not be viewed as a substitute for a detailed clinical history in which the circumstances of onset, time course, and progression of the disorder, relationship to other risk factors or comorbidities, and overall impact on the patient's life should all be assessed.^{12,57} An example by Blander *et al*⁵⁸ illustrates that assessment of etiology is not the IIEF's strongest suit. In that study of 89 ED patients, five specific erectile function questions of the IIEF (items 1–4, 15) were compared with findings from a comprehensive diagnostic evaluation. Results indicated that the IIEF scores did not differentiate between different forms of vasculogenic impotence identified by penile Doppler blood flow studies. On the other hand, the broad psychometric and cross-cultural validation, extensive clinical trial use, and high degree of sensitivity and specificity of the instrument make the IIEF ideally suited for efficacy evaluation in clinical trials of ED.

From a clinical perspective, the IIEF provides limited information about male sexual function and should not substitute for a detailed medical history and physical examination. From an epidemiological perspective, it has been noted that the instrument may be longer than necessary, thus leading to poorer compliance.⁵³ Derby *et al*⁵³ compared responses to the EF domain (six items) with a single item, self-assessment ED question in a sample of 254 men, aged 40 and older. Results indicated that single-item responses correlated well with the EF domain scores overall, although a higher percentage of respondents completed the single item. A single-item question, though, may provide a more limited assessment of ED severity, no information on specific components of erectile function (eg ability to achieve or maintain erection), and no information on other domains of sexual function. Thus, while a single-item question is useful in a case-finding or epidemiological context, it is generally not as desirable and sensitive as the multi-dimensional IIEF in a clinical trial setting.

Finally, some controversy exists concerning the validation and potential clinical use of the SHIM for diagnostic classification of ED severity.^{59–62} Among the issues discussed were cultural differences on how terms are viewed and the extension of results to general practice settings based on a sample of men with ED from clinical trials. Despite these limitations, the SHIM continues to enjoy widespread use and clinical utility as a brief screening tool for ED.

Conclusion: implications for future research

Similar to sildenafil's effects on the management of ED, the worldwide adoption of the IIEF has

profoundly altered the assessment of efficacy in clinical trials of ED. Whereas laboratory-based or physiological measures were formerly the 'gold standard' of efficacy assessment,^{1–3} this function now has been superceded by self-report measures generally—and the IIEF in particular. As evidenced in this review, results from a large number of controlled studies have demonstrated replicability and validity of the instrument, in addition to its being a highly sensitive and specific measure of treatment outcome. The IIEF also provides a quantitative index of ED severity for diagnostic and classification purposes. The brief form of the instrument (SHIM) has found use as a diagnostic aid. A noteworthy degree of consistency and robustness, both statistically and clinically, has been observed in the results obtained from randomized trials across different geographic regions, etiological sub-groups, and treatment interventions. A consistent pattern of findings has also been shown in comparison to other measures of treatment outcome, such as global efficacy assessments, event logs, and partner ratings. Despite the limitations noted above, the IIEF has met or exceeded expectations as a highly reliable and valid measure of erectile function. It is undoubtedly the questionnaire instrument of choice for clinical trials of ED.

Specific areas for future research on the IIEF include recommendations on how to best address incomplete or missing items (ie analysis of incomplete responses). Also encouraged would be additional methodological studies to investigate patient and item response properties using advanced psychometric techniques, such as item response theory,⁶³ to help refine our understanding of the relationship between response patterns on the IIEF and the effects of specific interventions or etiological factors. Finally, further studies are needed on the effects of aging, partner status, and other potential demographic or health characteristics on IIEF responses. Most clinical trials have been limited to heterosexual patients with steady sexual partners. Generalizability of the findings would be enhanced by inclusion of more heterogeneous patient groups in validation studies in the future.

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