Approved by the AUA Board of Directors
April 2018

Authors' disclosure of potential conflicts of interest and author/staff contributions appear at the end of the article.

ERECTILE DYSFUNCTION: AUA GUIDELINE

Arthur L. Burnett, MD; Ajay Nehra, MD; Rodney H. Breau, MD; Daniel J. Culkin, MD; Martha M. Faraday, PhD; Lawrence S. Hakim, MD; Joel Heidelbaugh, MD; Mohit Khera, MD; Kevin T. McVary, MD; Martin M. Miner, MD; Christian J. Nelson, PhD; Hossein Sadeghi-Nejad, MD; Allen D. Seftel, MD; Alan W. Shindel, MD

The Panel would like to dedicate this Guideline to the memory of our friend and colleague, Ralph Alterowitz. We will forever be grateful to his contributions and devotion to the field of men's sexual health. He brought compassion and joy to all of those who were fortunate enough to work with him.

Executive Summary

The sexual response cycle is conceptualized as a sequential series of psychophysiological states that usually occur in an orderly progression. These phases were characterized by Masters and Johnson as desire, arousal, orgasm, and resolution. Erectile dysfunction (ED) can be conceptualized as an impairment in the arousal phase of sexual response and is defined as the consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual satisfaction, including satisfactory sexual performance.[1,2] The Panel believes that shared decision-making is the cornerstone of the treatment and management of ED, a model that relies on the concepts of autonomy and respect for persons in the clinical encounter. It is also a process in which the patient and the clinician together determine the best course of therapy based on a discussion of the risks, benefits and desired outcome. Using this approach, all men should be informed of all treatment options that are not medically contraindicated to determine the appropriate treatment. Although many men may choose to begin with the least invasive option, the Panel notes that it is valid for men to begin with any type of treatment, regardless of invasiveness or reversibility. Men also may choose to forego treatment. In each scenario, the clinician's role is to ensure that the man and his partner have a full understanding of the benefits and risks/burdens of the various management strategies.

Methodology

A systematic review of the literature using the Pubmed, Embase, and Cochrane databases (search dates 1/1/1965 to 7/29/17) was conducted to identify peer-reviewed publications relevant to the diagnosis and treatment of ED. The review yielded an evidence base of 999 articles after application of inclusion/exclusion criteria. These publications were used to create the guideline statements. If sufficient evidence existed, then the body of evidence for a particular treatment was assigned a strength rating of A (high quality evidence; high certainty), B (moderate quality evidence; moderate certainty), or C (low quality evidence; low certainty). Evidence-based statements of Strong, Moderate, or Conditional Recommendation, which can be supported by any body of evidence strength, were developed based on the balance of benefits and risks/burdens to men and their partners. Additional information is provided as Clinical Principles and Expert Opinion when insufficient evidence existed.

Guideline Statements:

Evaluation and Diagnosis:

1. Men presenting with symptoms of ED should undergo a thorough medical, sexual, and psychosocial history; a physical examination; and selective laboratory testing. (Clinical Principle)
2. For the man with ED, validated questionnaires are recommended to assess the severity of ED, to measure treatment effectiveness, and to guide future management. (Expert Opinion)
3. Men should be counseled that ED is a risk marker for underlying cardiovascular disease (CVD) and other health conditions that may warrant evaluation and treatment. (Clinical Principle)
4. In men with ED, morning serum total testosterone levels should be measured. (Moderate Recommendation; Evidence Level: Grade C)
5. For some men with ED, specialized testing and evaluation may be necessary to guide treatment. (Expert Opinion)

Treatment:

6. For men being treated for ED, referral to a mental health professional should be considered to promote treatment adherence, reduce performance anxiety, and integrate treatments into a sexual relationship. (Moderate Recommendation; Evidence Level: Grade C)
7. Clinicians should counsel men with ED who have comorbidities known to negatively affect erectile function that lifestyle modifications, including changes in diet and increased physical activity, improve overall health and may improve erectile function. (Moderate Recommendation; Evidence Level: Grade C)
8. Men with ED should be informed regarding the treatment option of an FDA-approved oral phosphodiesterase type 5 inhibitor (PDE5i), including discussion of benefits and risks/burdens, unless contraindicated. (Strong Recommendation; Evidence Level: Grade B)
9. When men are prescribed an oral PDE5i for the treatment of ED, instructions should be provided to maximize benefit/efficacy. (Strong Recommendation; Evidence Level: Grade C)
10. For men who are prescribed PDE5i, the dose should be titrated to provide optimal efficacy. (Strong Recommendation; Evidence Level: Grade B)
11. Men who desire preservation of erectile function after treatment for prostate cancer by radical prostatectomy (RP) or radiotherapy (RT) should be informed that early use of PDE5i post-treatment may not improve spontaneous, unassisted erectile function. (Moderate Recommendation; Evidence Level: Grade C)
12. Men with ED and testosterone deficiency (TD) who are considering ED treatment with a PDE5i should be informed that PDE5i may be more effective if combined with testosterone therapy. (Moderate Recommendation; Evidence Level: Grade C)
13. Men with ED should be informed regarding the treatment option of a vacuum erection device (VED), including discussion of benefits and risks/burdens. (Moderate Recommendation; Evidence Level: Grade C)
14. Men with ED should be informed regarding the treatment option of intraurethral (IU) alprostadil, including discussion of benefits and risks/burdens. (Conditional Recommendation; Evidence Level: Grade C)
15. For men with ED who are considering the use of IU alprostadil, an in-office test should be performed. (Clinical Principle)
16. Men with ED should be informed regarding the treatment option of intracavernosal injections (ICI), including discussion of benefits and risks/burdens. (Moderate Recommendation; Evidence Level: Grade C)

17. For men with ED who are considering ICI therapy, an in-office injection test should be performed. (Clinical Principle)
18. Men with ED should be informed regarding the treatment option of penile prosthesis implantation, including discussion of benefits and risks/burdens. (Strong Recommendation; Evidence Level: Grade C)
19. Men with ED who have decided on penile implantation surgery should be counseled regarding post-operative expectations. (Clinical Principle)
20. Penile prosthetic surgery should not be performed in the presence of systemic, cutaneous, or urinary tract infection. (Clinical Principle)
21. For young men with ED and focal pelvic/penile arterial occlusion and without documented generalized vascular disease or veno-occlusive dysfunction, penile arterial reconstruction may be considered. (Conditional Recommendation; Evidence Level: Grade C)
22. For men with ED, penile venous surgery is not recommended. (Moderate Recommendation; Evidence Level: Grade C)
23. For men with ED, low-intensity extracorporeal shock wave therapy (ESWT) should be considered investigational. (Conditional Recommendation; Evidence Level: Grade C)
24. For men with ED, intracavernosal stem cell therapy should be considered investigational. (Conditional Recommendation; Evidence Level: Grade C)
25. For men with ED, platelet-rich plasma (PRP) therapy should be considered experimental. (Expert Opinion)

SECTION 1: PURPOSE

This guideline's purpose is to provide direction to clinicians and to men who have ED. The guideline focuses on how to recognize ED, how to conduct a valid diagnostic process, and how to approach treatment with the goals of restoring sexual function and enhancing the man and his partner's quality of life (QoL) while minimizing adverse events (AEs) and diagnosis- and treatment-associated burden. The strategies and approaches recommended in this document were derived from evidence-based and consensus-based processes. There is a continually expanding literature on ED; the Panel notes that this document constitutes a clinical strategy; it is intended to be interpreted with appreciation for the dynamic, evolving understanding of ED causes and treatments. The most effective approach for a particular man is best determined by that man (in consultation with his partner, when applicable) in collaboration with the clinician and with full consideration of the relevant history, values, and goals for treatment using a shared decision-making (SDM) approach. As our understanding of ED evolves and improves, the strategies presented here will be amended to remain consistent with the highest standards of clinical care.

SECTION 2: METHODOLOGY

Systematic review. A systematic review was conducted to identify published articles relevant to the diagnosis and treatment of ED. Literature searches were performed on English-language publications using the Pubmed, Embase, and Cochrane databases from 1/1/1965 to 7/29/2017. Data from studies published after the literature search cut-off will be incorporated into the next version of this guideline. Preclinical studies (e.g., animal models), commentary, and editorials were excluded. Additional exclusion criteria included data not relevant to current practice (e.g., reports on medications not in current clinical use, outcomes for prostheses models that are no longer available), articles focused primarily on surgical technique with minimal or no patient information or outcomes reported, no outcomes reported or outcomes data not extractable, or duplicate report of data presented elsewhere. Review article references were checked to ensure inclusion of all possibly relevant studies. Multiple reports on the same patient group were carefully examined to ensure inclusion of only non -redundant information. The systematic review yielded a total of 999 publications relevant to preparation of the guideline.

Data on study type (e.g., published systematic review/ meta-analysis, randomized controlled trial [RCT], controlled clinical trial [CCT], observational study), treatment parameters (e.g., type of treatment, dosing, follow-up), patient characteristics (e.g., age, symptom duration, ED severity), outcomes (e.g., effects on erectile function, QoL), and AEs were extracted.

Quality of Studies and Determination of Evidence Strength. The quality of published systematic reviews was assessed using A Measurement Tool to Assess Systematic Reviews (AMSTAR).[1] Individual studies that were RCTs or CCTs were assessed using the Cochrane Risk of Bias tool.[2] The quality of case-control studies and comparative observational studies was rated using the Newcastle-Ottawa Quality Assessment Scale.[1004] Because there is no widely-agreed upon quality assessment tool for single cohort observational studies, the quality of these studies was not assessed.

The categorization of evidence strength is conceptually distinct from the quality of individual studies. Evidence strength refers to the body of evidence available for a particular question and includes not only individual study quality but consideration of study design; consistency of findings across studies; adequacy of sample sizes; and generalizability of samples, settings, and treatments for the purposes of the guideline. The American Urological Association (AUA) categorizes body of evidence strength as Grade A (well-conducted and highly-generalizable RCTs or exceptionally strong observational studies with consistent findings), Grade B (RCTs with some weaknesses of procedure or generalizability or moderately strong observational studies with consistent findings), or Grade C (RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data). By definition, Grade A evidence is evidence about which the Panel has a high level of certainty, Grade B evidence is evidence about which the Panel has a moderate level of certainty, and Grade C evidence is evidence about which the Panel has a low level of certainty.[3]

AUA Nomenclature: Linking Statement Type to Evidence Strength. The AUA nomenclature system explicitly links statement type to body of evidence strength, level of certainty, magnitude of benefit or risk/burdens, and the Panel's judgment regarding the balance between benefits and risks/burdens (Table 1).

TABLE 1: AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength

	Evidence Strength A (High Certainty)	**Evidence Strength B (Moderate Certainty)**	**Evidence Strength C (Low Certainty)**
Strong Recommendation (Net benefit or harm substantial)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears substantial Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)
Moderate Recommendation (Net benefit or harm moderate)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears moderate Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (No apparent net benefit or harm)	Benefits = Risks/Burdens Best action depends on individual patient circumstances Future research unlikely to change confidence	Benefits = Risks/Burdens Best action appears to depend on individual patient circumstances Better evidence could change confidence	Balance between Benefits & Risks/Burdens unclear Alternative strategies may be equally reasonable Better evidence likely to change confidence
Clinical Principle	A statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature		
Expert Opinion	A statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence		

Strong Recommendations are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is substantial. ***Moderate Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is moderate. ***Conditional Recommendations*** are non-directive statements used when the evidence indicates that there is no apparent net benefit or harm or when the balance between benefits and risks/burden is unclear. All three statement types may be supported by any body of evidence strength grade. Body of evidence strength Grade A in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most men in most circumstances and that future research is *unlikely to change confidence*. Body of evidence strength Grade B in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most men in most circumstances but that better evidence *could change confidence*. Body of evidence strength Grade C in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most men in most circumstances but that better evidence *is likely to change confidence*. Body of evidence strength Grade C is only rarely used in support of a Strong Recommendation. Conditional Recommendations also can be supported by any body of evidence strength. When body of evidence strength is Grade A, the statement indicates that benefits and risks/burdens appear balanced, the best action depends on the man's circumstances, and future research is *unlikely to change confidence*. When body of evidence strength Grade B is used, benefits and risks/burdens appear balanced, the best action also depends on individual man's circumstances and better evidence *could change confidence*. When body of evidence strength Grade C is used, there is uncertainty regarding the balance between benefits and risks/burdens, alternative strategies may be equally reasonable, and better evidence is *likely to change confidence*.

For some clinical issues there was little or no evidence from which to construct evidence-based statements. Where gaps in the evidence existed, the Panel provides guidance in the form of *Clinical Principles* or *Expert Opinion* with consensus achieved using a modified Delphi technique if differences of opinion emerged.[4] A *Clinical Principle* is a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. *Expert Opinion* refers to a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence.

Process. The Male Sexual Dysfunction Panel was created in 2013 by the American Urological Association Education and Research, Inc. The Practice Guidelines Committee of the AUA selected the Panel Co-Chairs who in turn appointed the additional panel members with specific expertise in this area. The AUA conducted a thorough peer review process. The draft guideline document was distributed to 35 peer reviewers. The Panel reviewed and discussed all submitted comments and revised the draft as needed. Once finalized, the guideline was submitted for approval to the Practice Guidelines Committee, the Science and Quality Council, and subsequently to the AUA Board of Directors for final approval. Funding of the panel was provided by the AUA; panel members received no remuneration for their work.

SECTION 3: BACKGROUND

Definition. ED is defined as the inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance.[5] The Panel also endorses the Fourth International Consultation on Sexual Medicine's ED definition as the consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual satisfaction.[6]

Conceptualization of ED. Sexuality is a uniquely complex aspect of humanness. Sexual function depends on intact anatomical, physiological, and behavioral capacities but occurs in the multi-layered context of a man's beliefs and values about sexuality and maleness, his upbringing and sociocultural mores, his relationship with his partner and the quality of that partnership, and the partner's beliefs and values about sexual activity. No other aspect of human functioning touches upon so many components of a man's identity and leverages this degree of complexity.

In this complex human context, the Panel conceptualizes ED as the inability to attain and/or maintain sufficient penile rigidity for sexual satisfaction. The Panel advocates that awareness of this perspective informs every aspect of the process in which clinicians support and guide men and their partners in evaluation, diagnosis, and choice of management.

Ample evidence indicates that ED is a risk marker for the presence of treatable underlying medical conditions that, left untreated, reduce quality and length of life (e.g., undiagnosed diabetes, CVD).[7,8] In addition, ED can negatively affect a man's mental health, his relationship, and his general well-being. The presence of ED, therefore, provides an opportunity to potentially address multiple issues that affect a man's general health.

Shared decision-making (SDM). SDM is the cornerstone of patient-centered care, applying the concepts of autonomy and respect for persons to the clinical encounter.[1005] SDM is a process in which information about the best available evidence for diagnostic procedures and treatments is shared by clinicians and patients. Patients are then supported during the decision-making process to express preferences and values that ultimately lead to an informed choice aligned with those preferences and values.[9] SDM rests on the assumption that individual self-determination is desirable and that patient autonomy is best supported by a strong relationship with an informed and committed clinician who respects the patient's competence and capacity to make decisions.[9] To be effective, this process requires commitments by both clinician and patient. The clinician's commitment includes communicating objectively and clearly regarding the patient's condition and the available diagnostic and treatment options, using language and concepts that are understandable to the patient.[10,11] This commitment includes the awareness that health literacy varies widely across patients and that patients at all levels of health literacy may struggle to objectively apply information about benefits and risks/burdens of various management options.[11] This commitment also requires that the clinician be cognizant that social, cultural, religious, educational, and other factors are important and valid determinants of treatment selection.[12,13] The patient's commitment includes the willingness to absorb information, ask questions, and clearly express his and his partner's preferences and values. This process results in a sharing of information and responsibility, allowing a collaborative decision regarding diagnostic and treatment plans. Because of the complexity of sexuality and the impact of a sexual relationship on a man's life, the Panel strongly advocates that a man's partner be invited to participate in this process whenever possible and clinically appropriate.

Treatment of ED. Although the principles underlying the treatment of ED are the same for all men – restoring or enhancing sexual function, improving overall physical health, and optimizing QoL and well-being for a man and his partner – every man who presents with ED is unique. Each man brings to the clinical encounter not only his symptoms, but his degree of distress; his associated health conditions; his partner's concerns and issues of relationship quality; and his sociocultural, educational, and religious context. Determining an appropriate treatment requires that the man, his clinician, and ideally his partner navigate all of these issues in order to arrive at a treatment choice that is aligned with the man and his partner's priorities and values. Men should be informed of all treatment options that are not medically contraindicated and supported in the SDM process to determine the appropriate treatment. Although many men may choose to begin with the least invasive options (i.e., oral medications), the Panel notes that it is valid for men to begin with any type of treatment, regardless of invasiveness or reversibility. Men also may choose to forego treatment. In each scenario, the clinician's role is to ensure that the man and his partner have full understanding of the benefits and risks/burdens of the various management strategies. All men, regardless of the decision to treat ED, should be strongly advised to address any underlying medical issues that may contribute to the ED and that constitute independent risk factors for poor health, reduced QoL, and decreased survival.

Epidemiology. Up to 30 million men in the United States and 150 million men worldwide are estimated to be affected by ED.[14,15] Independent risk factors for ED and CVD are well recognized and include age, smoking, diabetes mellitus, hypertension, dyslipidemia, depression, obesity, and a sedentary lifestyle.[16-19] Compelling evidence exists that the most common underlying mechanism of ED is vascular and that CVD and ED share etiologies as well as pathophysiology.[20-22] The degree of ED strongly correlates with severity of CVD, and recent studies suggest that ED may be considered a sentinel marker in men with occult CVD.[23, 24] Symptoms of ED may precede a cardiovascular event by up to five years.[25, 26] Further, when ED is present in younger men, it predicts a marked increase (up to 50 fold) in the risk of future cardiac events, suggesting that young men with ED in particular would benefit from CVD risk factor screening and intervention.[27] The increased number of men with CVD risk factors is paralleled by the worldwide increase in the prevalence of ED.[15, 28-30]

Hypertension. Hypertension is a highly prevalent condition, affecting 29.1% of U.S. adults between 2011 and 2012.[31] It is frequently associated with ED and often contributes to its etiology (i.e., hypertension-related arterial stenotic lesions). It is present in 38% to 42% of men with ED, and approximately 35% of men with hypertension have some degree of ED.[32-35]

Dyslipidemia. Data from the National Health and Nutrition Examination Survey (2003-2006) indicate that approximately 53% of U.S. adults have lipid abnormalities.[36] Up to 42.4% of men with ED also have hyperlipidemia.[33] Elevated levels of total cholesterol and low-density lipoprotein cholesterol are significantly correlated with moderate to severe ED.[33] Men with poor to very poor erectile function had twice the odds of an elevated total cholesterol/high-density lipoprotein cholesterol ratio compared with men with good and very good erectile function.[37]

Diabetes mellitus. ED is one of the most common complications of diabetes mellitus. Depending on the severity and duration of diabetes, the prevalence of ED ranges from 20% to 85%.[32,38,39] With a projected increase in the number of patients with diabetes to 29 million by 2050, a corresponding increase in those with ED is also expected. Approximately 20% of men with ED also had diabetes.[33] The Massachusetts Male Aging Study reported a 28% age-adjusted prevalence of ED in men with diabetes compared with 10% in men without diabetes (a 3-fold increased risk).[19] Prevalence of ED is higher in men with diabetes who are older than 50 years, nearly double that in age-matched men without diabetes (45.8% versus 24.1%). In addition, an increase in the relative risk of ED was associated with increased duration of diabetes.[37] ED is known to occur at an earlier age in men with diabetes than in those without it.[38] In some cases, ED may be a manifestation of previously undiagnosed diabetes mellitus, which highlights the importance of screening men with ED for diabetes-related risk factors.

Other non-cardiovascular comorbidities. Other comorbidities or risk factors commonly associated with ED include depression, smoking, premature ejaculation (PE), lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH), and other causes of voiding dysfunction, such as overactive bladder. In 3 surveys of men with ED, depression was reported by 11% and PE by approximately 30% to 60% of respondents.[33] Several studies have documented a strong association between LUTS and ED. LUTS/BPH, reported in up to 72% of men with ED, are independent risk factors for each other and share both non-cardiovascular (e.g., age, mental disorders) and cardiovascular (e.g., obesity, hypertension, diabetes mellitus) risk factors.[40-43] These relationships underscore the importance of assessing ED in men who present with these common conditions.

SECTION 4: EVALUATION AND DIAGNOSIS

The Diagnostic Approach. Insufficient literature was identified to constitute an evidence base for diagnosis of ED in clinical practice. This section, therefore, is based primarily on Clinical Principles or Expert Opinions. This section is intended to provide clinicians and men who present to them with a framework for determining whether a diagnosis of ED is appropriate; it is not intended to replace the judgment and experience of the individual clinician faced with a particular man.

1. Men presenting with symptoms of ED should undergo a thorough medical, sexual, and psychosocial history; a physical examination; and selective laboratory testing. (Clinical Principle)

The sexual response cycle is conceptualized as a sequential series of psychophysiological states that usually occur in an orderly progression; these phases were characterized by Masters and Johnson as desire, arousal, orgasm, and resolution. ED can be conceptualized as an impairment in the arousal phase of sexual response; however, impairments in arousal are likely to have secondary effects on a man's sexual interest and ability to achieve orgasm.[44,45] In addition, men may have an inadequate understanding of the sexual response cycle and may confuse changes in sexual desire, orgasm/refractory period, ejaculatory function (i.e., premature or rapid ejaculation), and conditions such as Peyronie's Disease (PD) with ED. Information regarding reduced or absent libido is important to elicit given that successful ED treatment will not address this issue, and it may continue to generate frustration and anxiety for the man and his partner. For these reasons, thoughtful, detailed, and compassionate inquiry regarding sexual concerns is necessary. Given that many men are uncomfortable broaching the topic of sexual concerns with a physician, it is critical that the physician initiate the inquiry.[46, 47]

When the man's presenting concern is ED, a comprehensive evaluation and targeted physical exam should be performed. Detailed assessment of sexual

concerns may be difficult in a clinical setting when the presenting complaint is not ED; however, basic inquiry into sexual health should be a standard of care in any encounter in which conditions are discussed or interventions contemplated that may influence a man's sexual life.

Medical, sexual, and psychosocial history. The etiology of ED is often multifactorial. General medical history factors to consider when a man presents with ED are age, comorbid medical and psychological conditions, prior surgeries, medications, family history of vascular disease, and substance use. Common risk factors for ED include vascular disease, tobacco use, neurologic disease, endocrinopathies, medication-related side effects, and psychosocial issues. Vascular issues are particularly important because in some cases they can be improved with lifestyle interventions, such as dietary changes, weight loss, and increased physical activity (see Guideline Statement 7).

Key questions regarding ED include identifying the onset of symptoms, symptom severity, degree of bother, specification of whether the problem involves attaining and/or maintaining an erection, situational factors (e.g., occurring only in specific contexts, only when with a partner, only with specific partners), the presence of nocturnal and/or morning erections, the presence of masturbatory erections, and prior use of erectogenic therapy.[47] The presence of nocturnal and/or morning erections suggests (but does not confirm) a psychogenic component to ED symptoms that would benefit from further investigation. Additional important information includes whether symptoms have been stable or are progressive; worsening symptoms may suggest the presence of progressive underlying comorbidities, particularly cardiovascular comorbidities, that need to be definitively addressed. Categorizing ED severity involves integrating findings from the history and physical, responses to questionnaire content, and any additional diagnostic tests undertaken.

It is important to distinguish ED from PE or early ejaculation, defined as ejaculation before or shortly after penile penetration[48] leading to subsequent loss of erection due to the resolution phase, and from the refractory period, an interval after ejaculation/orgasm in which the penis will not become erect and which tends to increase in duration as a man ages. Information about changes in libido, orgasm, and penile morphology (e.g., the possible presence of PD) also is needed. The timing of specific symptoms should be ascertained in relation to the onset of ED as these symptoms may be primary causes of ED or secondary effects of the ED condition.

The man's sexual partner(s) plays a key role in determining the appropriateness and efficacy of any intervention.[12,47] The ideal clinical situation is one in which the assessments and treatment discussions include the partner. If the man has a partner, then the partner's views on ED and treatment should be assessed, when possible. Additional details, such as the partner's gender, the duration of the relationship, ongoing or unresolved interpersonal/relationship issues, the partner's views on sexuality, and the partner's personal health/sexual issues, are useful to support a man in the evaluation of ED and to select an appropriate management strategy.

Physical exam. Vital signs including pulse and resting blood pressure should be assessed. Obesity is a key indicator of ED risk.[49] Consideration should be given to the assessment of waist circumference.[50] BMI is an alternative but has less specificity for central adiposity, which is a more robust indicator of underlying CVD. The general physical examination should include assessment for signs of TD (e.g., gynecomastia, under-developed facial/pubic/axillary hair). Genital examination should include assessment of penile skin lesions and placement/configuration of the urethral meatus. If the man is considering penile prosthesis implantation or surgical intervention, then documentation of flaccid stretched penile length (a proxy for erect length) can be useful information to guide expectations for outcomes.

Examination of the penis for occult deformities or plaque lesions should occur with the penis held stretched and palpated from the pubic bone to the coronal sulcus.[51] The presence/absence of a palpable plaque should not be taken as definitive evidence for clinically relevant penile deformity such as PD. If PD is suspected, then additional diagnostic procedures should be undertaken (i.e., an in-office ICI test; see AUA Peyronie's Disease guideline). General consistency of the penile tissue can be assessed. Scrotal examination may include general assessment of the scrotal skin and palpation of the testicles to assess for size, consistency, and location. Digital rectal examination (DRE) is not required for evaluation of ED; however, BPH is a common comorbid condition in men with ED and may merit evaluation and treatment. Because BPH/LUTS are commonly comorbid and detected at the same time as ED, appropriate evaluation and therapy for these conditions should be considered. For a detailed

discussion of BPH/LUTS, please see the AUA Guideline on this topic. DRE may also permit assessment of the bulbocavernous reflex, which provides information on neural integrity of the pelvis. Absence of the bulbocavernous reflex is not in itself diagnostic, however, as this reflex is absent in up to 30% of normal patients.[51] DRE should be considered for men with TD who may proceed with testosterone therapy.

Selected laboratory tests. With the possible exception of serum testosterone, glucose/hemoglobin A1c, and in some cases serum lipids, no routine serum study is likely to alter ED management. However, serum studies are an important component of evaluation because they may provide information on the etiology of ED and reveal the presence of additional conditions that require treatment. Basic studies appropriate in some men that may be ordered by the treating clinician if recent laboratory results are not available include serum BUN/ Cr, fasting lipids, fasting glucose or hemoglobin A1c, and morning testosterone (see Guideline Statement 4). Thyroid function studies (i.e. thyroid-stimulating hormone, free T4) and PSA may be appropriate for some men with ED. If elevated serum PSA is detected during evaluation for ED, then appropriate counseling should occur; please see the AUA guideline on the early detection of prostate cancer for further information.[1006]

The importance of psychological factors. Psychological factors (i.e., depression, anxiety, relationship conflict) and psychosexual issues may be primary or secondary contributors to ED.[52,53] Men may not appreciate that depression, anxiety, stress, and relationship conflicts can interfere with the physiological processes necessary for erectile function. Thoughtful discussion of these issues with men and their partners is a key component of patient education and can promote acceptance of incorporating a mental health/sexuality expert into the treatment plan. Involvement of a mental health expert with knowledge and experience to address issues of sexuality with men and their partners can benefit most patients (see Guideline Statement 6) and should be strongly considered when unresolved issues appear to be affecting the sexual relationship.[54-56] In situations in which sudden or severe ED is likely to develop (e.g., men considering definitive therapy for pelvic cancers) or in cases with complex psychosocial issues (e.g., history of sexual trauma, long-term/lifelong sexual dysfunction), early inclusion of psychosexual expertise on the treatment team is critical to development of an effective and feasible treatment plan.

2. For the man with ED, validated questionnaires are recommended to assess the severity of ED, to measure treatment effectiveness, and to guide future management. (Expert Opinion)

Validated questionnaires quantify ED severity and the consequences of ED (e.g., bother, sexual satisfaction, relationship impact). These instruments, or incorporation of their content as part of history and follow-up interviews, are useful to measure treatment effectiveness and to adjust management plans based on outcomes over time. They can be used to quantify unassisted erectile function compared to erectile function with treatment or across treatments (e.g., at a different medication doses). Questionnaires also can provide an opportunity to initiate a conversation about ED when sexual concerns are not the presenting issue. Note that questionnaires will not generate a valid score for the man who is not sexually active. In some settings, a short form validated questionnaire may be most appropriate; examples include the Erection Hardness Score (EHS)[57] and the Sexual Health Inventory for Men (SHIM).[58] The EHS is a single-item instrument that asks men to rate erection hardness on a scale that ranges from 0 (penis does not enlarge) to 4 (penis is completely hard and fully rigid). The SHIM is comprised of five questions scored from 1 to 5; total scores of 22-25 are interpreted as no ED, 17-21 as mild ED, 12-16 as mild-to-moderate ED, 8-11 as moderate ED, and 5-7 as severe ED.

For specialty practices when the presenting issue is ED, a more detailed instrument such as the full form of the International Index of Erectile Function (IIEF) may be more useful.[59,60] Multi-component surveys (e.g. the IIEF) permit a brief but nuanced assessment of sexual function in men. The IIEF consists of 15 questions that quantify 5 domains (sexual desire, erectile function, intercourse satisfaction, ejaculatory/orgasmic function, overall sexual satisfaction). The erectile function (EF) domain quantifies ED severity on a scale of 5-30; scores of 26-30 are consistent with normal erectile function, 18-25 consistent with mild ED, 11-17 consistent with moderate ED, and ≤10 consistent with severe ED.[60] Note that the SHIM is sometimes referred to as the IIEF-5 because it uses five of the six questions that comprise the IIEF-EF subscale, but the interpretation of scoring ranges is different. Clinicians should be aware that clinically significant degrees of erectile function improvement depend on initial symptom severity, with greater improvements necessary for satisfactory results in men with more severe symptoms at baseline.[61]

The Male Sexual Health Questionnaire also provides a more in-depth assessment of sexual function.[62] This instrument has 25 questions that constitute subscales for Erection, Ejaculation, and Satisfaction. A four-question version of the Ejaculation subscale also is available to measure ejaculatory dysfunction.[63]

3. Men should be counseled that ED is a risk marker for underlying cardiovascular disease (CVD) and other health conditions that may warrant evaluation and treatment. (Clinical Principle)

Risk markers are attributes that predict increased probability of a disease state but are not part of the causal pathway. ED is a risk marker for systemic CVD.[25,26,64] The relationship between ED and clinical CVD was originally posited based on a shared clinical risk factor model (including hypertension, smoking, and diabetes) and the presumed overlap in pathophysiological mechanisms including inflammation, endothelial dysfunction, and atherosclerosis.[65] In the early 2000s, longitudinal studies on CVD and ED suggested a two-way relationship such that patients with CVD are more likely to have ED and patients with ED are more likely to develop future CVD, even when adjusted for shared risk factors.[28,66-68] The Princeton Consensus Conference, an inter-specialty meeting centered on preserving cardiac function and optimizing sexual health, has identified ED as a substantial independent risk marker for CVD.[69] Data from the Prostate Cancer Prevention Trial indicated that the presence of ED was as strong a predictor of future cardiac events as cigarette smoking or a family history of myocardial infarction.[66] Most recently, the QRISK group incorporated ED as an independent risk factor into their updated 10-year cardiovascular risk model, with the presence of ED conferring a 25% increased risk for the average middle-aged man.[70]

The diagnosis of ED provides a pivotal opportunity to discuss and address cardiovascular risk. The clinician should communicate this increased risk to the man with ED, to his partner, and to other relevant clinicians (e.g., the primary care provider) so that appropriate referrals and interventions can be discussed and implemented. The diagnosis of ED, and the associated interference with sexual life, may motivate re-evaluation of lifestyle choices and create the motivation for behavioral changes that ultimately may reduce future vascular risks and improve erectile function.[16]

Because vascular disease and ED are frequently comorbid, consideration must be given to the possible cardiac risks of sexual activity. Sexual activity has been associated with increased risk for cardiac events, although the absolute risk is small, particularly in men who regularly engage in other physical activities.[71] If there is uncertainty regarding a man's exercise tolerance and fitness for sexual activity, then he should be referred for in-depth evaluation of cardiac reserve by a cardiologist.

The Princeton III criteria provide guidance regarding when further cardiac evaluation is warranted prior to treating ED by designating patients as low-, intermediate-, or high-risk.[69] Low-risk patients may be treated for ED without additional cardiovascular evaluation. Low-risk patients are men without cardiac disease who are able to exercise with no to minimal cardiac symptoms. Low-risk patients also include men with diagnosed cardiac disease who have undergone successful revascularization procedures (e.g., coronary artery stenting, coronary artery bypass graft), men with controlled asymptomatic hypertension, men with low grade heart failure (i.e., New York Heart Association Class I and II heart failure), and men with mild cardiac valve disease. All other men with cardiovascular conditions require a cardiology consultation and additional cardiac evaluation.

4. For men with ED, morning serum total testosterone levels should be measured. (Moderate Recommendation; Evidence Level: Grade C)

Total testosterone should be measured in all men with ED to determine if TD, defined as total testosterone < 300 ng/dL with the presence of symptoms and signs, is present. In the European Male Aging Study, the symptoms of weak morning erections, low sexual desire, ED, the inability to perform vigorous activity, depression, and fatigue were significantly associated with testosterone level. The three sexual symptoms had an inverse relationship with testosterone levels such that the lower the testosterone levels, the more sexual symptoms reported.[72] Men who are diagnosed as testosterone deficient should be evaluated and counseled according to the AUA Guideline on The Evaluation and Management of Testosterone Deficiency.[1007]

Circulating testosterone levels vary substantially among healthy men and are influenced by episodic and diurnal fluctuations, day to day and seasonal variations, the

presence of acute and chronic illness, and by medications.[73] These factors may account for the intra-individual variability of approximately 10% on samples drawn from the same person at the same time of day one to three days apart or three months apart.[73] Diurnal variations also are substantial. Late afternoon levels can be approximately 20% lower than morning values in young men, but the difference may be as high as 50% with a much smaller difference in older men.[74,75] Ideally, therefore, samples should be obtained in the morning.[75]

At least two morning serum total testosterone measures should be obtained before making the diagnosis of TD. If the values are similar and <300 ng/dL, then the man may be diagnosed with TD. If the values are discrepant, then a third value may be obtained at clinician discretion. Men should not have testosterone measured during acute illness, which may result in artificially low values.[76] Other conditions, such as chronic illness and use of certain medications (e.g., opioids),[77] also may alter testosterone values. Clinicians should be aware that there can be substantial variability in values across assay types and that laboratories typically have different definitions of the "normal range." Please see the AUA Guideline on this topic for more detailed guidance.[1007]

Body of evidence strength. Most studies that documented the range of testosterone values in men were observational and many did not focus on testosterone values as a primary outcome.

5. For some men with ED, specialized testing and evaluation may be necessary to guide treatment. (Expert Opinion)

For some men with ED, generally those who present with complex histories, specialized testing and evaluation may be necessary. Situations that may require more detailed evaluation include men with ED who are 1) young, 2) have a strong family history of cardiac illness, 3) have a history of pelvic trauma, 4) have failed prior ED therapies, 5) have a strong likelihood of primary psychogenic etiology, 6) have concomitant PD, and 7) have had lifelong ED.

Specialized testing should only occur if findings will affect management. Testing should be undertaken by an experienced examiner who is familiar with interpretation of results. To minimize burden, it should be established *a priori* how a given result will be interpreted and used (e.g. to influence management selection, to determine need for specialist referral).

Nocturnal Penile Tumescence and Rigidity testing. Nocturnal penile tumescence testing involves placement of two strain gauges on the penile shaft to measure radial rigidity during sleep. The device is used over several nights' sleep to quantify the number, rigidity, and duration of nocturnal erections.[78,79] The test has been used historically to differentiate psychogenic from organic etiologies for ED, with the presumption that men with psychogenic ED would have preservation of nocturnal penile erections. However, the test is prone to false negatives and may be less useful in men with impaired sleep schedules.

In office testing. ICI testing assesses veno-occlusive function of penis. In ICI testing, an erectogenic agent (e.g., prostaglandin E1, papaverine, and/or phentolamine) is injected into the corpora cavernosa of the penis.[80,81] Erectile response is assessed 5-10 minutes post injection and typically after sexual stimulation (e.g. masturbation, exposure to audiovisual sexual stimulation). For some men, the sympathetic tone and anxiety involved with in-office penile injection may override the injection agent's activity, leading to a false positive diagnosis of ED.[82,83] Repeat dosing is recommended in such cases.[84] In addition to providing information on penile vascular status, in office erectile function testing may be useful to assess for penile deformities such as PD (see AUA Guideline: Peyronie's Disease).

Penile duplex ultrasound (DUS) may be combined with ICI to produce a more detailed and quantitative assessment of penile vascular response, including arterial sufficiency.[80] DUS also permits observation of plaques and/or fibrosis of the tunica and corporal bodies. DUS is a nuanced procedure and should be performed and interpreted only by those urologists with extensive experience and training in the technique.

DUS is currently the gold-standard in penile vascular evaluation as it is minimally invasive and provides robust information about both cavernous arterial inflow and the veno-occlusive capacity of the penis.[80] These data may be useful for the following:

- differentiation of primary psychogenic versus organic etiology for ED
- assessment of arterial function in men who may warrant assessment by a cardiologist (i.e., men with predominantly vascular ED)
- identification of men with severe veno-occlusive dysfunction resulting in ED who are unlikely to respond to medical therapy

- identification of young men who may be candidates for penile revascularization procedures

Key parameters derived from DUS include peak systolic velocity ([PSV], cavernosal artery blood flow rate at start of systole) and end diastolic velocity ([EDV], cavernosal artery blood flow rate at the end of diastole). The velocities are measured in cm/s. Some authorities recommend assessment of PSV and EDV prior to ICI and after ICI with sexual stimulation. However, flaccid PSV is a poor predictor of post-ICI PSV.[85]

Different cut-points have been applied for PSV and EDV to diagnose arterial insufficiency and veno-occlusive dysfunction. Generally, a PSV <30 cm/s is considered evidence of arterial insufficiency (arteriogenic or vascular ED) and EDV >5 cm/s is consistent with veno-occlusive dysfunction. Resistive Index (defined as PSV-EDV/PSV) is an adjunctive assessment of veno-occlusive dysfunction preferred by some experts. Resistive Index values >0.80 have been cited as indicative of normal veno-occlusive function.[86] Interestingly, men with a very low PSV (<25 cm/s) have a 3-fold higher risk of major adverse cardiac events when compared to men with PSV > 35 cm/s.[87]

Biothesiometry is a non-specific term for testing intended to assess for peripheral neuropathies. Biothesiometry has been applied to the penis, most commonly by applying a device that administers vibrations of controlled and consistent intensity. This device is applied at various penile locations (typically glans but possibly other sites), and the minimal amount of vibration intensity detectable by the patient is quantified. This threshold may then be compared to vibration sensitivity on other parts of the body (e.g., fingertips). Lower thresholds for detection imply greater sensitivity and intact peripheral nerves. Vibration to assess mechanoreceptors is the modality most commonly utilized for biothesiometry; however, light touch and nociceptive nerve fibers may also be tested using the application of sharp versus dull and/or cool versus warm stimuli. Biothesiometry may be informative, but there are few data to suggest that it leads to substantive changes in management in most cases.

Invasive testing. Cavernosometry quantifies intracorporal pressure after ICI and is useful primarily for establishing a diagnosis of veno-occlusive dysfunction. Typically, cavernosometry is performed in conjunction with cavernosography (intracorporal installation of a radio-opaque dye), permitting detailed localization of any area(s) of leak. The procedure is performed by cannulation of the corpora by two butterfly needles; pressure measurements are obtained through one cannula whereas the other is used for infusion of an erectogenic agent followed by continuous infusion of injectable saline with or without radio-opaque dye to maintain a rigid erection.

Intracorporal pressure of > 60 mm Hg 10 minutes post ICI is consistent with normal veno-occlusive function. Additional metrics of potential interest include the flow to maintain erection (volume of saline infusion to maintain a fixed corporal pressure, < 3-5 mL/min being normal), pressure decay (decline of intracorporal pressure after cessation of infusion, < 45 mm Hg/30 seconds considered normal), and brachial arterial inflow gradient (differential between brachial artery and cavernous artery pressure, < 30 mm Hg considered normal). Cavernosometry and cavernosography are seldom performed in the modern era. Further, surgery for veno-occlusive dysfunction is not recommended (see Guideline Statement 22), making anatomical localization from cavernosography largely irrelevant.

Selective Internal Pudendal Angiography (SIPA) is a means to precisely elucidate the arterial inflow of the penis and is performed after ICI as corporal blood flows are too low in the flaccid state to permit interpretable information. SIPA involves cannulation of the internal pudendal artery and infusion of a radio-opaque dye to delineate penile arterial anatomy.[88] SIPA is indicated in the rare circumstance of a young patient with arterial insufficiency (confirmed by DUS and most frequently the result of trauma) who may be a candidate for a penile revascularization procedure.

Miscellaneous testing. A variety of alternative modalities have been used to assess ED, including pudendal somatosensory evoked potentials, cavernous electromyograph, bulbocavernous reflex time, and sympathetic skin response). The clinical utility of these tests is unclear at this time; they are not recommended for use outside of a research setting.[89]

SECTION 5: TREATMENT

Treatment Framework. The Panel advocates the use of a treatment framework that is not predicated on men progressing through ED treatments in order of invasiveness or reversibility (see Appendix A: Erectile Dysfunction Algorithm). Although many men may

choose to begin with the least invasive options (i.e., oral medications), any type of treatment as an initial treatment is a valid choice. For each treatment, the clinician's role is to ensure that the man and his partner have full understanding of the benefits and risks/ burdens associated with that choice.

6. For men being treated for ED, referral to a mental health professional should be considered to promote treatment adherence, reduce performance anxiety, and integrate treatments into a sexual relationship. (Moderate Recommendation; Evidence Level: Grade C)

The Panel conceptualizes ED as the inability to attain and/or maintain sufficient penile rigidity for sexual satisfaction that occurs in the complex psychosocial context that includes a man's background and beliefs about sexuality, his partner, and that partner's values relevant to sexuality. Psychosocial factors inform and influence every aspect of sexual functioning. The Panel notes that placebo effects reliably occur in trials of ED treatments (i.e., PDE5i) in which men meet diagnostic criteria for organically-caused ED; these effects suggest that even men with organically-driven ED are likely to have unmet needs for psychosocial and relationship support during ED treatment.

Psychotherapy and psychosexual counseling focus on helping patients and their partners improve communication about sexual concerns, reduce anxiety related to entering a sexual situation and during a sexual situation, and discuss strategies for integrating ED treatments into their sexual relationship. Many men avoid using ED treatments or discontinue using effective ED treatments because of beliefs about loss of masculinity and distress related to possible failure in a sexual situation. For men with predominantly psychogenic ED, providers should offer a referral to psychotherapy as either an alternative to medical treatment or as an adjunct to medical treatment. Psychogenic ED is generally driven by a man's anxiety related to the ability to achieve an erection. Medical treatments can be effective in these situations, but the addition of psychotherapy or psychosexual counseling may help men to use the medications more effectively and ultimately transition off medical ED therapies.

A diverse group of studies indicates that support and guidance from mental health professionals for the man with ED and his partner can increase the likelihood of treatment success. In trials that evaluated outcomes for medical therapies with and without psychotherapy, outcomes generally were better in the combined treatment groups. For example, Banner and Anderson (2007) randomized 53 men with psychogenic ED to use sildenafil only or sildenafil in combination with couples cognitive-behavioral therapy. After 4 weeks, more men in the combined condition met criteria for success on the IIEF-EF subscale (48%) and the Overall Satisfaction subscale (65.5%) compared to the sildenafil only condition (29% and 37.5%, respectively).[90] When cognitive-behavioral therapy was added to the sildenafil only group, rates of success became comparable to the original combined treatment group. Melnick et al. (2012) randomized 30 men with psychogenic ED to sildenafil only, group psychotherapy only, or a combined condition.[91] Three questions from the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) questionnaire were used to assess treatment satisfaction, confidence in engaging in sexual activity, and naturalness in engaging in sexual activity. At both the end of treatment and three months post-treatment, men in the group therapy only group and the combined treatment group had significantly higher scores on all three questions compared to the sildenafil only group. Titta et al. (2006) randomized 57 men to ICI alprostadil for ED post-non-nerve-sparing RP or cystectomy or ICI in combination with sexual counseling.[92] The counseling intervention involved education about successful ICI use and short-term sexual therapy. At 18 months post-surgery, IIEF-EF scores were statistically significantly higher in the combined treatment group (26.5) compared to the ICI only group (24.3) (note that the magnitude of difference is not clinically significant). Scores on the other IIEF subscales also were significantly higher in the combined treatment group compared to the ICI only group. More patients in the combined group were able to transition to sildenafil 100 mg successfully (27.5%) compared to the ICI only group (17.8%). The dropout rate in the combined group was 0% compared to 28.6% in the ICI only group.

In trials that compared combined medical and psychotherapy to psychotherapy only, the combined groups generally also exhibited greater improvement than the single treatment modalities. For example, Wylie et al. (2003) randomized 45 couples to psychotherapy alone or psychotherapy in combination with a vacuum device.[93] A greater proportion of couples reported improvement in the combined treatment group (84%) compared to the psychotherapy only group (60%).

In addition, randomized trials generally reported significant improvement in outcomes with psychological therapies compared to usual care or wait-list control groups. Three trials of internet-based cognitive-behavioral and modified Masters and Johnson therapy all demonstrated improvements in sexual functioning compared to control groups.[94-96] Meta-analysis of six trials that compared group therapy to a wait-list control or to no therapy revealed a significant reduction in ED persistence associated with group therapy (RR = 0.40; 95% CI 0.17-0.98; p<0.05).[97] Three trials reported ED persistence rates at six months of follow-up; the treatment effect continued to be significant (RR = 0.43; 95% CI 0.26-0.72; p<0.05). For men post-prostatectomy, trials reported an increased likelihood of using erectile aids compared to no therapy when men were supported by peer counseling or nurse counseling[98] and better erectile function with lower treatment dropout rates when psychotherapy was added to a medical ED protocol.[99]

Body of evidence strength. The strongest available evidence includes one high-quality systematic review and meta-analysis and a small group of randomized studies. The issues complicating interpretation of this literature are the varied therapeutic approaches used, the diverse outcome measures employed, and the range of patient types evaluated. Sample sizes in many trials were small. Trials ranged in quality from low- to high-risk of bias with most trials in the low- to moderate-risk range because of lack of information about randomization and allocation. Overall, although there is consistent evidence that psychological interventions are effective, there is a lack of a sufficient body of evidence of good quality for a particular type of psychological intervention in a particular type of patient group.

7. Clinicians should counsel men with ED who have comorbidities known to negatively affect erectile function that lifestyle modifications, including changes in diet and increased physical activity, improve overall health and may improve erectile function. (Moderate Recommendation; Evidence Level: Grade C)

The presence of ED indicates the likely presence of other conditions, particularly cardiovascular risk factors. A diverse literature that focused on lifestyle interventions, primarily diet and/or exercise interventions, in men with various comorbidities that often are present in the man with ED indicate that these interventions may have small positive effects on erectile function and broader, positive effects on overall health. The man's presentation for evaluation of ED creates an opportunity for the clinician to emphasize to him and his partner the importance of a healthy lifestyle to general health and QoL, but also to support optimal erectile function and increase the probability that ED treatments will be effective.

Men with metabolic conditions. Esposito et al. (2004) randomized obese men with ED (n = 110) without hypertension, diabetes, or hypercholesterolemia to a weight loss and increased physical activity intervention group or to a general information group.[100] After two years, BMI decreased more and physical activity increased more in the intervention group compared to the general information group. Mean IIEF-5 score improved from 13.9 to 17.0 in the intervention group but remained stable in the general information group (13.5 to 13.6). More men in the intervention group achieved an IIEF-EF score of 22 or greater (n = 17) than in the general information group (n = 3). Esposito et al. (2006) randomized men with metabolic syndrome (n = 65) to a Mediterranean or control diet.[101] ED was not an inclusion criterion. At two years of follow-up, men in the intervention group had improved endothelial function and inflammatory markers (C-reactive protein) compared to the control group. IIEF scores increased more in the intervention group (from 14.4 to 18.1) than in the control group (14.9 to 15.2). More men in the intervention group achieved an IIEF-5 score of 22 or higher (n = 13) compared to the control group (n = 2). Esposito et al. (2009) reported on 209 men with ED or men with significant ED risk factors who underwent an intensive lifestyle change intervention (tailored advice regarding how to reduce body weight, increase physical activity, and improve diet quality).[102] The intervention included sessions with a nutritionist as well as individualized guidance on exercise. Control participants were offered general oral and written information about healthy food choices and increasing physical activity without tailored advice. More men in the intervention group had scores indicating no ED at two years (n = 58) compared to the control group (n = 40). Collins et al. (2013) randomized overweight/obese men (n = 185) to a weight loss resource intervention (SHED-IT Resources), the same intervention plus access to a website with e-feedback, or a wait-list control.[103] At six months of follow-up, the two weight loss groups had lost 4.7 and 3.7 kg, respectively. Analysis of only men with ED at baseline (31.2% of sample) indicated a significant mean 3.3 point increase in the IIEF-5; the wait-list group had a mean decrease of 0.9 points. The

authors note that this trial involved no face-to-face contact with participants and no prescribed dietary or exercise regimes. Khoo et al. (2010) randomized obese men with uncomplicated diet or oral hypoglycemic-treated type 2 diabetes (n = 25) or without diabetes (n=19) to a low calorie diet using meal replacements and compared them to a third group of obese non-diabetic men on a control diet.[104] ED was not an inclusion criterion. After eight weeks, IIEF-5 scores increased significantly (from 17.8 to 20.0 in the non-diabetic group and from 8.1 to 10.3 in the diabetic group) for the two intervention groups but not for the control group. Khoo et al. (2013) placed 90 obese men on a low calorie diet and randomized them to perform moderate-intensity exercise (< 150 min/week) or high-intensity exercise (200-300 min/week).[105] At six months follow-up, the men in the high-intensity group had greater increases in the IIEF-5 (from 18.1 to 20.7) compared to the low-intensity group (18.3 to 20.1), but the difference between groups was small (0.8 points). Measures of free testosterone, serum sex hormone-binding globulin, and serum total testosterone also improved in the high-intensity group. Wing et al. (2010) randomized 372 overweight men with type 2 diabetes to a diabetes support and education group or to an intensive lifestyle intervention group that involved individual and group sessions to reduce weight and increase physical activity.[106] These data are from a subset of men who participated in the Look AHEAD trial and completed the IIEF at baseline and at one year of follow-up. At one year, the intensive intervention group had lost more weight and was more fit than the support group. IIEF-EF scores improved more in the intensive intervention group than in the support group, but the magnitude of improvement was small – 17.3 to 18.6 in the intensive group and 18.3 to 18.4 in the support group. In the intensive group, 22% reported an improvement of ED, 70% stayed the same, and 8% reported worsening symptoms. In the support group, 23% reported improvement, 57% stayed the same, and 20% reported worsening symptoms.

Men with cardiovascular conditions. Lamina et al. (2009) randomized 50 hypertensive men with ED to an interval exercise training intervention or a control condition.[107] Men who were obese, had diabetes, smoked, or had other cardiac or renal conditions were excluded. Exercise was performed in three sessions per week for eight weeks. The exercise group had greater improvements in the IIEF-EF (11.5 to 15.1) compared to the control group (8.1 to 8.9), but note that the exercise group's end of treatment score remains in the moderate ED range. Begot et al. (2015) randomized 86 men who had experienced a recent myocardial infarction to a home walking program or a usual care control group; most men (84%) had ED.[108] After one month, 93% of men in the control group had some degree of ED as measured by the IIEF-EF, with 44% having severe ED, 33% having moderate ED, and 16% having mild to moderate ED. In contrast, only 12% of men in the walking group had ED, and all were in the mild category. Kalka et al. (2013, 2015) evaluated 138 men who had been treated invasively for ischemic heart disease and who scored 21 or less on four questions from the IIEF-5.[109,110] Men were randomized into a cardiac rehabilitation group or no rehabilitation control group. Cardiac rehabilitation consisted of interval endurance training three times a week and general fitness and resistance training twice a week. After six months, the mean score on the four IIEF-5 questions was significantly higher in the intervention group (14.4) compared to the control group (12.4).

Overall, these data suggest that dietary changes, weight loss, and physical activity increases improve overall health, ameliorate comorbidities associated with ED, and result in small improvements in erectile function overall and may lead to clinically significant improvements in a subset of men. In addition, the Panel notes that given ample evidence that cigarette smokers are at a higher risk of developing ED, men who smoke should be counseled regarding the overall health benefits of smoking cessation.[111]

Body of evidence strength. Although most of the available studies are randomized trials, diverse patient populations were evaluated. These include men who are overweight/obese, have metabolic syndrome or type 2 diabetes, or who have various types of cardiovascular conditions. Most trials were not designed with ED as a primary outcome; therefore, not all patients had ED. Lifestyle interventions varied in types of exercise and dietary changes as well as in duration of the interventions. The trials in this group of studies ranged in quality from high- to low-risk of bias with about half in the high-risk category because of lack of information about randomization and allocation. Although it appears to be generally true that improvements in overall health may also improve erectile function, there is a lack of a sufficient body of evidence of good quality for a particular intervention in a particular type of patient group.

8. Men with ED should be informed regarding the treatment option of an FDA-approved oral phosphodiesterase type 5 inhibitor (PDE5i), including discussion of benefits and risks/ burdens, unless contraindicated. (Strong Recommendation; Evidence Level: Grade B)

The FDA-approved oral PDE5i available for management of ED in the U.S. include sildenafil, tadalafil, vardenafil, and avanafil. Several other PDE5i have been approved for use in other countries.

The mechanism of action for all commercially available PDE5i is similar. PDE5i inhibit the phosphodiesterase type 5 enzyme from breaking down cyclic guanasine monophosphate (cGMP). This inhibition results in an increase in the concentration of penile cavernosal cGMP that then causes smooth muscle relaxation in the corpus cavernosum vasculature resulting in increased erection hardness and duration in men with ED who have sufficient intact vasculature.

Contraindications. The use of nitrate-containing medications in combination with a PDE5i can cause a precipitous drop in blood pressure; men taking nitrates regularly should not use PDE5i medications. Men who carry sublingual nitroglycerin for angina should be advised not to use this medication within 24 hours of taking a PDE5i, and possibly longer in the case of use of a PDE5i with a long half-life (i.e., tadalafil). Many other medications also potentially can interact with or influence the metabolism of PDE5i, including anti-depressants, anti-fungals, anti-hypertensives, and HIV/ AIDS drugs. The clinician who prescribes PDE5i must be conversant with all potential medication contraindications.

For detailed discussion of cardiovascular contraindications to PDE5i use, see guidance from the Princeton III guidelines.[69] In men with mild to moderate hepatic or renal impairment or men with spinal cord injury, PDE5i should be used with caution at least initially at lower doses given the potential for delayed metabolism. In men with severe renal or liver disease, use of PDE5i is generally not recommended.

Efficacy. The PDE5i medications have been extensively studied; nearly a quarter of a million men have been evaluated from the general ED population[#] and approximately 25,000 men evaluated from various special populations* (e.g., diabetes, BPH/LUTS, post-prostatectomy, post-spinal cord injury). Most studies of men from the general ED population involved on-demand use of medications (approximately 90%). Of the four FDA-approved PDE5i drugs, most men were administered sildenafil or vardenafil with relatively fewer men administered tadalafil and limited data available on avanafil (fewer than 2,000 men).

The general ED population. Data from individual studies and trials, including analyses that pooled data across multiple trials[112-303] and reports of published systematic reviews[304-319] suggest the following major findings:

i.) The PDE5i medications, particularly sildenafil, tadalafil, and vardenafil, appear to have similar efficacy in the general ED population. Relative efficacy is less clear for avanafil because the published literature is limited. In general, the literature lacks trials in which medications were compared to each other. However, given the large number of trials and participants overall, it is likely that any differences across the most frequently studied medications would be evident. The pattern of similar efficacy across medications is consistent across various measures of erectile function. The most frequently used measure across trials was the erectile function subscale of the IIEF. Table 2 presents changes (minimum, maximum, mean) in IIEF-EF scores by medication from the pre-treatment baseline to post-treatment for trials that provided extractable information; the magnitude of change across medications is similar.

TABLE 2: General ED Population:

Change in IIEF-EF Scores from Pre-Treatment Baseline to Post-Treatment

Treatment	# study arms^	Minimum	Maximum	Mean
Placebo	62	-1.60	7.10	+1.78
Sildenafil	26	+1.70	+11.75	+9.00
Tadalafil	37	+1.98	+12.00	+7.82
Vardenafil	26	+5.30	+12.90	+8.80
Avanafil	5	+5.50	+9.40	+8.10

#Studies of the general ED population included men who had a variety of underlying conditions that could contribute to ED symptoms without selecting men for any particular condition.

*Studies of special populations explicitly recruited men with a specific underlying condition (i.e., diabetes, BPH/LUTS, post-radical prostatectomy, etc.).

^ The term "study arm" refers to a group of patients who experienced the same treatment (e.g., received placebo, received active medication, received a particular dose of active medication) for whom data were extractable.

When data from the subset of trials that provided sufficient information for meta-analysis were pooled (approximately 60% of the studies included in the table above), the analysis yielded similar values across active medications (for tables of additional frequently-used measures and associated plots, see Appendix B).

ii.) Dose-response effects across PDE5i medications are small and non-linear (i.e., doubling the dose does not double the effect). Higher doses may produce higher average effects, but dose groups generally were not statistically significantly different unless comparing extremely low doses to extremely high doses. The magnitude of average increased effects with increased doses is small and often not clinically significant (e.g., a one or two point increase on the IIEF-EF; see Appendix B). In contrast, stronger dose-response patterns are present for many AEs (see below regarding AEs), suggesting the need for men to use the lowest dose that produces acceptable outcomes.

iii.) On-demand dosing versus daily dosing for tadalafil appears to produce the same level of efficacy. For detailed tables, see Appendix B. Note that daily dosing trials generally used lower doses than did on-demand trials and that only tadalafil is currently FDA-approved for daily dosing, although two trials of vardenafil evaluated daily dosing. Trials of sildenafil and avanafil used only on-demand dosing.

Special populations. Fewer studies focused on special populations, but in general, findings are similar to those reported in the general ED population.[320-499] For example, the available data suggest that the PDE5i have similar efficacy. Note, however, that not all PDE5i have been evaluated in all special populations of men with ED. For men with diabetes, sildenafil, tadalafil, and vardenafil appear equally effective with limited data reported for avanafil. For men with BPH/LUTS and ED, sildenafil and tadalafil appear to have similar efficacy to treat ED. There are no studies of vardenafil or avanafil that focused on men with BPH/LUTS and ED. All studies of men with BPH/LUTS and ED used daily dosing because of the beneficial urinary tract effects of PDE5i. For men with ED post-prostatectomy, efficacy also appears similar across the PDE5i but with limited data for avanafil. For men post-RT for prostate cancer, sildenafil and tadalafil appear to have similar efficacy, but the tadalafil data are limited. No studies evaluated vardenafil or avanafil in men post-RT for prostate cancer. For other special populations (i.e., spinal cord injury, renal transplant) there are insufficient data for different PDE5i to come to a definitive conclusion. Overall, there are insufficient data at different PDE5i doses to evaluate dose-response effects in special populations. The data suggest, however, that men with diabetes and men who are post-prostatectomy have more severe ED at baseline and respond less robustly to PDE5i (for detailed discussion of men who have undergone treatment for prostate cancer, see Guideline Statement 11).

AEs. Most AEs associated with the administration of PDE5i are mild to moderate. The most frequently reported AEs were dyspepsia, headache, flushing, back pain, nasal congestion, myalgia, visual disturbance, and dizziness (data for avanafil are limited; see Appendix B for detailed tables). On average, rates of dyspepsia and dizziness were relatively similar across sildenafil, tadalafil, and vardenafil. There were sufficient dyspepsia data to meta-analyze. When studies were collapsed across medications, the Relative Risk (RR) for dyspepsia in an active treatment arm compared to placebo was 3.21 (95% CI 2.5-4.3; $p<0.05$; I^2 n.s.). For individual PDE5i, the RRs were statistically similar (sildenafil – 2.7; 95% CI 1.9-3.8; $p<0.05$; $I^2=0$; tadalafil – 4.2; 95% CI 2.3-7.6; $p<0.05$; $I^2=0$; vardenafil – 4.2; 95% CI 2.3-7.4; $p<0.05$; $I^2=0$).

Raw data suggested that sildenafil and vardenafil were associated with the highest rates of headache and flushing. When these data were meta-analyzed, the RR for headache was statistically significantly higher for vardenafil (RR = 4.1; 95% CI 2.9-5.6; $p<0.05$; I^2 n.s.) compared to tadalafil (RR = 2.0; 95% CI 1.5-2.8; $p<0.05$; I^2 n.s.). The RR for sildenafil was 2.62 (95% CI 2.1-3.3; $p<0.05$; $I^2=36\%$) but characterized by significant heterogeneity reflected in raw values that ranged from 0% to 32% and resulting in an RR that was not statistically different from those for the other PDE5i. For flushing, there was a trend ($p<0.06$) for the RR for vardenafil to be statistically significantly higher (RR = 7.6; 95% CI 5.1-11.5; $p<0.05$; $I^2 = 0\%$) compared to tadalafil (RR = 2.5; 95% CI 1.2-5.3; $p<0.05$; $I^2 = 0\%$). The RR for sildenafil was 4.8 (RR = 4.8; 95% CI 3.5-6.5; $p<0.05$; I^2 n.s.) and not statistically different from the other PDE5i. Raw data and meta-analyzed values were generally consistent for back pain and myalgia (tadalafil tended to have higher rates), nasal congestion (vardenafil tended to have higher rates), and visual disturbance (sildenafil tended to have the highest rates).

Tadalafil was the only medication for which there were substantial on-demand versus daily dosing studies. Generally, daily dosing (which allows men to take a lower dose) was associated with lower rates of frequently-reported AEs – particularly for headaches – compared to on-demand use, which requires a higher dose (see Appendix B). Meta-analysis of headache data indicated that on-demand dosing was associated with a significantly higher risk of headache (RR = 2.65; 95% CI 1.8-3.8; $p<0.05$; $I^2 = 0\%$) compared to daily dosing (RR = 1.1; 95% CI 0.6-1.8; $p>0.05$; $I^2 = 0\%$; risk not significantly different from placebo groups).

Most AEs followed a dose-response pattern such that men in active treatment arms reported statistically significantly higher rates of AEs than did men in placebo arms, and the percentage of men reporting a particular AE increased as dose increased. Within individual studies, however, the differences between dose groups were usually not statistically significantly different.

When means for the general and four special populations (men with diabetes, BPH/LUTS, post-RP, or post-RT) for which there are substantial data were examined, it appears that men post-RP and men post-RT reported substantially higher rates of AEs than did men in the general ED population (see Appendix B). Whether men who have had prostate cancer treatment are more likely to experience AEs or are more likely to report AEs is not clear. Men post-RP reported higher rates of AEs in response to sildenafil than in response to other PDE5i. Men post-RT reported high rates of AEs across PDE5i and in placebo groups. The high rates of AEs reported by men in placebo groups suggest that men post-RT may have heightened sensitivity to body sensations and may have unmet needs for psychosocial support.

Other concerns. *Nonarteritic anterior ischemic optic neuropathy (NAION).* NAION is a rare visual condition characterized by the sudden onset of loss of vision in one eye. The estimated annual incidence is 2.5 to 11.8 cases per 100,000 men aged 50 years or older with older age, Caucasian ethnicity, small optic discs with low cup-to-disc ratio, and various kinds of vascular conditions appearing to confer greater risk.[500-502] Several studies have suggested that PDE5i use is associated with an increased risk of NAION,[503-505] although the absolute risk is small (3 additional cases per 100,000 men aged 50 years or older.[506] Men in higher-risk groups (e.g., older men, men of Caucasian ethnicity, men with vascular risk factors) should be counseled about this small increased risk, including the fact that the absolute risk of NAION is extremely low with or without the use of PDE5i, and that the association does not imply causation.

Skin cancers. Several investigations have addressed the possible relationship between PDE5i use and increased risk for skin cancers, particularly malignant melanoma. Most papers report a small positive association for at least one indicator of increased risk.[507-511] However, none of the available studies was designed to adequately address the potentially important confounders of increased medical surveillance among PDE5i users that could result in more frequent detection of skin cancers and the possibility that men who take PDE5i have more ultraviolet radiation exposure than do non-PDE5i using men. The issue of ultraviolet radiation exposure via sunlight is suggested by the positive association between PDE5i use and increased risk of basal cell carcinoma and solar keratosis – both conditions related to sun exposure.[511] Further, men with a history of solar keratosis, an indicator of high sun exposure, were more likely to become PDE5i users.[511] Overall, the available findings fail to convincingly satisfy most of Hill's causal criteria (i.e., strength, consistency, specificity, temporality, biological gradient in which higher levels of exposure increase risk, plausibility) for determining whether an epidemiological association constitutes a causal relationship.[512] The Panel interpreted these data to indicate that there is no increased risk of skin cancers reliably associated with PDE5i use.

Prostate cancer recurrence. Several studies have focused on the possible relationship between PDE5i use after prostate cancer treatment and an increased risk of prostate cancer recurrence. The initial report of this relationship indicated that PDE5i use was an independent risk factor for prostate cancer recurrence among men with localized disease who underwent bilateral nerve-sparing RP.[513] However, three subsequent studies that performed a more nuanced analysis of this relationship (i.e., assessed dose-response relationships) did not confirm this finding[514-516] for men post-RP or post-RT. In contrast, all three studies reported that PDE5i use non-significantly reduced prostate cancer recurrence rates. The Panel interpreted these data to indicate that there is no increased risk of prostate cancer recurrence associated with PDE5i use after prostate cancer treatment.

Body of evidence strength. Body of evidence strength for outcomes and AEs associated with PDE5i therapy for the general ED population is Grade B. Most of the data were provided by RCTs that ranged in quality from poor (high risk of bias based on the Cochrane rating system) to high-quality (low risk of bias), with the majority of RCTs rated as moderate-quality (unclear risk of bias). The most frequent reason for a rating of unclear risk of bias was inadequate information regarding randomization and/or blinding. Strengths of this group of studies are the use of randomization, blinding, and placebo control groups to protect internal validity and the extremely large sample sizes. The weaknesses of these studies are in two areas. First, approximately 70% of studies had industry associations in terms of authorship affiliations and/or financial support. Second, most trials (approximately 75%) ended at three months or less of follow-up. Given that PDE5i use is likely to continue for periods much longer than three months, there is an important gap in information regarding the long-term treatment consequences.

Published systematic reviews, meta-analyses, and network analyses also constitute an important source of evidence. The body of published systematic reviews on the effects of PDE5i medications in the general ED population constitutes Grade B evidence. AMSTAR scores, which range from 1 to 11 points and quantify the methodological quality of the systematic review, ranged from 3 to 10 points with one-half of studies scoring 6 or less. The most common deficits were inadequate study selection and data extraction procedures, failure to use quality ratings in interpreting findings, failure to report or address heterogeneity across individual studies, and failure to assess for publication bias. Most published systematic reviews exhibited an additional weakness that can affect validity – collapsing data across general and special populations. In addition, all systematic reviews were handicapped by the fact that many RCTs did not provide sufficient information for data to be included in a meta-analysis. Body of evidence strength for special populations was Grade C. Limited numbers of randomized studies were available for specific subgroups, limiting conclusions.

9. When men are prescribed an oral PDE5i for the treatment of ED, instructions should be provided to maximize benefit/efficacy. (Strong Recommendation; Evidence Level: Grade C)

Men who are prescribed a PDE5i should be carefully instructed in the appropriate use of the medication. In particular, it should be explained that sexual stimulation is necessary and that more than one trial with the medication may be required to establish efficacy. It should also be explained that the medications differ in onset of action, duration of action, and whether food intake limits efficacy (see Table 3).

TABLE 3: Characteristics of PDE5i Medications

PDE5i	Onset of action	Duration of action	Effect of food intake
Avanafil	15-30 min	Up to 6 hours	Not affected
Sildenafil	30-60 min	Up to 12 hours	High-fat meal decreases efficacy
Vardenafil	30-60 min	Up to 10 hours	High-fat meal decreases efficacy
Tadalafil	60-120 min	Up to 36 hours	Not affected

Studies of men who report non-response to PDE5i indicate that incorrect use (e.g., lack of sexual stimulation, medication taken with a large meal) accounts for 56% to 81% of treatment failures.[517-520] When men were re-educated regarding appropriate medication use, including medication-specific requirements, from 23.6% to 58.5% experienced treatment success.

10. For men who are prescribed PDE5i, the dose should be titrated to provide optimal efficacy. (Strong Recommendation; Evidence Level: Grade B)

When prescribing a PDE5i, the clinician must balance these priorities: the goals of the man and his partner for successful sexual activity, the need to prescribe an effective PDE5i dose, and the need to minimize AEs. It is important for clinicians, men who desire a PDE5i, and partners to communicate regarding how treatment success is defined. The clinician's goal is to work with the man and his partner to find the dose that meets treatment expectations without resulting in unacceptable levels of AEs. Although in the context of fixed-dose clinical trials, dose groups generally did not exhibit statistically significantly different average response levels. For the individual patient, dose titration is a key step to optimize efficacy. This process may require that initial doses are titrated up or down until the optimal dose is identified. To minimize

distress, men and partners should be counseled that initial non-response or inadequate response may be readily overcome with a dose increase just as initial unacceptable levels of AEs may be ameliorated with a dose decrease. Given that men with diabetes or post-prostatectomy often present with more severe levels of ED, clinicians may consider initiating therapy at a higher dose.

The clinician should be aware that when PDE5i studies were examined in aggregate, the differences in response rates between dose groups were extremely small, rarely statistically significant, and generally not clinically significant. For example, in studies in which men were administered 50 mg sildenafil, pre-treatment IIEF-EF scores averaged 14.0 and post-treatment scores averaged 22.6; in studies in which men were administered 100 mg sildenafil, pre-treatment IIEF-EF scores averaged 14.4 and post-treatment scores averaged 23.8 (see table in Appendix B). This pattern in which large dose increases (i.e., doubling the dose) resulted in small differences in average response level or rate was consistent across the PDE5i (see discussion under Guideline Statement 8).

In contrast, although reported AE rates vary considerably from study to study, on average AE rates generally increased as dose increased (see discussion under Guideline Statement 8 and data in Appendix B). The goal of dose titration, therefore, is to achieve patient- and partner-defined success while minimizing AEs.

As part of the process of identifying the optimal dose, men may be offered dosing frequency changes or different PDE5i. For example, Kim, Seftel et al. (2013) evaluated 623 men who had suboptimal results with on -demand maximum dose sildenafil, tadalafil, or vardenafil; men were offered daily tadalafil (2.5mg or 5mg) or placebo for 12 weeks.[521] Approximately 40% of men in the tadalafil groups achieved IIEF-EF scores indicating normal erectile function (IIEF-EF ≥26) compared to 12% in the placebo group. Carson, Hatzichristou et al. (2004) reported that when men unresponsive to sildenafil were randomized to flexible dose vardenafil (5mg to 20mg) or placebo, positive responses to the Sexual Encounter Profile (SEP) 2 question doubled (from 30.3% at baseline to 62.3% post-treatment), and positive response to the SEP 3 question quadrupled (from 10.5% at baseline to 46.1% post-treatment).[522] However, these approaches will not benefit men with severe arterial insufficiency.[523-525]

For men who appear to have ED primarily or entirely of psychogenic origin, consideration should be given to dose reduction and/or medication weaning once treatment of the psychological issues has occurred and confidence has been restored.

Body of evidence strength. Body of evidence strength for outcomes and AEs associated with dose titration of PDE5i therapy is Grade B. See discussion under Guideline Statement 8.

11. Men who desire preservation of erectile function after treatment for prostate cancer by radical prostatectomy (RP) or radiotherapy (RT) should be informed that early use of PDE5i post-treatment may not improve spontaneous, unassisted erectile function. (Moderate Recommendation; Evidence Level: Grade C)

In the modern era of prostate cancer management, improving functional outcomes, particularly sexual function, has become a priority. Accordingly, "penile rehabilitation" or "erectile function rehabilitation" has emerged as a clinical management practice that focuses on preserving erectile capability that is at risk of decline during treatment of pelvic malignancies such as prostate cancer.[526,527] Although this practice is widely accepted as a general concept, it is variously defined.[528] In strict terms, "penile rehabilitation" comprises strategic approaches that promote natural erectile capability and facilitate resumption of medically unassisted sexual activity after prostate cancer treatment.[529] However, more broadly considered, "penile rehabilitation" encompasses the application of interventions in any form that address the negative effects of cancer treatment on erectile ability as well as related health aspects.[526,527,530] This practice differs conceptually and practically from treating ED that is present post-prostate cancer therapy with oral or other therapies.

Clinically localized treatments such as RP and RT as well as systemic therapies used for advanced disease (e.g., hormonal therapy), result in various degrees of ED. Although erectile function outcomes in these contexts have improved over time, many men will experience clinically significant ED as a consequence of prostate cancer treatment. With respect to RP, for example, the development of cavernous nerve-sparing surgical procedures (i.e., the application of techniques that preserve the peri-prostatic penile nerve supply required for penile erection) has led to improved rates

of erectile function recovery,[531,532] but even with use of this technique many men will experience ED.[533-535] A meta-analysis of studies with >12 months follow-up post-RP reported that use of a bilateral nerve-sparing technique was associated with a 60% erectile function recovery rate (95% CI 58.0 – 62.0; 21 studies) compared to a rate of 47% (95% CI 42.0 – 53.0; 12 studies for use of a unilateral nerve-sparing technique.[536] For RT, modifications in the delivery of radiation have resulted in better erection preservation after treatment,[537] but rates of new-onset ED have been reported at 36% and 38% two and three years post-RT, respectively.[538]

The natural history of erectile function loss and recovery depends on the type of prostate cancer intervention. The classically observed immediate effects of RP on penile erection are absent responses under all stimulatory conditions.[539,540] When cavernous nerves are spared, a gradual recovery of erectile function is possible, although this recovery may be delayed for several months at a minimum. Commonly, the interval of spontaneous erectile function recovery occurs 12 to 24 months after surgery, although recovery may still be possible as much as 36 months after surgery.[541] RP studies indicate that while improvements in erectile function may occur over time post-operatively, relatively few men recover baseline erectile function, particularly those over age 60 years at the time of surgery.[542] When cavernous nerves are not spared, which may occur when wide excision of locally advanced prostate cancer is necessary or when nerve-sparing attempts are inadequate, the expected effect is an unrecoverable loss of erectile function.[539,540] The natural history of erectile impairment after radiation, in contrast, involves a delayed onset of ED that may occur 24 to 36 months after treatment and may worsen over time thereafter.[543]

The pathophysiology of post-prostatectomy ED principally involves "neuropraxia" (i.e., temporary traumatic functional loss of nerve function) that may occur despite "nerve-sparing," or complete nerve function loss that occurs after cavernous transection or removal. In addition to nerve injury, concomitant injury of accessory penile vasculature and secondary structural and functional derangements of the denervated cavernosal tissue may contribute to ED.[527] The pathophysiology of post-radiation therapy ED involves radiation-induced damage of the nerve and vascular supply of the penis.[544]

Strategies for penile rehabilitation aim to prevent or reduce the extent of long-term erectile impairment and/or latency of erectile function recovery. The objective of these strategies is to counteract pathophysiologic mechanisms of ED induced by prostate cancer treatments. Theorized objectives at the tissue or cellular level include improving oxygenation of cavernosal tissue, promoting protection of penile vascular and sinusoidal endothelial function, and reducing cavernosal tissue damage associated with the penile denervation effect.[545] The rationale for their use on the molecular level centers on biological principles of sustaining and modulating nerve function (i.e., neuroprotection, neurogenesis, and neuroregeneration) as well as vascular/cavernosal tissue function (i.e., vasculoprotection, vasculogenesis, angiogenesis and anti-fibrosis).[546-548]

A variety of treatments have been introduced as penile rehabilitation strategies, with prescribed recommendations for their implementation that consider timing, schedule, and delivery of treatment. It is strongly perceived that rehabilitation should be initiated at the beginning of if not before prostate cancer treatment with its continuation over a prescribed interval thereafter. The rationale for this timing is that an early, preventative scheme is maximally protective of mechanisms of penile erection.[526,527,545] A common strategic approach has been to apply erectogenic treatments used to treat ED according to precise rehabilitative protocols. This approach is based on the theory that induced penile vascular blood flow enhances the functional status and recovery of erectile tissue.[545]

PDE5i have been investigated most extensively for the purpose of penile rehabilitation because of their non-invasiveness and ease of administration. Several rigorous randomized, CCTs have been performed in settings of RP and pelvic irradiation.[429,430,438,470,526,527] These trials have not demonstrated that early PDE5i use (i.e., within 45 days of prostate cancer therapy) improves unassisted erectile function. Meta-analysis performed for this guideline of the three trials that compared a PDE5i to placebo among men who had RP yielded a pooled RR of 1.0 (95% CI 0.66 – 1.64; p=0.85; nonsignificant heterogeneity), indicating no difference in rates of restored erectile function between groups. In addition, although most studies reported that PDE5i are effective in assisting erections on-demand during the course of the trial, early administration of PDE5i does not improve later responses to these medications compared to early administration of placebo.

One possible confounding issue is whether the treatment schedule of 12 months or less in these trials was insufficient to provide erectile function rehabilitative benefit; it is possible that a longer term treatment schedule may be necessary to achieve erectile health recovery effects. Use of other types of therapy in a rehabilitative framework, such as VED or ICI, also has been reported.[549] Although some studies reported positive findings, given the small numbers of men treated and the lack of control groups in several studies, more mature data are needed to establish these therapies as proven.

Overall, the Panel interpreted the PDE5i data to indicate that erectile function rehabilitative protocols tested to date remain unproven. Psychosocial support, however, is an important strategy for penile rehabilitation. Given the impact of ED after prostate cancer treatment, particularly its suddenness and severity for many men undergoing RP, it is not surprising that men in this setting commonly experience depression, anxiety, and relationship stress.[550,551] Psychotherapeutic regimens have been prescribed with reported rehabilitative benefits of such treatment.[526] Clinicians should educate men regarding the sexual effects of prostate cancer treatments and set realistic expectations regarding functional recovery, including the possibility that recovery may be more challenging for men who have multiple ED risk factors. Men should be coached and monitored during and after prostate cancer treatments.[552] These efforts, including combining psychosocial support and somatic erectogenic treatments, may motivate men and their partners to maintain intimacy during sexual function recovery.[526,530,551]

Body of evidence strength. Most of the available randomized trials were rated as having an unclear risk of bias (moderate quality) because of lack of information regarding randomization and/or blinding. Whether a sufficient duration of treatment has been tested to achieve erectile function restoration is unclear.

12. Men with ED and testosterone deficiency (TD) who are considering ED treatment with a PDE5i should be informed that PDE5i may be more effective if combined with testosterone therapy. (Moderate Recommendation; Evidence Level: Grade C)

If a man with ED has TD, defined as total testosterone <300 ng/dl and the presence of symptoms and signs, and is considering ED treatment with a PDE5i, then he should be counseled that testosterone therapy in combination with a PDE5i is more likely to be effective than the PDE5i alone. Five randomized trials evaluated PDE5i treatment in combination with testosterone therapy compared to a PDE5i alone[553-556] or compared to testosterone alone;[557] all men had TD (variously defined). Four trials administered sildenafil on-demand; one trial administered daily tadalafil.[554] Modes of testosterone administration varied across trials and included oral testosterone, testosterone patch, and testosterone gel. Criteria for testosterone deficiency also varied across trials. Primary outcome measures were the IIEF, IIEF-EF, or SHIM. Across trials, men who received combined therapy reported greater erectile function score increases compared to baseline levels and higher erectile function scores at treatment end than did men who received a PDE5i alone or testosterone alone. Meta-analysis performed for this guideline of the four studies that compared combined treatment to a PDE5i alone yielded a weighted mean difference of 2.69 points on the IIEF-EF between treatment groups (95% CI 0.96-4.41; p=0.002; nonsignificant I^2). An additional group of observational studies reported that the addition of testosterone to a PDE5i among men in whom the PDE5i alone was ineffective resulted in improved erectile function.[558-562] Although the differences between the combined and monotherapy groups in the randomized studies were not statistically significant in all trials, the Panel interpreted these data to indicate that for symptomatic testosterone deficient men, optimum efficacy of PDE5i medication is most likely to be achieved when testosterone levels are normalized. Similar conclusions were reported by three published systematic reviews.[308,563,564]

The Panel notes that it is likely that the restoration of testosterone levels supports maximum efficacy of other ED treatment options; however, there are insufficient data at this time to address other combined treatments.

Men should be advised that testosterone therapy is not an effective mono-therapy for ED.[565-567] If the man's goal is amelioration of ED symptoms, then he should be counseled regarding the need for ED therapies in addition to testosterone therapy. However, testosterone therapy may provide more global health benefits (e.g., improved bone density). For detailed information on possible health benefits of testosterone therapy, AEs associated with testosterone therapy, and

recommended monitoring protocols for men prescribed testosterone, see AUA guideline on this topic.[1007]

Body of evidence strength**.** The best evidence consists of five randomized trials and three published systematic reviews. The consensus across reviews is that the available trials are mostly of low quality. Four trials compared combined testosterone + PDE5i treatment with PDE5i only treatment; one trial compared combined treatment to testosterone only treatment. The trials differed in mode of testosterone administration and in PDE5i dosing regimen (i.e., on-demand versus daily). Trial sample sizes were small with three of five trials evaluating samples smaller than 40 men (two trials had sample sizes of 10 per treatment group). Definitions of TD differed across trials and follow-up durations were short, ranging from one to 3.5 mos.

13. Men with ED should be informed regarding the treatment option of a vacuum erection device (VED), including discussion of benefits and risks/ burdens. (Moderate Recommendation; Evidence Level: Grade C)

Vacuum devices are associated with high rates of patient and partner satisfaction and are an effective and low-cost treatment option for select men with ED. They are effective in the general ED population as well as in men with diabetes, spinal cord injury, post-prostatectomy, and other conditions.[93,496,568-617] Only VEDs containing a vacuum limiter (a feature that limits the amount of vacuum pressure and reduces the potential for penile injury) should be used, whether purchased over-the-counter or procured via prescription.

Studies on VED satisfaction and efficacy largely pre-date the era of the IIEF, EDITS, and the Self-Esteem And Relationship Questionnaire (SEAR), etc. Clinicians should be aware that many studies were carried out before the availability of PDE5i medications, and some studies suggest that when men have a choice, more men prefer PDE5i[496,618] The most commonly-reported outcome measure was in terms of a responder criterion and/or patient and partner satisfaction rates (see Table 4). Responders were usually defined as men who obtained an erection sufficient for intercourse with use of the device although some studies defined responders as men who purchased the device after a trial period or who continued to use the device. Rates for patient and partner satisfaction and for successful responses exhibited a wide range but the majority of studies reported high rates. Of the 12 studies that reported patient satisfaction rates, six rates were 80% or higher and eleven studies reported rates of 60% or higher. Of the seven studies that reported partner satisfaction rates, all rates were above 70% except for one. Of the 28 studies that reported a success criterion, 19 reported rates of 75% or higher. Twenty-five studies reported rates of 56% or higher. Lewis, Witherington (1997) performed a survey of approximately 6,000 VED users and reported that 75% remained continuous users, 83.5% reported having sex as frequently as desired, and 70% reported improved relationships (note that this survey was performed before the introduction of PDE5i).[587] One study reported findings in terms of IIEF scores. Khayyamfar, Forootan (2013) reported on 1,530 men at an unspecified follow-up duration.[583] Statistically significant improvements in all the IIEF subscales were reported with vacuum device use. These authors also reported that 92.7% of patients successfully used the device to have intercourse.

TABLE 4: Outcomes for VED Studies

Measure	# studies	Min	Max	Mean
Patient satisfied percent	12	34	100	76.49
Partner satisfied percent	7	45	100	77.39
Responder other criteria Percent	28	20	100	76.23

In men who are PDE5i non-responders, VED may have a role as a "rescue" device. A study of 69 men who had failed PDE5i therapy and were subsequently treated with a combination of PDE5i and VED for 4 weeks demonstrated a significant increase in the IIEF, SEP 2 and 3, and the Global Patient Assessment Scale indicating that this regimen may be effective in at least a subset of this cohort.[619]

Men with diabetes. One randomized design[608] and six observational studies[602-607] evaluated the use of vacuum devices in diabetic men. The randomized design compared men who used a vacuum device with 100 mg sildenafil to men who used only a vacuum device; these patients were non-responders to sildenafil alone, and all had Type 2 diabetes. Two studies evaluated a mixed group of Type I and II diabetes patients. One study compared patients with Type I to patients with Type II diabetes. Three studies did not specify diabetes type. Follow-up durations ranged from 2 months to two years. Sample sizes were small except for Israilov et al. (2005), which began with 162

patients.[605] The duration of diabetes ranged from 5.3 years to 17.5 years.

Sun, Peng (2014) reported that men in the VED + sildenafil group had larger increases in SHIM scores and reported higher rates of "yes" responses to the SEP 2 and 3 than did men in the VED only group.[608] Five observational studies reported outcomes in terms of patient satisfaction (two studies – range 81.2 to 84%), partner satisfaction (two studies – range 72.7 to 80%), and/or a successful responder criterion. These varied from the achievement of an erection sufficient for intercourse to an undefined "positive response." Successful responses ranged from 70.4% to 90%. Pajovic, Dimitrovski (2017) reported outcomes in terms of IIEF scores; at 6 months scores on the IIEF-EF subscale had increased significantly among men with Type I and men with Type II diabetes as had scores on the intercourse satisfaction subscale and the overall satisfaction subscale.[606]

Men post-prostatectomy. Three randomized designs and one observational study evaluated the use of VED in men who were post-prostatectomy. Kohler, Pedro (2007) randomized men who had undergone unilateral or bilateral nerve-sparing RP to early (one month postoperatively) or late (six months postoperatively) use of a VED.[620] Engel (2011) compared men post-bilateral nerve-sparing prostatectomy who used tadalafil to men who used tadalafil + vacuum device.[609] Raina, Agarwal (2006) compared no treatment to use of a vacuum device in a group of men who had bilateral, unilateral or non-nerve-sparing prostatectomy.[611] Nason, McNamara (2016) also evaluated a mixed group of men post-RP.[610] The three randomized studies began treatment approximately one -month post-RP with the goal of optimizing unassisted erectile function. The observational study began treatment 8.7 months post-RP with the goal of treating ED. Sample sizes were extremely small across studies.

Kohler, Pedro (2007) reported that unassisted (i.e., without use of the device) IIEF-EF scores at 3 and 6 months were significantly higher in the early intervention group compared to the late group (11.5 and 12.4 versus. 1.8 and 3.0) and that stretched penile length was preserved in the early intervention group but reduced by mean 2 cm in the late intervention group.[620] Engel (2011) reported that men in the tadalafil + vacuum group had higher unassisted SHIM scores (18.9) compared to men in the tadalafil only group (11.1).[609] Similarly, 92% of men in the combined treatment group achieved an erection sufficient for penetration compared to 57% of men in the tadalafil only group. Raina, Agarwal (2006) reported higher SHIM scores for men who used a vacuum device (16.0) compared to men who had no treatment post-RP (11.2).[611] The observational study reported that 81.8% of men achieved an erection sufficient for intercourse.[610]

Clinicians should counsel men with ED prior to beginning VED treatment about the potential occurrence of AEs. Most AEs were minor and resolved without intervention. The most commonly-reported AEs were transient penile petechiae or bruising (16 studies: mean 17.7%; range 0 to 50%), discomfort or pain (17 studies: mean 18.2%; range 0 to 64%), difficulty with ejaculation (9 studies: mean 21.6%; range 3.4 to 40%), and difficulty with the device (10 studies: mean 19.8%; range 0 to 66.6%). Some men also noted loss of sensitivity (7 studies: mean 14.5%; range 3.2 to 45%). Men who are receiving anti-coagulant therapy and/or who have bleeding disorders or have a history of priapism should use VEDs with caution.[621]

Body of evidence strength. More than 90% of study arms were contributed by observational designs. Inclusion criteria varied and limited information was reported regarding patient characteristics such as the severity of ED or the presence of comorbidities. Most studies pre-date the era of validated questionnaires (e.g., the IIEF, SEAR, EDITS) and the era of PDE5i. AE reporting was variable with most studies not indicating the severity of AEs. Study dropout rates complicate interpretation because only successful patients continued to use the devices. Sample sizes were small. Although approximately 11,000 men participated in vacuum device studies, two post-marketing surveys accounted for more than half of these patients (approximately 7,000 men).[587, 601]

14. Men with ED should be informed regarding the treatment option of intraurethral (IU) alprostadil, including discussion of benefits and risks/ burdens. (Conditional Recommendation; Evidence Level: Grade C)

IU medication involves the insertion of a delivery catheter into the meatus and depositing an alprostadil pellet in the urethra to induce an erection sufficient for intercourse. Alprostadil is prostaglandin E1. IU alprostadil is a treatment option for men for whom PDE5i are contraindicated, for men or partners who prefer to avoid oral medication, and/or for men or

partners who prefer not to use the needles required for ICI medications.

In the general ED population, two RCTs,[622,623] one randomized design that compared IU alprostadil to ICI alprostadil,[624] one open-label crossover that compared IU alprostadil to ICI alprostadil,[625] and a group of observational studies,[626-635] evaluated this medication.

Importantly, most studies proceeded with chronic treatment only in men who had erections firm enough for intercourse in response to in-office testing. The success rates among men who used the medication chronically, therefore, are relevant to responsive intra-office testing – not men with ED in general. In-office positive testing rates across studies exhibited a large range, from 20% to 65.9%. Clinicians and men with ED should be aware that a large proportion of men who have a positive in-office test will not be successful in the home environment.

Successful intercourse rates (variously defined across studies) with IU alprostadil ranged from 29.5% to 78.1%. The largest study to assess the efficacy of IU alprostadil reported that 995 of 1,511 (65.8%) men had positive responses in the office; only men with positive in-office responses were then randomized to the IU alprostadil or placebo groups. Of the 461 men assigned to the alprostadil condition, only 299 (64.9%) achieved at least one episode of intercourse at home,[622] indicating that a positive in-office test does not guarantee efficacy in the home environment. In addition, only 73% of doses (2,634 of 3,593) were successful in facilitating intercourse, orgasm, or a 10-minute erection sufficient for intercourse.

Overall, in the two placebo-controlled studies, success rates were statistically significantly higher in the IU alprostadil conditions compared to the placebo condition. In the two studies that compared IU alprostadil to ICI alprostadil, success rates were significantly higher in the ICI group. In the four studies that reported outcomes using the IIEF subscales or the SHIM,[627,629,634,636] scores after treatment were significantly higher than pre-treatment baseline scores but generally were not indicative of normal erectile function. Men should be counseled that that IU approach is generally less effective than the ICI approach.[624,636]

AEs were frequently reported but minor and short-term. The most common AEs were genital pain (ranging from 6.5 to 34.7%), minor urethral trauma (ranging from 1 to 5.1%), urethral pain or burning (0 to 29%), and dizziness (0 to 7.0%). Episodes of hypotension or syncope were rare. One study reported that 1% of men experienced an episode of prolonged or painful erection.[623] There were no reports of priapism.

Body of evidence strength. The randomized studies were of moderate quality (unclear risk of bias), but follow-up durations were short at three months. Measures of success across studies were defined in ways that are not clearly comparable. These include the occurrence of intercourse at least once during the study, the occurrence of intercourse at least twice during the first two months of the study, 75% of erections adequate for intercourse, erection sufficient for intercourse without need for an additional soft rubber band, improved erection quality or increased intercourse frequency or improved SHIM score, percentage of men who continued to use the medication at study end, and percentage of successful medication uses. Approximately 69% of studies reported an authorship or funding association with the pharmaceutical industry.

15. For men with ED who are considering the use of IU alprostadil, an in-office test should be performed. (Clinical Principle)

IU alprostadil should not be prescribed until a man has undergone instruction in the method, an initial dose-titration in the office, and detailed counseling regarding possible AEs and actions to take in response to potentially serious AEs.

IU alprostadil is available in doses of 100 µg, 250 µg, 500 µg, and 1,000 µg. The clinician should select a dose for in-office testing that is expected to produce an erection sufficient for intercourse. The higher the dose, the more likely the man will experience an AE; therefore, the lowest dose expected to be effective should be used. Instructions for application include urinating before use because residual urine in the urethra aids in dissolution and dispersal of the medicine along the urethra. The penis is then pulled straight and held pointing up. The applicator stem is placed approximately 3 cm into the urethra and the button is depressed. The applicator is moved slightly to separate the pellet from the applicator tip and the applicator is removed. The penis is kept upright and rolled between the hands to aid in dissolution and dispersal of medication. The man is advised to walk or stand for approximately 10 min to aid in blood flow.

Although episodes of priapism were not reported in IU alprostadil trials, the man should be thoroughly educated about priapism and instructed on safe responses and maneuvers in a prolonged erection situation. Commonly-used strategies (but for which no evidence was retrieved) include attempting ejaculation and, if this effort is unsuccessful, oral pseudephedrine followed by the application of an ice pack to the penis for 30 minutes to an hour. If a painful, non-bendable erection persists after these strategies, then the man should proceed to the emergency room within two to four hours of medication administration.

16. Men with ED should be informed regarding the treatment option of intracavernosal injections (ICI), including discussion of benefits and risks/ burdens. (Moderate Recommendation; Evidence Level: Grade C)

ICI medications are administered by injecting a substance into the corpus cavernosa of the penis to produce an erection. The four substances commonly used in clinical practice are alprostadil, papaverine, phentolamine, and atropine. Only alprostadil is FDA-approved in the U.S. for ICI injection, and it is the only medication typically used as a single agent. Combinations of medications also are used (i.e., papaverine + phentolamine, alprostadil + papaverine + phentolamine; alprostadil + papaverine + phentolamine + atropine). The choice of medication or medication combination is a collaborative decision among the man, partner, and physician and depends on what agent or agents produce an adequate response without unacceptable AEs.

Men who have contraindications to the use of PDE5i, men who prefer not to take an oral medication, or men who find that PDE5i are inadequate or ineffective may choose the ICI approach to treating ED. PDE5i are ineffective in about 40% of men.[216] In addition, a significant proportion of men initially responsive to PDE5i eventually will become non-responsive as ED progresses and will require a different ED treatment approach. Further, a subset of men who find PDE5i effective prefer the ICI alternative.[637]

ICI medications have been reported to be effective in diverse groups of men, including men from the general ED population as well as among men with other conditions such as diabetes, cardiovascular risk factors, men who are post-prostatectomy, and men with spinal cord injuries.[624,636,638-771] The most commonly used outcome measure in ICI studies was the percentage of men who reported achieving an erection sufficient for successful intercourse. These percentages ranged from 53.7% to 100% without marked differences across medications or medication combinations. The second most commonly used outcome measure was the percent of men who reported being satisfied with the treatment. These percentages ranged from 46.3% to 98.8% with the lowest satisfaction rates associated with papaverine use (mean 53.4%).

Note that these two outcome measures reflect different qualities of treatment. Achieving an erection sufficient for intercourse focuses on whether the medication produced the desired physiological outcome. Asking whether a man is satisfied with the treatment is a broader, more complex question and may include whether AEs occurred, the partner's views about the mode of administration, the man's comfort with injections, etc.

Relative efficacy of specific medications or medication combinations is difficult to determine because men who are administered single medications or combined medications also differ in presenting ED severity. A stepped care approach can be used to maximize the proportion of men who are treated successfully with ICI. For example, Baniel, Israilov (2000) reported on 625 men who entered a progressive treatment program that used four ICI protocols: (1) papaverine + phentolamine; (2) alprostadil; (3) papaverine + phentolamine + alprostadil; (4) atropine + papaverine + phentolamine + alprostadil.[646] A positive response was defined as erection sufficient for penetration. Positive responses were achieved by 66.4% of the 625 men administered protocol 1. The remaining 210 men were administered protocol 2 (n=75), protocol 3 (n=135) and protocol 4 (n=37). These groups achieved success rates of 36%, 72.6%, and 59.5%, respectively. Only 15 of the 625 men failed to respond to any of the protocols. At three years of follow-up in 610 men, 43.7% had achieved successful intercourse (n=65 without an injection and n=202 with injections).

AEs. Although rates of successful intercourse are similar across medications and medication combinations, AE profiles in the extracted data differed. Men should be thoroughly counseled regarding the potential differential risk profiles of the various ICI substances (see Appendix B). The most serious AE associated with ICI medications is priapism. Most study authors defined priapism as an erection that required intervention in order to resolve; prolonged or painful erections were generally defined as resolving without intervention. The

lowest rates of priapism (mean 1.8%) were reported in studies using alprostadil as a single medication (but note that studies of alprostadil reported a mean rate of 6.3% for prolonged or painful erections). The Panel notes that identifying the appropriate dose of medication and thoroughly instructing the man in dose titration is critical to minimize the risk of priapism regardless of the medication or medication combination selected.

Pain is a common consequence of ICI injections; in published studies men reported pain described as pain with injection, penile pain, and genital pain. The literature suggests that pain rates are highest when papaverine (high rates of pain with injection) or alprostadil (high rates of pain with erection) are used as single agents, and when papaverine is used in combination with phentolamine (see table in Appendix B), but there are relatively few studies that used other medication combinations and reported on the incidence of pain.

Penile fibrosis or plaque and penile deformities have been reported with use of ICI. There is considerable range across studies in these reports without any single medication or medication combination clearly associated with higher risk. In addition, the percentage of men who reported these AEs did not increase with follow-up duration. In the absence of reliable predictors for these issues, the Panel suggests that any pre-existing fibrosis or plaque or deformity be documented before initiating ICI and that men be monitored regularly for progression of these conditions or for the onset of a new condition.

Body of evidence strength. More than 90% of study arms were contributed by observational designs – the weakest design in terms of controlling for confounders. Limited information was reported regarding patient characteristics such as the severity of ED or the presence of comorbidities. Most studies pre-date the era of validated questionnaires (e.g., the IIEF, SEAR, EDITS) and rely on patient reports of outcomes. Adverse event reporting was variable with most studies not indicating the severity of AEs. Study dropout rates also complicate interpretation because only successful patients continued to use the medications.

17. For men with ED who are considering ICI therapy, an in-office injection test should be performed. (Clinical Principle)

Men considering ICI therapy should first have an in-office injection test to determine the appropriate dose and medication(s) to produce sufficient duration of response and to minimize AEs. The in-office experience also is important to help the man achieve confidence with the technique and to facilitate adherence. It may take several visits to determine the correct drug(s) and titrate the dose. Men should be informed that although injectable non-prostaglandin agents have been used to successfully manage ED for decades, none are formally FDA-approved for this indication. This visit also should include educating men and their partners regarding how to titrate the dose, the advisability of alternating sites with each dose, and how to proceed if a serious AE occurs (i.e., priapism). The man should be thoroughly educated about priapism and instructed in actions to take in a prolonged erection situation. It is recommended all education be documented. Commonly -used strategies (but for which no evidence was retrieved) include attempting ejaculation and, if this effort is unsuccessful, then oral pseudephedrine followed by the application of an ice pack to the penis for 30 minutes to an hour. If a painful, non-bendable erection persists after these strategies, then the man should proceed to the emergency room within 2-4 hours of medication administration.

The Panel notes that there can be significant cost differences across medications based on how they are obtained (e.g., brand name medications versus compounded medications). Optimizing the medication choice for a particular man ideally includes discussion of costs.

ICI Combination Medications. ICI combination therapy was developed to improve efficacy as a result of the synergistic effects of the drugs and to reduce side effects as a result of using lower dosages of each agent. One complexity encountered with the use of combination medications is the need for the pharmacy to compound these agents because there are no combination ICI drugs currently approved by the FDA. In addition, some substances (e.g., alprostadil) may have a limited shelf-life.[772]

No standardized mixture is approved by the FDA; these combinations must be compounded by the pharmacy based on physician instructions. Concentrations of each component vary widely in the literature, but ratios of 12 –30 mg papaverine: 10–20 µg alprostadil:1 mg phentolamine are common. A standard dose regimen includes a mixture of 30 mg papaverine + 10 µg alprostadil + 1 mg phentolamine per 1 mL with a starting dose of 0.1–0.5 mL.

18. Men with ED should be informed regarding the treatment option of penile prosthesis implantation, including discussion of benefits and risks/burdens. (Strong Recommendation; Evidence Level: Grade C)

Another choice for the man with ED is the surgical implantation of a penile prosthesis. Prosthesis implantation has been performed successfully in men from the general ED population as well as men from a variety of special populations.[773-885] Men and their partners should be thoroughly counseled regarding the benefits and potential risks of this treatment to ensure appropriate choice of device, realistic post-operative expectations, and high levels of satisfaction.[886] The man and his partner should understand that several devices are currently available, including malleable (non-inflatable) models as well as two- or three-piece inflatable prostheses. The benefits of prostheses include the ability to generate an erection sufficient for intercourse on-demand, for as long as is desired, and as frequently as is desired. The potential risks and burdens of prosthesis surgery include the risks inherent in the surgical procedure, possible changes in the appearance of the penis, and the potential for device malfunction or failure. Men should understand that this treatment choice is best conceptualized as irreversible; although prostheses can be removed, it is unlikely that a man's penis will be reliably responsive to other ED therapies after prosthesis explant.

The most commonly-used outcome measure among this group of studies was the percentage of men who reported being satisfied with prosthesis surgery. The mean satisfaction rate across studies of implanted inflatable models was 86.2%. The mean satisfaction rate across studies of implanted malleable models was somewhat lower at 75.1%. When studies were broken down by prosthesis model groups, satisfaction rates for inflatable models ranged from 85.6% to 88.3% and from 66.1% to 88.7% for malleable models (see table in Appendix B; some studies did not specify prosthesis models).

A smaller number of studies reported partner satisfaction rates (see Appendix B). Rates were generally high for inflatable models (AMS 700 series – 83.3% and studies that used other, multiple, or unspecified inflatable models – 88.2%), and the AMS Spectra malleable model (89.5%).

A subgroup of studies reported outcomes using the IIEF or the EDITS. These studies also suggest high levels of satisfaction and functionality.[773-776,779,783,793,826,828,850,870,873,874,882,884] In this group of studies, post-operative IIEF-EF scores ranged from 21.8 to 28.8, post-operative SHIM scores ranged from 20.0 to 22.5, and post-operative patient EDITS scores ranged from 57.0 to 90.5, with nine of 11 studies reporting values >75.

AEs. Men and their partners should be counseled regarding AEs. Commonly-reported AEs in the early peri - and post-operative period include penile edema or hematoma (23 studies: range 0.2% to 13.4%; mean 3.4%), corpus injury (11 studies: range 0.06% to 6.2%; mean 2.3%), urethral injury (9 studies: range 0% to 3.1%; mean 1.2%), acute urinary retention (9 studies: range 0% to 4.2%; mean 2.0%), and crura injury (7 studies: range 0.02% to 4.0%; mean 1.5%). These AEs were rarely serious and generally resolved with supportive care or minimal intervention (i.e., short -term use of an indwelling catheter to manage acute urinary retention). Pain in the early post-operative period is not well-documented in the literature, but in the Panel's experience, most men will experience some degree of pain after surgery with complete resolution within one to three months.

Infection. Infection is a serious AE that typically occurs within the first three months after surgery and usually requires removal of the prosthesis. Although no randomized studies have compared outcomes between prosthesis models with and without infection-inhibiting coatings, observational studies indicate that coated models have greatly reduced infection rates with most series reporting rates of 1-2% when these models are implanted. For example, Serefoglu et al. (2012) used patient information forms to compare the Coloplast Titan model with the hydrophilic coating (n=29,360) to the same model without the hydrophilic coating (n=7,031).[867] The infection rate was significantly lower (1.4%) with the hydrophilic coating compared to no coating (4.6%). Similarly, Carson et al. (2011) used 39,005 patient information forms to assess revision for infection in antibiotic-impregnated inflatable devices compared to non-inflatable devices at up to 7.7 years of follow-up.[787] Revision rates for antibiotic-impregnated devices were significantly lower at 1.1% (n = 35,737) than those for non-impregnated devices at 2.5% (n = 3,268). In a retrospective chart review, Droggin, Shabsigh (2005) compared AMS 700 series devices with Inhibizone (n=58) to devices without Inhibizone (n=94).[799] Infection rates for the Inhibizone devices were significantly less (0%) compared to the non-Inhibizone devices (3.2%). Eid et al. (2012)

examined infection rates among men implanted with the Coloplast Titan model or the AMS 700 series (results not separated by model), which were without any infection-inhibiting coating (n=132) or had an infection-inhibiting coating (n=704).[801] Infection rates were 5.3% in the non-coated models and 1.99% in the coated models. In this study, a third group of men had coated models implanted, and the surgeons also used a "no-touch" technique. The "no touch" technique involves discarding all surgical instruments and changing all surgical gloves after an incision is made in the penoscrotal raphe and the dissection is carried down through the subcutaneous tissue and dartos to the level of Buck's fascia. Among 1,511 men who were implanted with an infection retardant coated device and who had the "no touch" technique, the infection rate was 0.46%. Antibiotic coatings also appear to reduce infection rates when used to replace a prosthesis. Nehra et al. (2012) reported that at up to 6.6 years of follow-up, secondary revisions as a result of infection were significantly less likely to occur among patients with antibiotic-impregnated replacement implants (2.5%; n = 9,300) compared to non-impregnated implants (3.7%; n = 1.764).[887]

This pattern also was evident among diabetic men. At up to 7 years of follow-up in a group of 6,695 diabetic men, significantly fewer patients experienced revision as a result of infection with use of an antibiotic-impregnated prosthesis (1.5%; n = 6,071) compared to men who received non-impregnated models (4.2%; n = 624).[888]

Christodoulidou and Pearce (2016) conducted a systematic review to assess whether diabetic men were more vulnerable to infection with prosthesis implant compared to non-diabetic men.[889] The authors noted that most case series reporting higher infection rates among diabetic men date from the 1970s to 1990s and reported rates of 5.5 to 20%; these studies were small. Studies published in the 1990s reported on larger case series and noted lower infection rates, but rates were as high as 10.6%. In 2001, with the use of antibiotic coated implants, infection rates dropped further, with most studies reporting rates of 2% or less. In particular, the sample of 1,511 men described in Eid et al. (2012) who received coated implants using the "no-touch" technique and had an infection rate of 0.46% included 41% diabetic men.[801] The authors conclude that there is no relevant current evidence that diabetic men are at higher risk of prosthesis infection than men from the general ED population.

In select cases, an infected prosthesis can be removed, the location of the device washed out using an antibiotic salvage procedure and a new device immediately placed. This approach should be restricted to men without evidence of sepsis or severe local infection. More typically, the infected device is removed, the infection is addressed with antibiotics, and the tissues are allowed to heal (for six weeks to six months). Once healing has occurred, a new prosthesis may be implanted. However, delayed replacement of a prosthesis after initial removal is a complex operation and it is possible that device placement will not be feasible because of scarring. In addition, in this scenario other problems such as penile shortening, change in penile shape, and loss of sensation are more likely to occur.

Erosions. Erosion or cylinder extrusion occurs when the tissues at the tip of the penis are weakened, allowing the prosthetic cylinder to migrate into the head of the penis and requiring surgical repair and reposition. Erosion rates were on average lower for inflatable models (20 studies: range 0% to 6.5%; mean 2.5%) than for malleable models (7 studies: range 0% to 17.5%; mean 4.1%).

Mechanical failure. Mechanical failure is most common with inflatable models and most likely to occur when a component (usually the connecting tubing) ruptures, resulting in a fluid leak. Numerous refinements in prosthesis design and materials over time have resulted in decreased failure rates. Recent reports suggest that 90% to 95% of men will have a functioning prosthesis 10 years post-surgery. For example, Mirheydar et al. (2016) reported on 5- and 10-year cumulative reoperation rates for 7,666 men with first implant between 1995 and 2010 using the California Office of Statewide Health Planning and Development database.[845] Most men had an inflatable device implanted (88.4%). The total reoperation rate was 11% (904 men), but only 54% of these revision surgeries (in 488 men) were undertaken because of mechanical failure. Of the mechanical failure revisions, more than half involved pump malfunction followed by malfunction of the cylinders and the reservoir. Enemchukwu et al. (2013) examined patient information forms submitted for the AMS 700CX and LGX/Ultrex models; 55,013 devices were implanted between 1997 and 2008, including 39,443 CX devices and 14,470 Ultrex/LGX devices.[802] Devices with and without parylene coating were compared. For CX models, revision rates for mechanical failure at 8.4 years of follow-up were 11.8% for the non-parylene coated device and 6.2% for the

parylene coated device. For the Ultrex/LGX models, at 7 years of follow-up mechanical failure revision rates were 7.7% for the non-coated device and 5.5% for the coated device.

Changes in penis appearance. Several studies have reported that some men perceive that the penis is shorter post-implant when the prosthesis is inflated compared to a full erection before the surgery. Few studies, however, have actually measured penile length before and after surgery. Deveci, Martin (2007) measured stretched penile length of 56 men undergoing a first inflatable implant before the surgery and six months post-operatively.[890] Although 72% of men reported that penile length was decreased, the pre - to post-surgery measurements were statistically indistinguishable for the entire group (baseline – 5.2 inches; six months – 5.1 inches) as well as for the group that reported subjective shortening (baseline – 5.1 inches; six months – 5.2 inches). Wang, Howard (2009) compared erect penile length (EPL) induced by ICI injection pre-surgery to erect length after inflatable prosthesis implant.[891] Before surgery, EPL in response to ICI was mean 13.2 cm (5.2 inches); at 6 months and 1 year post-surgery, EPL was 12.5 cm (4.9 inches). These studies suggest that when objective measures are used, small length decreases may be documented.

It is imperative that clinicians discuss and document expectations of post-prosthesis penile length with men and their partners prior to surgery to ensure appropriately calibrated post-operative expectations. In addition, common reasons why men might perceive penile shortening should be discussed. These include possibly inaccurate memories regarding penile dimensions when ED has been present long-term, loss of tissue elasticity over time from the long-term absence of a full erection, weight gain in the pubic area that partially obscures the penis, and the fact that inflation of the prosthesis will not result in glans engorgement, which may make the penis appear to be shorter. Men who have a history of conditions causing tunical scarring, corporal fibrosis, or loss of cavernous smooth muscle should be informed that the prosthesis is unlikely to restore penile dimensions to those present before these conditions occurred.

Several pre-surgical, intraoperative, and post-operative strategies have been examined to maximize penile length and girth after implant. These include the use of pre-surgical penile traction to maximize pre-operative length,[892] the use of pre-surgical VED therapy to facilitate easier corporeal dilatation[893] or to allow longer cylinder placement at the time of surgery.[894] Use of a VED pre-surgically to soften corporeal fibrosis in men with a history of ischemic priapism or infection to facilitate successful implant of a device also has been reported.[895] There also is some evidence that surgeons who are frequent implanters use longer cylinders (median 2 cm longer) compared to surgeons who are less frequent implanters.[896] Several intra-operative techniques also have been examined, including ventral phalloplasty and suspensory ligament release.[781,844,897]. Post-operatively, IU alprostadil and PDE5i medications have been used to improve glans temperature, sensation, and enlargement.[898-900] Successful penile dimension enhancement by using aggressive cylinder sizing and daily cylinder inflation post-operatively with maximal cylinder inflation for one-two hours during post-operative months 6 to 24 also has been reported.[817,901] The Panel notes that currently there are insufficient data on specific approaches and techniques to constitute a reliable evidence base from which to provide clinical guidance regarding these approaches.

Body of evidence strength. The available data were contributed by observational designs and the majority of studies were retrospective. Limited information was reported regarding patient characteristics such as the severity of ED or the presence of comorbidities. Most studies did not use validated questionnaires (e.g., the IIEF, SEAR, EDITS) and rely on patient report or medical chart review. AE reporting was variable and sparse with many studies not addressing AEs, and of the studies that did address AEs, most did not indicate the severity of AEs. Many studies reported large numbers of patients lost to follow-up, creating uncertainty regarding whether additional longer-term AEs (i.e., mechanical failure) may have occurred.

19. Men with ED who have decided on penile implantation surgery should be counseled regarding post-operative expectations. (Clinical Principle)

Given the invasive and essentially irreversible nature of penile prosthesis implantation surgery, thorough counseling regarding short- and long-term postoperative expectations is essential. This counseling helps to support the man and his partner in choosing an ED treatment that aligns with their values and priorities and ensures that, should they choose prosthesis surgery, the surgical outcome matches expectations and produces high levels of satisfaction.

One element of setting appropriate expectations is explaining the differences between the inflatable and malleable devices in terms of the ease of operation, appearance, and concealability of the device. For inflatable models, the steps in operation should be thoroughly reviewed and demonstrated so that the man and his partner are confident regarding the technique. For men in whom an abdominal reservoir may pose a risk (e.g., extensive scarring, kidney transplant), a two-piece inflatable model may be considered if a hydraulic device is desired. Two-piece models are also easier to manipulate than three-piece models and may be advisable if a man has poor manual dexterity. Although generally higher satisfaction rates are associated with inflatable devices, there are some circumstances in which a malleable implant is more appropriate (e.g., limited manual dexterity, cost concerns). Men should understand, however, that although these models can be bent to lay flat against the groin, they cannot be "deflated."

It also should be made clear that a penile implant will not have a direct effect on libido; the difference between penile rigidity and desire/libido should be thoroughly explained, and a man who is struggling with loss of libido should have this issue addressed separately. The man and his partner (if present) should understand that although the penile implant will enhance shaft rigidity, it does not generally enhance glans rigidity or enhance or improve the processes of orgasm and ejaculation.

The man and his partner also should be counseled regarding the typical early and late post-operative course in terms of the likelihood of pain and the time course for its resolution, the healing process, and the typical latency to be able to safely use the device. Discussion of possible changes in the appearance of the penis also should occur, including the possibility of perceived loss of length and, in men with pre-existing scarring from a prior device or a priapism episode, the possible loss of girth (see detailed discussion under Guideline Statement 18).

Kramer and Schweber (2010) examined the impact of preoperative counseling about penile length, penile girth, penile sensation, risk of infection or other major complications, pain, latency to use the device, and ease of device use on pre-operative expectations and post-operative satisfaction among 21 men implanted with the Coloplast Titan.[886] More realistic pre-operative expectations were associated with higher post-operative satisfaction (r^2= 0.24; 24% of variance explained).

20. Penile prosthetic surgery should not be performed in the presence of systemic, cutaneous, or urinary tract infection. (Clinical Principle)

The Panel notes that penile prosthesis surgery should not be undertaken if the man has evidence of systemic or cutaneous infections or if he has a urinary tract infection. The 2008 AUA best practice policy on the use of parenteral antibiotics for broad spectrum coverage prior to penile prosthesis surgery recommends use of vancomycin or a first- or second-generation cephalosporin as well as an aminoglycoside 1 hour before surgery and up to 24 hours after surgery.

21. For young men with ED and focal pelvic/penile arterial occlusion and without documented generalized vascular disease or veno-occlusive dysfunction, penile arterial reconstruction may be considered. (Conditional Recommendation; Evidence Level: Grade C)

Penile arterial reconstruction surgery may be considered for the man with ED who is young and who does not have veno-occlusive dysfunction or any evidence of generalized vascular disease or other comorbidities that could compromise vascular integrity. The Panel cautions that this literature presents many challenges to interpretation; therefore, consideration of this procedure should be limited to the small proportion of men who meet these criteria, and performance of the procedure should be limited to the highly-skilled and experienced surgeon with a track record of success in a center of excellence. Men and their partners must be counseled that the long-term success of the procedure is not well-established.

Thirty-six study arms reported outcomes for arterial reconstruction procedures (i.e., additional procedures such as venous ligation or embolization were not used).[902-934] The most commonly used outcome measure was the percentage of men in different response categories post-surgery; however, not all studies provided the information in all categories. Complete responders were defined as men able to have intercourse without the use of oral or IU or ICI medications and without a vacuum device. Partial responders were defined as men who before surgery could not have intercourse even with the use of medications or a vacuum device but had sufficient response to medications or a device that intercourse became possible post-operatively. In most studies, partial responders were men who became responsive to ICI medications. Nonresponders were defined as men who did not improve post-surgery. Follow-up durations varied considerably (range 6 months to

73.2 months; mean 30.4 months). Some studies reported responder rates at various follow-up durations post-surgery. Typically, high response rates (complete or partial) were reported at short intervals post-surgery, with declining rates over time. Overall, there was considerable variability regarding response rates, particularly complete (range 12 to 81.6%) and partial response rates (range 7.7 to 53.3%).

Interpreting these data is challenging because some studies included men with comorbidities that could influence vascular status and, ultimately, the long-term success of the surgery. In addition, some studies did not report whether men had relevant comorbidities. Of the 36 study arms that reported outcomes, only nine explicitly excluded men with comorbidities. However, even in men without comorbidities, the complete responder rate ranged from 27.0% to 81.6%, and the partial responder rate ranged from 27.0% to 47.0%.

Further, most studies included men who had diagnoses other than or in addition to focal arterial or pelvic occlusion (i.e., men who had veno-occlusive dysfunction) or did not report this information. In the subgroup of studies that focused on men with only arterial disease, mean complete response rate ranged from 27.0% to 81.6%, and partial responder rate ranged from 7.7% to 45.6%. These rates are not markedly better than those for the entire body of literature.

It is worth noting, however, that some authors have reported positive long-term outcomes using validated questionnaires. Munarriz (2010) reported on 71 men without vascular risk factors and with pure cavernosal arterial insufficiency with mean follow-up of 34.5 months; 55% of men reported IIEF-EF scores ≥ 26 and 73% of men reported IIEF-EF scores ≥ 21.[935]

Overall, these data indicate that predicting whether reconstructive surgery will result in long-term success for a given man is extremely difficult, even in men without comorbidities and with good vascular health. In addition, proper diagnosis requires a thorough investigation. A recent study reported that nearly 50% of men initially identified as good candidates for reconstruction were not properly diagnosed.[936] When discrepancies between DUS and/or cavernosometry and selective internal pudendal arteriography were investigated with repeat studies, 73% had normal findings and were no longer candidates for reconstruction.

The most frequently-reported AEs were penile hypervascularity or glans hyperemia (23 study arms; mean 12.7%; range 0% to 100%), anastomosis occlusion (14 study arms; mean 17.7%; range 4 to 51%), and postoperative edema or hematoma (12 study arms; mean 9.2%; range 0% to 24%). In addition, penile numbness was reported in 7 study arms (mean 6.5%; range 0% to 25.4%), infection in 5 study arms (mean 3.8%; range 0% to 9%), penile shortening in 5 study arms (mean 8.9%; range 0% to 28.2%), bleeding in 4 study arms (mean 10.6%; range 5% to 18%), anastomosis site hematoma or seroma in 3 study arms (mean 9.3%; range 3.8% to 20%), and inguinal hernia in 3 study arms (mean 6.5%; range 3.4% to 10%).

Body of evidence strength. The available data were contributed by observational designs; most studies were retrospective. Limited information was reported regarding patient characteristics such as the presence of comorbidities, particularly those that contribute to vascular integrity. There was considerable variability in patient types, with some men diagnosed with one vascular condition (i.e., veno-occlusive dysfunction or arterial disease) and some men diagnosed with both conditions. Further, there was considerable variability in surgical technique across studies, making findings interpretation challenging, and follow-up durations were generally short. Finally, most studies did not use validated questionnaires (e.g., the IIEF, SEAR, EDITS) and relied on men's reports or medical chart review.

22. For men with ED, penile venous surgery is not recommended. (Moderate Recommendation; Evidence Level: Grade C)

Penile venous surgery is not recommended because of the lack of compelling evidence that it constitutes an effective ED management strategy in most men. Sixty-five study arms reported data on approximately 3,000 men who underwent various versions of penile venous ligation surgery.[903,907,921,931,937-987] This literature is characterized by diverse inclusion criteria and varied surgical techniques, making it difficult to definitively establish subpopulations of men and surgical methods with a high likelihood of long-term success.

Similar to the arterial reconstruction literature, the most commonly used outcome measure was the percentage of men who were complete responders, partial responders or non-responders. Complete responders were defined as men able to have intercourse without the use of oral or IU or ICI

medications and without a vacuum device. Partial responders were defined as men who before surgery could not have intercourse even with the use of medications or a vacuum device but after surgery had sufficient response to medications or a device that intercourse was then possible. In most studies, partial responders were men who became responsive to ICI medications. Nonresponders were defined as men who did not improve post-surgery. Follow-up durations varied considerably (range 4 months to 92.4 months; mean 23.9 months). In studies that reported responder rates at various follow-up durations post-surgery, short -term high positive response rates generally declined rapidly over time.

Interpreting these data is challenging because approximately half of studies included men who had diagnoses other than or in addition to veno-occlusive dysfunction (i.e., men who had arterial disease) or did not report this information. However, even among studies that focused on men with only veno-occlusive dysfunction, complete response rates ranged from 11.4% to 84.0%; partial responder rates ranged from 8.3% to 64.3%. These rates are similar to rates for the entire body of literature, calling into question the utility of venous ligation to manage ED even in men who appear to be ideal candidates (see Appendix B). Overall, these data indicate that penile venous ligation surgery is unlikely to result in long-term successful management of ED for the overwhelming majority of men and delays treatment with other more reliable options such as penile prosthesis surgery.

Body of evidence strength. The available data were contributed by observational designs; most studies were retrospective. Limited information was reported regarding patient characteristics such as the presence of comorbidities, particularly those that contribute to vascular integrity. There was considerable variability in patient types, with some men diagnosed with one vascular condition (i.e., veno-occlusive dysfunction or arterial disease) and some men diagnosed with both conditions. Further, there was considerable variability in surgical technique across studies, making findings interpretation challenging, and follow-up durations were generally short. Finally, most studies did not use validated questionnaires (e.g., the IIEF, SEAR, EDITS) and relied on men's reports or medical chart review.

23. For men with ED, low-intensity extracorporeal shock wave therapy (ESWT) should be considered investigational. (Conditional Recommendation; Evidence Level: Grade C)

Findings from randomized sham-controlled trials that have evaluated low-intensity ESWT do not clearly indicate that benefits reliably outweigh risks/burdens for men with ED. In particular, the treatment's ability to restore normal erectile function remains in question, the duration of treatment effects beyond possible short-term efficacy is not well-established, and the burdens associated with obtaining the treatment (i.e., time and cost) are substantial. Given the availability of other treatments that are less burdensome and known to be effective and the fact that ESWT is not FDA-approved, the Panel concludes that ESWT should only be used in investigational settings in the context of an institutional review board (IRB)-approved clinical trial.

Seven RCTs compared responses to ESWT versus a sham treatment (quality range from low risk of bias to unclear risk of bias). The RCTs varied in methodology in terms the number of pulses per treatment (from 600 to 3,000), the number of treatments per week (one or two), the number of treatment sites (from 3 to 6), and the total number of treatments (from 5 to 12). Four trials focused on men who were PDE5i responders[988-990] or partial responders.[991] For these four trials, men were not permitted PDE5is during the study and outcomes reflect unassisted erectile function. All four trials reported statistically significant improvements in unassisted erectile function in response to ESWT but not the sham treatment; however, no trial reported that men experienced a return to normal erectile function (i.e., an IIEF-EF score ≥26), suggesting the continued need for adjunctive ED therapy.

Two trials followed men for one year. Srini et al. (2015) reported that mean IIEF-EF scores were 22.0 in the ESWT group compared to 10.5 in the sham group (baseline values of 9.5 and 9.2, respectively), and 90% of men in the ESWT group reported an EHS of 3 or 4 (the proportion in the sham group was not reported) at one-month post-treatment.[989] At one-year post-treatment, IIEF-EF scores in the ESWT group had declined to 18.2 with 83% reporting EHS ≥3; the sham group was not followed. The decay in function over time to mild to moderate ED, however, illustrates the Panel's concerns with this therapy; even after completing the protocol a substantial portion of men eventually would require another ED therapy. In addition, although 95 men began the ESWT protocol, only 60 men completed the treatment (only 17 of 40 completed the sham protocol), raising questions about the generalizability of findings. Kalyvianakis and Hatzichristou (2017) reported at 12 months after treatment that the mean IIEF-EF score in the ESWT group was 19.1 and in the

sham group was 16.0 – a non-significant difference (baseline values were 13.8 and 14.6, respectively).[991] More men in the ESWT group (75%) reported a minimal clinically important difference in the IIEF-EF compared to the sham group (25%). There also were significant increases in penile peak systolic velocity in the ESWT group compared to the sham group (4.5 cm/s versus 0.6 cm/s, respectively).

Olsen et al. (2014) reported that at the end of the five-week treatment, 57% of men in the ESWT group (n = 51) had an EHS score of 3 or 4 compared to 9% in the sham group (n = 54), and 43% of men in the ESWT group reported an IIEF-EF score increase of 5 points or greater compared to 38% in the sham group.[990] The authors note that 37% of the ESWT group experienced no change in ED, however. The sham group was offered ESWT at the end of the initial blinded period. After ESWT, the sham group reported that 54% of men had an EHS score of 3 or 4, and 33% had a 5 point or greater score increase in the IIEF-EF. Both groups were followed for five months after treatment. At five months, the percentage of men with EHS scores of 3 or 4 was 19% in the original ESWT group and 23% in the original sham group, and 32% and 38% of men, respectively, continued to exhibit a 5 point or greater IIEF-EF score increase. No IIEF-EF scores were provided, making these data difficult to interpret in terms of ED severity, but the pattern of decaying scores is evident. Vardi et al. (2012) reported at one month post-treatment that IIEF-EF scores were mean 19.3 in the ESWT group compared to 14.5 in the sham group (baseline values of 12.6 and 11.5, respectively) and that more men in the ESWT group (65%) reported a 5 point or greater IIEF-EF score increase than in the sham group (20%).[988] However, the ESWT group mean score is in the mild to moderate ED range and suggests that many men may have continued to require adjunctive ED treatment.

One trial focused on men who had been responsive to PDE5is previously but for whom PDE5i had lost efficacy;[992] this trial evaluated men one month after treatment in response to PDE5i; unassisted EF was not evaluated. Median IIEF-EF score with use of PDE5i increased to 13.0 in the ESWT group (n = 37; from baseline mean 7) and to 8.5 in the sham group (n = 18; from baseline 8.0). In the ESWT group 54.1% of men achieved an EHS score of 3 compared to 0 men in the sham group. The sham group was then offered ESWT (n = 16) and reported an IIEF-EF score increase to 12.5 with PDE5i with an EHS score of 3 in 56.3%. Note that the therapy appeared to move men from the severe to moderate ED category with PDE5i, but this improvement may not be sufficient for satisfactory intercourse without additional ED treatment. Two trials did not specify whether men were responsive to PDE5i.[993,994] Both trials reported no differences between men who were treated with ESWT versus the sham protocol.

There were essentially no AEs reported in this group of studies; the most frequently reported reason for participant drop out was the inconvenience and/or cost of obtaining the treatment.

Four published systematic reviews with meta-analyses evaluated the use of ESWT.[995-998] These papers are compromised by conceptual weaknesses: the failure to address substantial heterogeneity that suggests flawed conclusions, the pooling of trials across non-comparable patient groups (i.e., ED, chronic pelvic pain; the pooling of trials that measured unassisted erectile function with trials that measured erectile function in response to PDE5is; and the use of non-standard data analytic procedures (i.e., separate analyses for active and sham -treated groups)). Therefore, collectively they offer little insight into this topic area.

Body of evidence strength. The available RCTs varied in inclusion criteria (i.e., men who were PDE5i responders vs. men who were PDE5i nonresponders) and in purpose (i.e., some evaluated change in unassisted erectile function and others assessed change in erectile function in response to PDE5is). Findings were inconsistent and sample sizes were small.

24. For men with ED, intracavernosal stem cell therapy should be considered investigational. (Conditional Recommendation; Evidence Level: Grade C)

Findings from studies that have evaluated ICI stem cell therapy do not indicate that benefits reliably outweigh risks/burdens for men with ED. In particular, the treatment's ability to restore normal erectile function in various populations of men with ED has not been convincingly demonstrated. Further, neither the most effective source and dose of stem cells nor the duration of treatment effects has been established, and the burdens associated with obtaining the treatment (i.e., cost, need for tissue harvest) can be substantial. Given the paucity of data obtained in human participants, the risks of treatment also are not well-established. Because other treatments that are well-characterized in terms of benefits and risks/burdens are available, the

Panel concludes that ICI stem cell therapy should only be used in investigational settings in the context of an IRB-approved clinical trial.

Five studies have evaluated the effects of ICI stem cell therapy for ED. Bahk et al. (2010) reported on the effects of umbilical cord stem cells administered ICI to seven men with type 2 diabetes and ED who were scheduled to have prosthesis surgery.[999] A control group of three men was administered saline. Measures included the SHIM, SEP questions 2 and 3, a global assessment question and an erection diary. The control men did not experience change in erectile function during the study. At two months post-procedure, six of seven stem cell-treated men reported the return of morning erections and increased penile hardness. Two men were able to achieve an erection sufficient for intercourse with the addition of 100 mg sildenafil. By nine months post-procedure, however, only one man was able to have intercourse with the use of sildenafil.

Garber and Carlos (2015) reported on six men with type 2 diabetes who were awaiting prosthesis surgery; men received stem cells from adipose tissue.[1000] By three months post-procedure, five of six men recovered morning erections and maintained them for approximately four months. Rigidity increased but was insufficient for intercourse. With use of a PDE5i, four men were able to have intercourse for approximately nine months.

Yiou et al. (2016) reported findings from a one-year dose-escalation study in which 12 men post-RP received one of four doses ICI of bone marrow cells.[1001] Measures included the IIEF, the EHS, and color DUS. At six months, significant improvements with the use of medications (unspecified) were reported in the IIEF-EF (baseline 7.3; six months 17.4) and the Intercourse satisfaction subscale (baseline 3.9; six months 6.8). The authors noted that findings were similar at 12 months post-procedure and that greater effects were associated with higher doses. Overall, 9 of 12 men were able to have intercourse with the use of medication. In addition, ultrasound parameters (i.e., basal PSV, 20-min PSV) demonstrated significant improvements.

Haahr et al. (2016) reported findings from a six-month study of 17 men post-RP administered stem cells obtained from abdominal fat.[1002] Eight of 17 men recovered sufficient erectile function to complete intercourse by six months post-procedure. The treatment did not benefit incontinent men, but SHIM and EHS scores improved significantly among continent men.

Levy et al. (2016) used placental matrix-derived stem cells in eight men with ED who were able to have intercourse pre-treatment with the use of ICI medications.[1003] Post-procedure, three men were able to achieve erections without medications and four were able to have intercourse using low-dose PDE5i. However, two men were lost to follow-up during the study, leaving it unclear whether effects were sustained.

The Panel interpreted these data to indicate that stem cell therapy is a nascent technique in need of more rigorous study before widespread use as a reliable ED therapy.

Body of evidence strength. This literature consists primarily of observational designs with extremely small sample sizes; the available literature reports findings from <50 men in total. The stem cell source and dose varied across studies, making it unclear which protocols might be effective. Patient populations also differed substantially across studies, including men with diabetes, men post-RP, and men from the general ED population. The safety profile of this therapy is unclear given the limited number of human participants. Overall, confidence in reliable outcomes without significant risks is compromised by an inadequate body of evidence comprised of robustly designed studies with sufficient sample sizes for a particular stem cell methodology in a particular patient group.

25. For men with ED, platelet-rich plasma (PRP) therapy should be considered experimental. (Expert Opinion)

PRP should not be offered to men with ED unless it is administered in the context of an IRB-approved experimental clinical research protocol. At this time, no full-text peer-reviewed publications are available to constitute an evidence base. Therefore, reliable information about potential benefits and risks/burdens of PRP therapy is not available. Because of the absence of evidence and given the availability of multiple other proven treatment options, it is the Panel's expert opinion that PRP therapy is not appropriate for men with ED except as part of an IRB-approved research trial.

Other Treatments.

The Panel reviewed the evidence on all therapies for ED. Treatments judged to be effective and that appear to be generally safe (e.g., PDE5i, VED, ICI) are reviewed above, and guidance is provided in the form of statements. Selected treatments that are available but that in the Panel's judgement are ineffective and involve substantial risks/burdens (e.g., venous ligation surgery, PRP, ESWT) and, based on current evidence, should not be offered also are addressed. Many additional oral treatments for ED have been evaluated in the peer-reviewed literature but, in the Panel's view, these treatments either are ineffective, are not safe, or lack a sufficient body of evidence from which to make generalizations. These treatments include apomorphine as an oral preparation, yohimbine, statins as monotherapy for ED, trazodone, ginseng, and l-arginine alone or in combination with other substances as well as various types of topical treatments. The Panel notes that the use of these treatments may preclude the use of other treatments known to be effective. The Panel will revisit these treatments each time the guideline is updated and re-evaluate the available evidence base.

SECTION 6: RESEARCH NEEDS AND FUTURE DIRECTIONS

Advancements in ED management can be expected to continue into the future in parallel with ongoing progress in the field of sexual medicine more broadly. Developments in health care delivery, diagnostics, and therapeutics will be the underpinnings of improved, evidence-based clinical practice in this field.

Although much has been learned in the physiology and molecular science of penile erection in recent decades, scientific discovery in this arena will predictably continue to be made. Science and technology are the cornerstone for new developments ranging from new pharmacotherapeutics to surgical innovations. Scientific discovery in the vascular biology and neurophysiology of penile erection will continue to take center stage with particular focus on molecular and cellular signaling pathways and growth factor mechanisms that may be exploited to produce the next generation of pharmacotherapeutics as well as gene, stem cell and regenerative therapies. Technologic advancements can also be expected to impact surgical procedures ranging from penile reconstructive to prosthetic to tissue replacement surgeries (e.g., penile transplantation).

The field is positioned to bring forward single or combination therapies that characterize angiogenic, neurogenic, anti-fibrotic, anti-apoptotic, and other potential systems biologic approaches, which can be directed toward ED pathophysiologic conditions existing at either peripheral (i.e., genitalia) or central (i.e., brain and spinal cord) axis levels. A near-term practical scheme is to apply such treatments based on the systemic deficiency and severity extent of ED, utilizing a SDM process that is guided by the clinician after thorough discussion of all management considerations and incorporates intervention preferences of the man and his partner. Accordingly, a lesser presentation of vasculogenic ED may do well with as needed oral pharmacotherapy and lifestyle improvement whereas a more severe, tissue fibrotic presentation may require tissue regenerative and/or surgical interventions.

In the future, diverse ED treatments likely will become available and can be offered in a highly effective, clinicopathologically targeted manner as linked with cause-specific ED-associated disease states. It is conceivable that the ED treatment armamentarium of the future will comprise therapies specific for diabetes-associated ED, for instance, that are distinct from those intended for neurogenic ED or severe vasculogenic ED. Improved diagnostics will have impact in this scope as well. Molecular profiling, genetic biomarkers and advanced imaging techniques may improve the specificity of treatment for each man and usher in an era of "personalized medicine" for ED.

Current interventions for ED are focused on symptomatic benefit. For example, although oral PDE5i were a major therapeutic breakthrough and now constitute a mainstay of ED management, these medications only mitigate symptoms rather than curing the underlying condition. Therapies with less restrictive, non-repetitive efficacy are greatly needed. The ultimate goal of ED management is to restore physiologically intact and natural erectile function. Durable and clinically significant improvement in erectile function is a less optimal but still desirable goal if total recovery is not an option. Improvements in our ability to definitively manage ED will likely contribute to better life satisfaction and superior overall health outcomes.

REFERENCES

1. Shea BJ, Hamel C, Wells GA et al: AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol 2009; **62:** 1013.
2. Cochrane handbook for systematic reviews of interventions. Chichester, West Sussex; Hoboken, NJ: John Wiley & Sons 2008.
3. Faraday M, Hubbard H, Kosiak B et al: Staying at the cutting edge: a review and analysis of evidence reporting and grading; the recommendations of the American Urological Association. BJU Int 2009; **104:** 294.
4. Hsu C and Sandford B: The Delphi technique: making sense of consensus. Practical Assessment, Research & Evaluation 2007; **12:** 1.
5. Impotence. NIH Consensus Statement 1992; **10:** 1.
6. McCabe MP, Sharlip ID, Atalla E et al: Definitions of sexual dysfunctions in women and men: a consensus statement from the Fourth International Consultation on Sexual Medicine 2015. J Sex Med 2016; **13:** 135.
7. Saigal CS, Wessells H, Pace J et al: Predictors and prevalence of erectile dysfunction in a racially diverse population. Arch Intern Med 2006; **166:** 207.
8. Bacon CG, Mittleman MA, Kawachi I et al: A prospective study of risk factors for erectile dysfunction. J Urol 2006; **176:** 217.
9. Elwyn G, Frosch D, Thomson R et al: Shared decision making: a model for clinical practice. J Gen Intern Med 2012; **27:** 1361.
10. Epstein RM, Alper BS and Quill TE: Communicating evidence for participatory decision making. JAMA 2004; **291:** 2359.
11. Hoffmann TC and Del Mar C: Patients' expectations of the benefits and harms of treatments, screening, and tests: a systematic review. JAMA Intern Med 2015; **175:** 274.
12. Hatzichristou D, Rosen RC, Derogatis LR et al: Recommendations for the clinical evaluation of men and women with sexual dysfunction. J Sex Med 2010; **7:** 337.
13. Vemulakonda VM, Sorensen MD and Joyner BD: The current state of diversity and multicultural training in urology residency programs. J Urol 2008; **180:** 668.
14. McKinlay JB: The worldwide prevalence and epidemiology of erectile dysfunction. Int J Impot Res 2000; **12 Suppl 4:** S6.
15. Ayta IA, McKinlay JB and Krane RJ: The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. BJU Int 1999; **84:** 50.
16. Jackson G, Boon N, Eardley I et al: Erectile dysfunction and coronary artery disease prediction: evidence-based guidance and consensus. Int J Clin Pract 2010; **64:** 848.
17. Martin-Morales A, Sanchez-Cruz JJ, Saenz de Tejada I et al: Prevalence and independent risk factors for erectile dysfunction in Spain: results of the epidemiologia de la disfuncion erectil masculina study. J Urol 2001; **166:** 569.
18. Corona G, Lee DM, Forti G et al: Age-related changes in general and sexual health in middle-aged and older men: results from the European Male Ageing Study (EMAS). J Sex Med 2010; **7:** 1362.
19. Feldman HA, Goldstein I, Hatzichristou DG et al: Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol 1994; **151:** 54.
20. Grover SA, Lowensteyn I, Kaouache M et al: The prevalence of erectile dysfunction in the primary care setting: importance of risk factors for diabetes and vascular disease. Arch Intern Med 2006; **166:** 213.
21. Sasayama S, Ishii N, Ishikura F et al: Men's health study: epidemiology of erectile dysfunction and cardiovascular disease. Circ J 2003; **67:** 656.
22. Kloner RA: Erectile dysfunction in the cardiac patient. Curr Urol Rep 2003; **4:** 466.
23. Montorsi P, Ravagnani PM, Galli S et al: The triad of endothelial dysfunction, cardiovascular disease, and erectile dysfunction: clinical implications. European Urology, Supplements 2009; **8:** 58.
24. El-Sakka AI: Association of risk factors and medical comorbidities with male sexual dysfunctions. J Sex Med 2007; **4:** 1691.
25. Hodges LD, Kirby M, Solanki J et al: The temporal relationship between erectile dysfunction and cardiovascular disease. Int J Clin Pract 2007; **61:** 2019.
26. Montorsi F, Briganti A, Salonia A et al: Erectile dysfunction prevalence, time of onset and association with risk factors in 300 consecutive patients with acute chest pain and angiographically documented coronary artery disease. Eur Urol 2003; **44:** 360.
27. Inman BA, Sauver JL, Jacobson DJ et al: A population-based, longitudinal study of erectile dysfunction and future coronary artery disease. Mayo Clin Proc 2009; **84:** 108.
28. Fung MM, Bettencourt R and Barrett-Connor E: Heart disease risk factors predict erectile dysfunction 25 years later: the Rancho Bernardo Study. J Am Coll Cardiol 2004; **43:** 1405.
29. Esposito K, Giugliano F, Martedi E et al: High proportions of erectile dysfunction in men with the metabolic syndrome. Diabetes Care 2005; **28:** 1201.
30. Ansong KS, Lewis C, Jenkins P et al: Epidemiology of erectile dysfunction: a community-based study in rural New York state. Ann Epidemiol 2000; **10:** 293.
31. Nwanko T, Yoon S, Burt V et al: Hypertension among adults in the United States: National Health and Nutrition Examination Survey, 2011-2012. Hyattsville, MD: National Center for Health Statistics 2013.
32. Selvin E, Burnett AL and Platz EA: Prevalence and risk factors for erectile dysfunction in the US. Am J Med 2007; **120:** 151.

33. Seftel AD, Sun P and Swindle R: The prevalence of hypertension, hyperlipidemia, diabetes mellitus and depression in men with erectile dysfunction. J Urol 2004; **171:** 2341.
34. Rosen RC, Fisher WA, Eardley I et al: The Multinational Men's Attitudes to Life Events and Sexuality (MALES) Study: I. Prevalence of erectile dysfunction and related health concerns in the general population. Curr Med Res Opin 2004; **20:** 607.
35. Manolis A and Doumas M: Sexual dysfunction: the 'prima ballerina' of hypertension-related quality-of-life complications. J Hypertens 2008; **26:** 2074.
36. Toth PP, Potter D and Ming EE: Prevalence of lipid abnormalities in the United States: The National Health and Nutrition Examination Survey 2003-2006. J Clin Lipidol 2012; **6:** 325.
37. Eaton CB, Liu YL, Mittleman MA et al: A retrospective study of the relationship between biomarkers of atherosclerosis and erectile dysfunction in 988 men. Int J Impot Res 2007; **19:** 218.
38. Romeo JH, Seftel AD, Madhun ZT et al: Sexual function in men with diabetes type 2: association with glycemic control. J Urol 2000; **163:** 788.
39. Bacon CG, Hu FB, Giovannucci E et al: Association of type and duration of diabetes with erectile dysfunction in a large cohort of men. Diabetes Care 2002; **25:** 1458.
40. Braun MH, Sommer F, Haupt G et al: Lower urinary tract symptoms and erectile dysfunction: co-morbidity or typical "aging male" symptoms? Results of the "Cologne Male Survey." Eur Urol 2003; **44:** 588.
41. Hoesl CE, Woll EM, Burkart M et al: Erectile dysfunction (ED) is prevalent, bothersome and underdiagnosed in patients consulting urologists for benign prostatic syndrome (BPS). Eur Urol 2005; **47:** 511.
42. Rosen R, Altwein J, Boyle P et al: Lower urinary tract symptoms and male sexual dysfunction: the Multinational Survey of the Aging Male (MSAM-7). Eur Urol 2003; **44:** 637.
43. Gonzalez RR and Kaplan SA: Tadalafil for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia. Expert Opin Drug Metab Toxicol 2006; **2:** 609.
44. Kaplan HS: The new sex therapy: active treatment of sexual dysfunctions: Brunner/ Mazel 1974.
45. Masters W, Johnson, V: Human sexual response. New York, NY: Little, Brown and Co. 1966.
46. Marwick C: Survey says patients expect little physician help on sex. JAMA 1999; **281:** 2173.
47. Althof SE, Rosen RC, Perelman MA et al: Standard operating procedures for taking a sexual history. J Sex Med 2013; **10:** 26.
48. Serefoglu EC, McMahon CG, Waldinger MD et al: An evidence-based unified definition of lifelong and acquired premature ejaculation: report of the second International Society for Sexual Medicine Ad Hoc Committee for the Definition of Premature Ejaculation. Sex Med 2014; **2:** 41.
49. Lee JH, Ngengwe R, Jones P et al: Erectile dysfunction as a coronary artery disease risk equivalent. J Nucl Cardiol 2008; **15:** 800.
50. Fillo J, Levcikova M, Ondrusova M et al: Importance of different grades of abdominal obesity on testosterone level, erectile dysfunction, and clinical coincidence. Am J Mens Health 2017; **11:** 240.
51. Ghanem HM, Salonia A and Martin-Morales A: SOP: physical examination and laboratory testing for men with erectile dysfunction. J Sex Med 2013; **10:** 108.
52. McCabe MP and Althof SE: A systematic review of the psychosocial outcomes associated with erectile dysfunction: does the impact of erectile dysfunction extend beyond a man's inability to have sex? J Sex Med 2014; **11:** 347.
53. Corona G, Petrone L, Mannucci E et al: Assessment of the relational factor in male patients consulting for sexual dysfunction: the concept of couple sexual dysfunction. J Androl 2006; **27:** 795.
54. McCabe M, Althof SE, Assalian P et al: Psychological and interpersonal dimensions of sexual function and dysfunction. J Sex Med 2010; **7:** 327.
55. Jannini EA, Isidori AM, Aversa A et al: Which is first? The controversial issue of precedence in the treatment of male sexual dysfunctions. J Sex Med 2013; **10:** 2359.
56. Althof SE, Buvat J, Gutkin SW et al: Sexual satisfaction in men with erectile dysfunction: correlates and potential predictors. J Sex Med 2010; **7:** 203.
57. Mulhall JP, Goldstein I, Bushmakin AG et al: Validation of the erection hardness score. J Sex Med 2007; **4:** 1626.
58. Rosen RC, Cappelleri JC, Smith MD et al: Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res 1999; **11:** 319.
59. Rosen RC, Riley A, Wagner G et al: The International Index of Erectile Function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 1997; **49:** 822.
60. Cappelleri JC, Rosen RC, Smith MD et al: Diagnostic evaluation of the erectile function domain of the International Index of Erectile Function. Urology 1999; **54:** 346.
61. Rosen RC, Allen KR, Ni X et al: Minimal clinically important differences in the erectile function domain of the International Index of Erectile Function scale. Eur Urol 2011; **60:** 1010.
62. Rosen RC, Catania J, Pollack L et al: Male Sexual Health Questionnaire (MSHQ): scale development and psychometric validation. Urology 2004; **64:** 777.
63. Rosen RC, Catania JA, Althof SE et al: Development and validation of four-item version of Male Sexual Health Questionnaire to assess ejaculatory dysfunction. Urology 2007; **69:** 805.

64. Dong JY, Zhang YH and Qin LQ: Erectile dysfunction and risk of cardiovascular disease: meta-analysis of prospective cohort studies. J Am Coll Cardiol 2011; **58:** 1378.
65. Vlachopoulos CV, Terentes-Printzios DG, Ioakeimidis NK et al: Prediction of cardiovascular events and all-cause mortality with erectile dysfunction: a systematic review and meta-analysis of cohort studies. Circ Cardiovasc Qual Outcomes 2013; **6:** 99.
66. Thompson IM, Tangen CM, Goodman PJ et al: Erectile dysfunction and subsequent cardiovascular disease. JAMA 2005; **294:** 2996.
67. Montorsi P, Ravagnani PM, Galli S et al: Association between erectile dysfunction and coronary artery disease. Role of coronary clinical presentation and extent of coronary vessels involvement: The COBRA trial. Eur Heart J 2006; **27:** 2632.
68. Hotaling JM, Walsh TJ, Macleod LC et al: Erectile dysfunction is not independently associated with cardiovascular death: data from the Vitamins and Lifestyle (VITAL) Study. J Sex Med 2012; **9:** 2104.
69. Nehra A, Jackson G, Miner M et al: The Princeton III consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc 2012; **87:** 766.
70. Hippisley-Cox J, Coupland C and Brindle P: Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ 2017; **357:** j2099.
71. Dahabreh IJ and Paulus JK: Association of episodic physical and sexual activity with triggering of acute cardiac events: systematic review and meta-analysis. JAMA 2011; **305:** 1225.
72. Wu FC, Tajar A, Beynon JM et al: Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med 2010; **363:** 123.
73. Brambilla DJ, O'Donnell AB, Matsumoto AM et al: Intraindividual variation in levels of serum testosterone and other reproductive and adrenal hormones in men. Clin Endocrinol (Oxf) 2007; **67:** 853.
74. Brambilla DJ, Matsumoto AM, Araujo AB et al: The effect of diurnal variation on clinical measurement of serum testosterone and other sex hormone levels in men. J Clin Endocrinol Metab 2009; **94:** 907.
75. Welliver RC, Jr., Wiser HJ, Brannigan RE et al: Validity of midday total testosterone levels in older men with erectile dysfunction. J Urol 2014; **192:** 165.
76. Woolf PD, Hamill RW, McDonald JV et al: Transient hypogonadotropic hypogonadism caused by critical illness. J Clin Endocrinol Metab 1985; **60:** 444.
77. Birthi P, Nagar VR, Nickerson R et al: Hypogonadism associated with long-term opioid therapy: a systematic review. J Opioid Manag 2015; **11:** 255.
78. Elhanbly S and Elkholy A: Nocturnal penile erections: the role of Rigiscan in the diagnosis of vascular erectile dysfunction. J Sex Med 2012; **9:** 3219.
79. Jannini EA, Granata AM, Hatzimouratidis K et al: Use and abuse of Rigiscan in the diagnosis of erectile dysfunction. J Sex Med 2009; **6:** 1820.
80. Sikka SC, Hellstrom WJ, Brock G et al: Standardization of vascular assessment of erectile dysfunction: standard operating procedures for duplex ultrasound. J Sex Med 2013; **10:** 120.
81. Vruggink PA, Diemont WL, Debruyne FM et al: Enhanced pharmacological testing in patients with erectile dysfunction. J Androl 1995; **16:** 163.
82. Diederichs W, Stief CG, Lue TF et al: Sympathetic inhibition of papaverine induced erection. J Urol 1991; **146:** 195.
83. Elhanbly S, Schoor R, Elmogy M et al: What nonresponse to intracavernous injection really indicates: a determination by quantitative analysis. J Urol 2002; **167:** 192.
84. Lehmann K, John H, Kacl G et al: Variable response to intracavernous prostaglandin E1 testing for erectile dysfunction. Urology 1999; **54:** 539.
85. Souper R, Hartmann J, Alvarez M et al: Correlation between peak systolic velocity and diameter of cavernosal arteries in flaccid versus dynamic state for the evaluation of erectile dysfunction. Int J Impot Res 2017; **29:** 132.
86. Papagiannopoulos D, Khare N and Nehra A: Evaluation of young men with organic erectile dysfunction. Asian J Androl 2015; **17:** 11.
87. Ioakeimidis N, Vlachopoulos C, Rokkas K et al: Dynamic penile peak systolic velocity predicts major adverse cardiovascular events in hypertensive patients with erectile dysfunction. J Hypertens 2016; **34:** 860.
88. Spiliopoulos S, Shaida N, Katsanos K et al: The role of interventional radiology in the diagnosis and management of male impotence. Cardiovasc Intervent Radiol 2013; **36:** 1204.
89. Giuliano F and Rowland DL: Standard operating procedures for neurophysiologic assessment of male sexual dysfunction. J Sex Med 2013; **10:** 1205.
90. Banner LL and Anderson RU: Integrated sildenafil and cognitive-behavior sex therapy for psychogenic erectile dysfunction: a pilot study. J Sex Med 2007; **4:** 1117.
91. Melnik T, Abdo CH, de Moraes JF et al: Satisfaction with the treatment, confidence and 'naturalness' in engaging in sexual activity in men with psychogenic erectile dysfunction: preliminary results of a randomized controlled trial of three therapeutic approaches. BJU Int 2012; **109:** 1213.
92. Titta M, Tavolini IM, Dal Moro F et al: Sexual counseling improved erectile rehabilitation after non-nerve-sparing radical retropubic prostatectomy or cystectomy--results of a randomized prospective study. J Sex Med 2006; **3:** 267.

93. Wylie KR, Jones RH and Walters S: The potential benefit of vacuum devices augmenting psychosexual therapy for erectile dysfunction: a randomized controlled trial. J Sex Marital Ther 2003; **29:** 227.
94. McCabe MP, Price E, Piterman L et al: Evaluation of an internet-based psychological intervention for the treatment of erectile dysfunction. Int J Impot Res 2008; **20:** 324.
95. van Lankveld JJ, Leusink P, van Diest S et al: Internet-based brief sex therapy for heterosexual men with sexual dysfunctions: a randomized controlled pilot trial. J Sex Med 2009; **6:** 2224.
96. Andersson E, Walen C, Hallberg J et al: A randomized controlled trial of guided internet-delivered cognitive behavioral therapy for erectile dysfunction. J Sex Med 2011; **8:** 2800.
97. Melnik T, Soares BG and Nasello AG: The effectiveness of psychological interventions for the treatment of erectile dysfunction: systematic review and meta-analysis, including comparisons to sildenafil treatment, intracavernosal injection, and vacuum devices. J Sex Med 2008; **5:** 2562.
98. Chambers SK, Occhipinti S, Schover L et al: A randomised controlled trial of a couples-based sexuality intervention for men with localised prostate cancer and their female partners. Psychooncology 2015; **24:** 748.
99. Ljunggren C and Stroberg P: Improvement in sexual function after robot-assisted radical prostatectomy: a rehabilitation program with involvement of a clinical sexologist. Cent European J Urol 2015; **68:** 214.
100. Esposito K, Giugliano F, Di Palo C et al: Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. JAMA 2004; **291:** 2978.
101. Esposito K, Ciotola M, Giugliano F et al: Mediterranean diet improves erectile function in subjects with the metabolic syndrome. Int J Impot Res 2006; **18:** 405.
102. Esposito K, Ciotola M, Giugliano F et al: Effects of intensive lifestyle changes on erectile dysfunction in men. J Sex Med 2009; **6:** 243.
103. Collins CE, Jensen ME, Young MD et al: Improvement in erectile function following weight loss in obese men: the SHED-IT randomized controlled trial. Obes Res Clin Pract 2013; **7:** e450.
104. Khoo J, Piantadosi C, Worthley S et al: Effects of a low-energy diet on sexual function and lower urinary tract symptoms in obese men. Int J Obes (Lond) 2010; **34:** 1396.
105. Khoo J, Tian HH, Tan B et al: Comparing effects of low- and high-volume moderate-intensity exercise on sexual function and testosterone in obese men. J Sex Med 2013; **10:** 1823.
106. Wing RR, Rosen RC, Fava JL et al: Effects of weight loss intervention on erectile function in older men with type 2 diabetes in the Look Ahead Trial. J Sex Med 2010; **7:** 156.
107. Lamina S, Okoye CG and Dagogo TT: Therapeutic effect of an interval exercise training program in the management of erectile dysfunction in hypertensive patients. J Clin Hypertens (Greenwich) 2009; **11:** 125.
108. Begot I, Peixoto TC, Gonzaga LR et al: A home-based walking program improves erectile dysfunction in men with an acute myocardial infarction. Am J Cardiol 2015; **115:** 571.
109. Kalka D, Domagala Z, Dworak J et al: Association between physical exercise and quality of erection in men with ischaemic heart disease and erectile dysfunction subjected to physical training. Kardiol Pol 2013; **71:** 573.
110. Kalka D, Domagala ZA, Kowalewski P et al: Effect of endurance cardiovascular training intensity on erectile dysfunction severity in men with ischemic heart disease. Am J Mens Health 2015; **9:** 360.
111. Kovac JR, Labbate C, Ramasamy R et al: Effects of cigarette smoking on erectile dysfunction. Andrologia 2015; **47:** 1087.
112. Afif-Abdo J, Teloken C, Damiao R et al: Comparative cross-over study of sildenafil and apomorphine for treating erectile dysfunction. BJU Int 2008; **102:** 829.
113. Ali ST: Effectiveness of sildenafil citrate (Viagra®) and tadalafil (Cialis®) on sexual responses in Saudi men with erectile dysfunction in routine clinical practice. Pak J Pharm Sci 2008; **21:** 275.
114. Althof SE, O'Leary M P, Cappelleri JC et al: Sildenafil citrate improves self-esteem, confidence, and relationships in men with erectile dysfunction: results from an international, multi-center, double-blind, placebo-controlled trial. J Sex Med 2006; **3:** 521.
115. Bai WJ, Li HJ, Dai YT et al: An open-label, multicenter, randomized, crossover study comparing sildenafil citrate and tadalafil for treating erectile dysfunction in Chinese men naive to phosphodiesterase 5 inhibitor therapy. Asian J Androl 2015; **17:** 61.
116. Bai WJ, Li HJ, Jin JJ et al: A randomized clinical trial investigating treatment choice in Chinese men receiving sildenafil citrate and tadalafil for treating erectile dysfunction. Asian J Androl 2016; **4**: 500.
117. Basar M, Tekdogan UY, Yilmaz E et al: The efficacy of sildenafil in different etiologies of erectile dysfunction. Int Urol Nephrol 2001; **32:** 403.
118. Becher E, Tejada Noriega A, Gomez R et al: Sildenafil citrate (Viagra) in the treatment of men with erectile dysfunction in southern Latin America: a double-blind, randomized, placebo-controlled, parallel-group, multicenter, flexible-dose escalation study. Int J Impot Res 2002; **14 Suppl 2:** S33.
119. Belkoff LH, McCullough A, Goldstein I et al: An open-label, long-term evaluation of the safety, efficacy and tolerability of avanafil in male patients with mild to severe erectile dysfunction. Int J Clin Pract 2013; **67:** 333.
120. Benard F, Carrier S, Lee JC et al: Men with mild erectile dysfunction benefit from sildenafil treatment. J Sex Med 2010; **7:** 3725.

121. Benchekroun A, Faik M, Benjelloun S et al: A baseline-controlled, open-label, flexible dose-escalation study to assess the safety and efficacy of sildenafil citrate (Viagra) in patients with erectile dysfunction. Int J Impot Res 2003; **15 Suppl 1:** S19.
122. Boddi V, Castellini G, Casale H et al: An integrated approach with vardenafil orodispersible tablet and cognitive behavioral sex therapy for treatment of erectile dysfunction: a randomized controlled pilot study. Andrology 2015; **3:** 909.
123. Brock G, Carrier S, Alarie P et al: The effect of physician and patient education when combined with vardenafil treatment in Canadian males with erectile dysfunction: an open-label, factorial-designed, cluster-randomized clinical trial. J Sex Med 2008; **5:** 705.
124. Brock GB, McMahon CG, Chen KK et al: Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. J Urol 2002; **168:** 1332.
125. Buvat J, Hatzichristou D, Maggi M et al: Efficacy, tolerability and satisfaction with sildenafil citrate 100-mg titration compared with continued 50-mg dose treatment in men with erectile dysfunction. BJU Int 2008; **102:** 1645.
126. Buvat J, Buttner H, Hatzimouratidis K et al: Adherence to initial PDE-5 inhibitor treatment: randomized open-label study comparing tadalafil once a day, tadalafil on demand, and sildenafil on demand in patients with erectile dysfunction. J Sex Med 2013; **10:** 1592.
127. Hatzimouratidis K, Buvat J, Buttner H et al: Psychosocial outcomes after initial treatment of erectile dysfunction with tadalafil once daily, tadalafil on demand or sildenafil citrate on demand: results from a randomized, open-label study. Int J Impot Res 2014; **26:** 223.
128. Buvat J, Hatzichristou D, Boess FG et al: Continuation and effectiveness of tadalafil once daily during a 6-month observational study in erectile dysfunction: the EDATE Study. Int J Clin Pract 2014; **68:** 1087.
129. Carrier S, Brock G, Casey R et al: Treatment satisfaction with sildenafil in a Canadian real-life setting. A 6-month prospective observational study of primary care practices. J Sex Med 2007; **4:** 1414.
130. Carrier S, Brock GB, Pommerville PJ et al: Efficacy and safety of oral tadalafil in the treatment of men in Canada with erectile dysfunction: a randomized, double-blind, parallel, placebo-controlled clinical trial. J Sex Med 2005; **2:** 685.
131. Carson C, Shabsigh R, Segal S et al: Efficacy, safety, and treatment satisfaction of tadalafil versus placebo in patients with erectile dysfunction evaluated at tertiary-care academic centers. Urology 2005; **65:** 353.
132. Carson CC, Rajfer J, Eardley I et al: The efficacy and safety of tadalafil: an update. BJU Int 2004; **93:** 1276.
133. Chen KK, Hsieh JT, Huang ST et al: ASSESS-3: a randomised, double-blind, flexible-dose clinical trial of the efficacy and safety of oral sildenafil in the treatment of men with erectile dysfunction in Taiwan. Int J Impot Res 2001; **13:** 221.
134. Chen KK, Jiann BP, Lin JS et al: Efficacy and safety of on-demand oral tadalafil in the treatment of men with erectile dysfunction in Taiwan: a randomized, double-blind, parallel, placebo-controlled clinical study. J Sex Med 2004; **1:** 201.
135. Cheng E: Real-life safety and efficacy of vardenafil in the treatment of erectile dysfunction-results from 30,010 US patients. J Sex Med 2007; **4:** 432.
136. Choi HK, Ahn TY, Kim JJ et al: A double-blind, randomised- placebo, controlled, parallel group, multicentre, flexible-dose escalation study to assess the efficacy and safety of sildenafil administered as required to male outpatients with erectile dysfunction in Korea. Int J Impot Res 2003; **15:** 80.
137. Choi HK, Kim JJ, Kim SC et al: A randomised, double-blind, parallel, placebo-controlled study of the efficacy and safety of tadalafil administered on-demand to men with erectile dysfunction in Korea. Korean J Urol 2006; **47:** 852.
138. Christiansen E, Guirguis WR, Cox D et al: Long-term efficacy and safety of oral Viagra (sildenafil citrate) in men with erectile dysfunction and the effect of randomised treatment withdrawal. Int J Impot Res 2000; **12:** 177.
139. Costa P, Buvat J, Holmes S et al: Predictors of tadalafil efficacy in men with erectile dysfunction: the SURE study comparing two dosing regimens. J Sex Med 2006; **3:** 1050.
140. Mirone V, Costa P, Damber JE et al: An evaluation of an alternative dosing regimen with tadalafil, 3 times/week, for men with erectile dysfunction: SURE study in 14 European countries. Eur Urol 2005; **47:** 846.
141. Costa P, Grandmottet G, Mai HD et al: Impact of a first treatment with phosphodiesterase inhibitors on men and partners' quality of sexual life: results of a prospective study in primary care. J Sex Med 2013; **10:** 1850.
142. Dean J, Hackett GI, Gentile V et al: Psychosocial outcomes and drug attributes affecting treatment choice in men receiving sildenafil citrate and tadalafil for the treatment of erectile dysfunction: results of a multicenter, randomized, open-label, crossover study. J Sex Med 2006; **3:** 650.
143. Eardley I, Mirone V, Montorsi F et al: An open-label, multicentre, randomized, crossover study comparing sildenafil citrate and tadalafil for treating erectile dysfunction in men naive to phosphodiesterase 5 inhibitor therapy. BJU Int 2005; **96:** 1323.

144. Dinsmore WW, Hodges M, Hargreaves C et al: Sildenafil citrate (Viagra) in erectile dysfunction: near normalization in men with broad-spectrum erectile dysfunction compared with age-matched healthy control subjects. Urology 1999; **53:** 800.
145. Donatucci C, Eardley I, Buvat J et al: Vardenafil improves erectile function in men with erectile dysfunction irrespective of disease severity and disease classification. J Sex Med 2004; **1:** 301.
146. Eardley I, Gentile V, Austoni E et al: Efficacy and safety of tadalafil in a western European population of men with erectile dysfunction. BJU Int 2004; **94:** 871.
147. Eardley I, Morgan R, Dinsmore W et al: Efficacy and safety of sildenafil citrate in the treatment of men with mild to moderate erectile dysfunction. Br J Psychiatry 2001; **178:** 325.
148. Eardley I, Wright P, MacDonagh R et al: An open-label, randomized, flexible-dose, crossover study to assess the comparative efficacy and safety of sildenafil citrate and apomorphine hydrochloride in men with erectile dysfunction. BJU Int 2004; **93:** 1271.
149. Edwards D, Hackett G, Collins O et al: Vardenafil improves sexual function and treatment satisfaction in couples affected by erectile dysfunction (ED): a randomized, double-blind, placebo-controlled trial in PDE5 inhibitor-naive men with ED and their partners. J Sex Med 2006; **3:** 1028.
150. El Khiat Y, Ghazi S, Allam A et al: Psychosocial impact and effectiveness of tadalafil among treatment-naive and previously-treated men with erectile dysfunction in Saudi Arabia and other Gulf-region countries. Curr Med Res Opin 2008; **24:** 1965.
151. Fagelman E, Fagelman A and Shabsigh R: Efficacy, safety, and use of sildenafil in urologic practice. Urology 2001; **57:** 1141.
152. Zonana Farca E, Francolugo-Velez V, Moy-Eransus C et al: Self-esteem, confidence and relationship satisfaction in men with erectile dysfunction: a randomized, parallel-group, double-blind, placebo-controlled study of sildenafil in Mexico. Int J Impot Res 2008; **20:** 402.
153. Fisher WA, Rosen RC, Mollen M et al: Improving the sexual quality of life of couples affected by erectile dysfunction: a double-blind, randomized, placebo-controlled trial of vardenafil. J Sex Med 2005; **2:** 699.
154. Goldstein I, Fisher WA, Sand M et al: Women's sexual function improves when partners are administered vardenafil for erectile dysfunction: a prospective, randomized, double-blind, placebo-controlled trial. J Sex Med 2005; **2:** 819.
155. Fugl-Meyer KS, Stothard D, Belger M et al: The effect of tadalafil on psychosocial outcomes in Swedish men with erectile distress: a multicentre, non-randomised, open-label clinical study. Int J Clin Pract 2006; **60:** 1386.
156. Fujisawa M and Sawada K: Clinical efficacy and safety of sildenafil in elderly patients with erectile dysfunction. Arch Androl 2004; **50:** 255.
157. Giammusso B, Colpi GM, Cormio L et al: An open-label, randomized, flexible-dose, crossover study to assess the comparative efficacy and safety of sildenafil citrate and apomorphine hydrochloride in men with erectile dysfunction. Urol Int 2008; **81:** 409.
158. Gil A, Martinez E, Oyaguez I et al: Erectile dysfunction in a primary care setting: results of an observational, no-control-group, prospective study with sildenafil under routine conditions of use. Int J Impot Res 2001; **13:** 338.
159. Gittelman M, McMahon CG, Rodriguez-Rivera JA et al: The POTENT II randomised trial: efficacy and safety of an orodispersible vardenafil formulation for the treatment of erectile dysfunction. Int J Clin Pract 2010; **64:** 594.
160. Giuliano F, Donatucci C, Montorsi F et al: Vardenafil is effective and well-tolerated for treating erectile dysfunction in a broad population of men, irrespective of age. BJU Int 2005; **95:** 110.
161. Giuliano F, Montorsi F, Mirone V et al: Switching from intracavernous prostaglandin E1 injections to oral sildenafil citrate in patients with erectile dysfunction: results of a multicenter European study. The Sildenafil Multicenter Study Group. J Urol 2000; **164:** 708.
162. Glina S, Bertero E, Claro J et al: Efficacy and safety of flexible-dose oral sildenafil citrate (Viagra) in the treatment of erectile dysfunction in Brazilian and Mexican men. Int J Impot Res 2002; **14 Suppl 2:** S27.
163. Glina S, Damiao R, Abdo C et al: Self-esteem, confidence, and relationships in Brazilian men with erectile dysfunction receiving sildenafil citrate: a randomized, parallel-group, double-blind, placebo-controlled study in Brazil. J Sex Med 2009; **6:** 268.
164. Cairoli C, Reyes LA, Henneges C et al: PDE5 inhibitor treatment persistence and adherence in Brazilian men: post-hoc analyses from a 6-month, prospective, observational study. Int Braz J Urol 2014; **40:** 390.
165. Gokce MI, Gulpinar O, Ozturk E et al: Effect of atorvastatin on erectile functions in comparison with regular tadalafil use. A prospective single-blind study. Int Urol Nephrol 2012; **44:** 683.
166. Goldstein I, Kim E, Steers WD et al: Efficacy and safety of tadalafil in men with erectile dysfunction with a high prevalence of comorbid conditions: results from MOMENTUS: multiple observations in men with erectile dysfunction in National Tadalafil Study in the US. J Sex Med 2007; **4:** 166.
167. Goldstein I, McCullough AR, Jones LA et al: A randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of avanafil in subjects with erectile dysfunction. J Sex Med 2012; **9:** 1122.

168. Goldstein I, Lue TF, Padma-Nathan H et al: Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. N Engl J Med 1998; **338:** 1397.
169. Goldstein I, Tseng LJ, Creanga D et al: Efficacy and safety of sildenafil by age in men with erectile dysfunction. J Sex Med 2016; **13:** 852.
170. Gomez F, Davila H, Costa A et al: Efficacy and safety of oral sildenafil citrate (Viagra) in the treatment of male erectile dysfunction in Colombia, Ecuador, and Venezuela: a double-blind, multicenter, placebo-controlled study. Int J Impot Res 2002; **14 Suppl 2:** S42.
171. Govier F, Potempa AJ, Kaufman J et al: A multicenter, randomized, double-blind, crossover study of patient preference for tadalafil 20 mg or sildenafil citrate 50 mg during initiation of treatment for erectile dysfunction. Clin Ther 2003; **25:** 2709.
172. Guo YL, Zhu JC, Pan TM et al: Efficacy and safety of on-demand tadalafil for the treatment of erectile dysfunction in South-East Asian men. Int J Urol 2006; **13:** 721.
173. Hartmann U, Hanisch JU and Mattern A: The real-life perception of efficacy, attitude, satisfaction and safety of vardenafil therapy (REPEAT): a prospective, non-interventional, observational study. Aging Male 2014; **17:** 117.
174. Hatzichristou D, Cuzin B, Martin-Morales A et al: Vardenafil improves satisfaction rates, depressive symptomatology, and self-confidence in a broad population of men with erectile dysfunction. J Sex Med 2005; **2:** 109.
175. Hatzichristou D, Montorsi F, Buvat J et al: The efficacy and safety of flexible-dose vardenafil (Levitra) in a broad population of European men. Eur Urol 2004; **45:** 634.
176. Hatzichristou D, Vardi Y, Papp G et al: Effect of tadalafil on sexual timing behavior patterns in men with erectile dysfunction: integrated analysis of randomized, placebo controlled trials. J Urol 2005; **174:** 1356.
177. Heiman JR, Talley DR, Bailen JL et al: Sexual function and satisfaction in heterosexual couples when men are administered sildenafil citrate (Viagra) for erectile dysfunction: a multicentre, randomised, double-blind, placebo-controlled trial. Bjog 2007; **114:** 437.
178. Hellstrom WJ, Gittelman M, Karlin G et al: Vardenafil for treatment of men with erectile dysfunction: efficacy and safety in a randomized, double-blind, placebo-controlled trial. J Androl 2002; **23:** 763.
179. Hellstrom WJ, Gittelman M, Karlin G et al: Sustained efficacy and tolerability of vardenafil, a highly potent selective phosphodiesterase type 5 inhibitor, in men with erectile dysfunction: results of a randomized, double-blind, 26-week placebo-controlled pivotal trial. Urology 2003; **61:** 8.
180. Huang ST: Use of sildenafil citrate in treatment of Taiwanese men with erectile dysfunction: a single center experience. Chang Gung Med J 2001; **24:** 91.
181. Hundertmark J, Esterman A, Ben-Tovim D et al: The South Australian couples sildenafil study: double-blind, parallel-group randomized controlled study to examine the psychological and relationship consequences of sildenafil use in couples. J Sex Med 2007; **4:** 1126.
182. Isidori AM, Corona G, Aversa A et al: The SIAMS-ED trial: a national, independent, multicentre study on cardiometabolic and hormonal impairment of men with erectile dysfunction treated with vardenafil. Int J Endocrinol 2014; **2014:** doi:10.1155/2014/858715.
183. Jamshidian H, Borhan A, Kooraki S et al: Evaluation of the efficacy of once-daily use of tadalafil vs. on-demand use. Is there a cumulative effect? J Pak Med Assoc 2012; **62:** 1195.
184. Jannini EA, Isidori AM, Gravina GL et al: The ENDOTRIAL study: a spontaneous, open-label, randomized, multicenter, crossover study on the efficacy of sildenafil, tadalafil, and vardenafil in the treatment of erectile dysfunction. J Sex Med 2009; **6:** 2547.
185. Jarow JP, Burnett AL and Geringer AM: Clinical efficacy of sildenafil citrate based on etiology and response to prior treatment. J Urol 1999; **162:** 722.
186. Jarvi K, Dula E, Drehobl M et al: Daily vardenafil for 6 months has no detrimental effects on semen characteristics or reproductive hormones in men with normal baseline levels. J Urol 2008; **179:** 1060.
187. Jiann BP, Yu CC, Tsai JY et al: What to learn about sildenafil in the treatment of erectile dysfunction from 3-year clinical experience. Int J Impot Res 2003; **15:** 412.
188. Jones LA, Klimberg IW, McMurray JG et al: Effect of sildenafil citrate on the male sexual experience assessed with the sexual experience questionnaire: a multicenter, double-blind, placebo-controlled trial with open-label extension. J Sex Med 2008; **5:** 1955.
189. Kadioglu A, Grohmann W, Depko A et al: Quality of erections in men treated with flexible -dose sildenafil for erectile dysfunction: multicenter trial with a double-blind, randomized, placebo-controlled phase and an open-label phase. J Sex Med 2008; **5:** 726.
190. Kamalov AA, Dorofeev SD, Efremov EA et al: The Russian experience of studying vardenafil efficacy and safety in men with erectile dysfunction of various aetiologies. Journal of Men's Health 2008; **5:** 36.
191. Kamel A, Khaouli R, Sabha M et al: The real-life safety and efficacy of vardenafil: an international post-marketing surveillance study of 2824 patients from the Middle East. Clin Drug Investig 2007; **27:** 339.
192. Kang DH, Lee JY, Park SY et al: Efficacy and safety of tadalafil 5 mg administered once daily in Korean men with erectile dysfunction: a prospective, multicenter study. Korean J Urol 2010; **51:** 647.

193. Kang DH, Lee JY, Chung JH et al: Comparison of efficacy for erectile function and lower urinary tract symptoms of tadalafil 20 mg on-demand and 5 mg once daily in patients with erectile dysfunction. Int J Clin Pract 2012; **66:** 813.
194. Kim E, Seftel A, Goldfischer E et al: Efficacy of as needed PDE5 inhibitor therapy vs. tadalafil once daily on improvement in erectile dysfunction. J Sex Med 2014; **11**: 176.
195. Seftel AD, Rosen RC, Hayes RP et al: Effect of once-daily tadalafil on confidence and perceived difficulty in performing sexual intercourse in men who were incomplete responders to as-needed PDE5 inhibitor treatment. Int J Clin Pract 2014; **68:** 841.
196. Kim E, Seftel A, Goldfischer E et al: Comparative efficacy of tadalafil once daily in men with erectile dysfunction who demonstrated previous partial responses to as-needed sildenafil, tadalafil, or vardenafil. Curr Med Res Opin 2015; **31:** 379.
197. Burns PR, Rosen RC, Dunn M et al: Treatment satisfaction of men and partners following switch from on-demand phosphodiesterase type 5 inhibitor therapy to tadalafil 5 mg once daily. J Sex Med 2015; **12:** 720.
198. Kim CM, Kim YS, Sunwoo S et al: Post-marketing surveillance study of the efficacy and safety of vardenafil among patients with erectile dysfunction in primary care. Int J Impot Res 2007; **19:** 393.
199. Kirby M, Creanga DL and Stecher VJ: Erectile function, erection hardness and tolerability in men treated with sildenafil 100 mg vs. 50 mg for erectile dysfunction. Int J Clin Pract 2013; **67:** 1034.
200. Kobayashi K, Hisasue S, Kato R et al: Outcome analysis of sildenafil citrate for erectile dysfunction of Japanese patients. Int J Impot Res 2006; **18:** 302.
201. Kongkanand A, Ratana-Olarn K, Ruangdilokrat S et al: The efficacy and safety of oral sildenafil in Thai men with erectile dysfunction: a randomized, double-blind, placebo controlled, flexible-dose study. J Med Assoc Thai 2003; **86:** 195.
202. Koulikov D, Fridmans A, Chertin B et al: Is sildenafil citrate associated with an amelioration of the symptomatology of androgen decline in the aging male? J Urol 2007; **177:** 2267.
203. Kumar S, Roat R, Agrawal S et al: Combination therapy of tadalafil and pentoxifylline in severe erectile dysfunction: a prospective randomized trial. Pol Przegl Chir 2015; **87:** 377.
204. Levinson IP, Khalaf IM, Shaeer KZ et al: Efficacy and safety of sildenafil citrate (Viagra) for the treatment of erectile dysfunction in men in Egypt and South Africa. Int J Impot Res 2003; **15 Suppl 1:** S25.
205. Lewis R, Bennett CJ, Borkon WD et al: Patient and partner satisfaction with Viagra (sildenafil citrate) treatment as determined by the erectile dysfunction inventory of treatment satisfaction questionnaire. Urology 2001; **57:** 960.
206. Li G, Lan H, Liang J et al: Efficacy of tadalafil de-escalation in the treatment of psychogenic erectile dysfunction. Urol Int 2017; **98:** 205.
207. Lim PH, Li MK, Ng FC et al: Clinical efficacy and safety of sildenafil citrate (Viagra) in a multi-racial population in Singapore: a retrospective study of 1520 patients. Int J Urol 2002; **9:** 308.
208. Loran OB, Stroberg P, Lee SW et al: Sildenafil citrate 100 mg starting dose in men with erectile dysfunction in an international, double-blind, placebo-controlled study: effect on the sexual experience and reducing feelings of anxiety about the next intercourse attempt. J Sex Med 2009; **6:** 2826.
209. Magoha GA: Sildenafil (Viagra) in the treatment of male erectile dysfunction in Nairobi. East Afr Med J 2000; **77:** 76.
210. Marks LS, Duda C, Dorey FJ et al: Treatment of erectile dysfunction with sildenafil. Urology 1999; **53:** 19.
211. Martin-Morales A, Graziottin A, Jaoude GB et al: Improvement in sexual quality of life of the female partner following vardenafil treatment of men with erectile dysfunction: a randomized, double-blind, placebo-controlled study. J Sex Med 2011; **8:** 2831.
212. Martin-Morales A, Gutierrez-Hernandez P, Romero-Otero J et al: Duration of erection: does it really matter? A randomized, double-blind clinical trial to assess the impact of vardenafil ODT on duration of erection and its correlation with patients' and partners' sexual quality of life and duration of intercourse: the VADEOPEN study. J Sex Med 2014; **11:** 1527.
213. Martin-Morales A, Haro JM, Beardsworth A et al: Therapeutic effectiveness and patient satisfaction after 6 months of treatment with tadalafil, sildenafil, and vardenafil: results from the erectile dysfunction observational study (EDOS). Eur Urol 2007; **51:** 541.
214. Martin-Morales A, Meijide F, Garcia N et al: Efficacy of vardenafil and influence on self-esteem and self-confidence in patients with severe erectile dysfunction. J Sex Med 2007; **4:** 440.
215. Martinez-Jabaloyas JM, Gil-Salom M, Villamon-Fort R et al: Prognostic factors for response to sildenafil in patients with erectile dysfunction. Eur Urol 2001; **40:** 641.
216. McMahon CG, Samali R and Johnson H: Efficacy, safety and patient acceptance of sildenafil citrate as treatment for erectile dysfunction. J Urol 2000; **164:** 1192.
217. McMahon C, Kloner RA, Hutter Jr AM et al: Comparison of efficacy, safety, and tolerability of on-demand tadalafil and daily dosed tadalafil for the treatment of erectile dysfunction. J Sex Med 2005; **2:** 415.
218. McMahon C, Lording D, Stuckey B et al: Vardenafil improved erectile function in a "real-life" broad population study of men with moderate to severe erectile dysfunction in Australia and New Zealand. J Sex Med 2006; **3:** 892.

219. McMahon CG, Stuckey BG, Lording DW et al: A 6-month study of the efficacy and safety of tadalafil in the treatment of erectile dysfunction: a randomised, double-blind, parallel-group, placebo-controlled study in Australian men. Int J Clin Pract 2005; **59:** 143.
220. McMurray JG, Feldman RA, Auerbach SM et al: Long-term safety and effectiveness of sildenafil citrate in men with erectile dysfunction. Ther Clin Risk Manag 2007; **3:** 975.
221. Meuleman E, Cuzin B, Opsomer RJ et al: A dose -escalation study to assess the efficacy and safety of sildenafil citrate in men with erectile dysfunction. BJU Int 2001; **87:** 75.
222. Mirone V, Palmieri A, Cucinotta D et al: Flexible -dose vardenafil in a community-based population of men affected by erectile dysfunction: a 12-week open-label, multicenter trial. J Sex Med 2005; **2:** 842.
223. Moncada I, Martinez-Jabaloyas JM, Rodriguez-Vela L et al: Emotional changes in men treated with sildenafil citrate for erectile dysfunction: a double-blind, placebo-controlled clinical trial. J Sex Med 2009; **6:** 3469.
224. Montorsi F and Althof SE: Partner responses to sildenafil citrate (Viagra) treatment of erectile dysfunction. Urology 2004; **63:** 762.
225. Montorsi F, Aversa A, Moncada I et al: A randomized, double-blind, placebo-controlled, parallel study to assess the efficacy and safety of once-a-day tadalafil in men with erectile dysfunction who are naive to PDE5 inhibitors. J Sex Med 2011; **8:** 2617.
226. Porst H, Brock GB, Kula K et al: Effects of once-daily tadalafil on treatment satisfaction, psychosocial outcomes, spontaneous erections, and measures of endothelial function in men with erectile dysfunction but naive to phosphodiesterase type 5 inhibitors. J Androl 2012; **33:** 1305.
227. Montorsi F, Hellstrom WJ, Valiquette L et al: Vardenafil provides reliable efficacy over time in men with erectile dysfunction. Urology 2004; **64:** 1187.
228. Montorsi F, McDermott TE, Morgan R et al: Efficacy and safety of fixed-dose oral sildenafil in the treatment of erectile dysfunction of various etiologies. Urology 1999; **53:** 1011.
229. Montorsi F, Padma-Nathan H, Buvat J et al: Earliest time to onset of action leading to successful intercourse with vardenafil determined in an at-home setting: a randomized, double-blind, placebo-controlled trial. J Sex Med 2004; **1:** 168.
230. Montorsi F, Verheyden B, Meuleman E et al: Long-term safety and tolerability of tadalafil in the treatment of erectile dysfunction. Eur Urol 2004; **45:** 339.
231. Moreira SG, Jr., Brannigan RE, Spitz A et al: Side-effect profile of sildenafil citrate (Viagra) in clinical practice. Urology 2000; **56:** 474.
232. Morgentaler A, Barada J, Niederberger C et al: Efficacy and safety of tadalafil across ethnic groups and various risk factors in men with erectile dysfunction: use of a novel noninferiority study design. J Sex Med 2006; **3:** 492.
233. Gomery P, Bullock A, McGettigan J et al: Tadalafil is efficacious in Black American and Hispanic men with erectile dysfunction: results from multiple observations in men with erectile dysfunction in national tadalafil study in the US (MOMENTUS). Int J Impot Res 2007; **19:** 76.
234. Muller A, Smith L, Parker M et al: Analysis of the efficacy and safety of sildenafil citrate in the geriatric population. BJU Int 2007; **100:** 117.
235. Nagao K, Ishii N, Kamidono S et al: Safety and efficacy of vardenafil in patients with erectile dysfunction: result of a bridging study in Japan. Int J Urol 2004; **11:** 515.
236. Nagao K, Kimoto Y, Marumo K et al: Efficacy and safety of tadalafil 5, 10, and 20 mg in Japanese men with erectile dysfunction: results of a multicenter, randomized, double-blind, placebo-controlled study. Urology 2006; **68:** 845.
237. O'Leary MP, Althof SE, Cappelleri JC et al: Self-esteem, confidence and relationship satisfaction of men with erectile dysfunction treated with sildenafil citrate: a multicenter, randomized, parallel group, double-blind, placebo controlled study in the United States. J Urol 2006; **175:** 1058.
238. Ochiai A, Naya Y, Soh J et al: Efficacy of sildenafil as the first-step therapeutic tool for Japanese patients with erectile dysfunction. Int J Impot Res 2005; **17:** 339.
239. Olsson AM, Speakman MJ, Dinsmore WW et al: Sildenafil citrate (Viagra) is effective and well tolerated for treating erectile dysfunction of psychogenic or mixed aetiology. Int J Clin Pract 2000; **54:** 561.
240. Osegbe DN, Shittu OB, Aghaji AE et al: Sildenafil citrate (Viagra) for the treatment of erectile dysfunction in Nigerian men. Int J Impot Res 2003; **15 Suppl 1:** S15.
241. Padma-Nathan H, McMurray JG, Pullman WE et al: On-demand IC351 (Cialis) enhances erectile function in patients with erectile dysfunction. Int J Impot Res 2001; **13:** 2.
242. Padma-Nathan H, Steers WD and Wicker PA: Efficacy and safety of oral sildenafil in the treatment of erectile dysfunction: a double-blind, placebo-controlled study of 329 patients. Sildenafil Study Group. Int J Clin Pract 1998; **52:** 375.
243. Palumbo F, Bettocchi C, Selvaggi FP et al: Sildenafil: efficacy and safety in daily clinical experience. Eur Urol 2001; **40:** 176.
244. Pavone C, Curto F, Anello G et al: Prospective, randomized, crossover comparison of sublingual apomorphine (3 mg) with oral sildenafil (50 mg) for male erectile dysfunction. J Urol 2004; **172:** 2347.
245. Perimenis P, Gyftopoulos K, Giannitsas K et al: A comparative, crossover study of the efficacy and safety of sildenafil and apomorphine in men with evidence of arteriogenic erectile dysfunction. Int J Impot Res 2004; **16:** 2.

246. Perimenis P, Markou S, Gyftopoulos K et al: Efficacy of apomorphine and sildenafil in men with nonarteriogenic erectile dysfunction. A comparative crossover study. Andrologia 2004; **36:** 106.
247. Porst H, Behre HM, Jungwirth A et al: Comparative trial of treatment satisfaction, efficacy and tolerability of sildenafil versus apomorphine in erectile dysfunction--an open, randomized cross-over study with flexible dosing. Eur J Med Res 2007; **12:** 61.
248. Porst H, Gacci M, Buttner H et al: Tadalafil once daily in men with erectile dysfunction: an integrated analysis of data obtained from 1913 patients from six randomized, double-blind, placebo-controlled, clinical studies. Eur Urol 2014; **65:** 455.
249. Porst H, Giuliano F, Glina S et al: Evaluation of the efficacy and safety of once-a-day dosing of tadalafil 5mg and 10mg in the treatment of erectile dysfunction: results of a multicenter, randomized, double-blind, placebo-controlled trial. Eur Urol 2006; **50:** 351.
250. Porst H, Rajfer J, Casabe A et al: Long-term safety and efficacy of tadalafil 5 mg dosed once daily in men with erectile dysfunction. J Sex Med 2008; **5:** 2160.
251. Porst H, Rosen R, Padma-Nathan H et al: The efficacy and tolerability of vardenafil, a new, oral, selective phosphodiesterase type 5 inhibitor, in patients with erectile dysfunction: the first at-home clinical trial. Int J Impot Res 2001; **13:** 192.
252. Porst H, Sharlip ID, Hatzichristou D et al: Extended duration of efficacy of vardenafil when taken 8 hours before intercourse: a randomized, double-blind, placebo-controlled study. Eur Urol 2006; **50:** 1086.
253. Potempa AJ, Ulbrich E, Bernard I et al: Efficacy of vardenafil in men with erectile dysfunction: a flexible-dose community practice study. Eur Urol 2004; **46:** 73.
254. Rajfer J, Aliotta PJ, Steidle CP et al: Tadalafil dosed once a day in men with erectile dysfunction: a randomized, double-blind, placebo-controlled study in the US. Int J Impot Res 2007; **19:** 95.
255. Ralph D, Eardley I, Kell P et al: Improvement in erectile function on vardenafil treatment correlates with treatment satisfaction in both patients and their partners. BJU Int 2007; **100:** 130.
256. Rosen R, Janssen E, Wiegel M et al: Psychological and interpersonal correlates in men with erectile dysfunction and their partners: a pilot study of treatment outcome with sildenafil. J Sex Marital Ther 2006; **32:** 215.
257. Rosenberg MT, Adams PL, McBride TA et al: Improvement in duration of erection following phosphodiesterase type 5 inhibitor therapy with vardenafil in men with erectile dysfunction: the ENDURANCE study. Int J Clin Pract 2009; **63:** 27.
258. Roumeguere T, Verheyden B, Arver S et al: Therapeutic response after first month of tadalafil treatment predicts 12 months treatment continuation in patients with erectile dysfunction: results from the detect study. J Sex Med 2008; **5:** 1708.
259. Perimenis P, Roumeguere T, Heidler H et al: Evaluation of patient expectations and treatment satisfaction after 1-year tadalafil therapy for erectile dysfunction: the DETECT study. J Sex Med 2009; **6:** 257.
260. Rubio-Aurioles E, Casabe A, Torres LO et al: Efficacy and safety of tadalafil in the treatment of Latin American men with erectile dysfunction: results of integrated analyses. J Sex Med 2008; **5:** 1965.
261. Rubio-Aurioles E, Kim ED, Rosen RC et al: Impact on erectile function and sexual quality of life of couples: a double-blind, randomized, placebo-controlled trial of tadalafil taken once daily. J Sex Med 2009; **6:** 1314.
262. Seftel AD, Buvat J, Althof SE et al: Improvements in confidence, sexual relationship and satisfaction measures: results of a randomized trial of tadalafil 5 mg taken once daily. Int J Impot Res 2009; **21:** 240.
263. Rubio-Aurioles E, Porst H, Kim ED et al: A randomized open-label trial with a crossover comparison of sexual self-confidence and other treatment outcomes following tadalafil once a day vs. tadalafil or sildenafil on-demand in men with erectile dysfunction. J Sex Med 2012; **9:** 1418.
264. Sairam K, Kulinskaya E, Hanbury D et al: Oral sildenafil (Viagra) in male erectile dysfunction: use, efficacy and safety profile in an unselected cohort presenting to a British district general hospital. BMC Urol 2002; **2:** 4.
265. Saylan M, Khalaf I, Kadioglu A et al: Efficacy of tadalafil in Egyptian and Turkish men with erectile dysfunction. Int J Clin Pract 2006; **60:** 812.
266. Seftel AD, Creanga DL and Levinson IP: Sildenafil reduces bother associated with erectile dysfunction: pooled analysis of five randomized, double-blind trials. Int J Impot Res 2007; **19:** 584.
267. Seftel AD, Wilson SK, Knapp PM et al: The efficacy and safety of tadalafil in United States and Puerto Rican men with erectile dysfunction. J Urol 2004; **172:** 652.
268. Shabsigh R, Kaufman J, Magee M et al: A multicenter, double-blind, placebo-controlled trial to assess the efficacy of sildenafil citrate in men with unrecognized erectile dysfunction. Urology 2010; **76:** 373.
269. Shin YS, Lee SW, Park K et al: Effect of Levitra on sustenance of erection (EROS): an open-label, prospective, multicenter, single-arm study to investigate erection duration measured by stopwatch with flexible dose vardenafil administered for 8 weeks in subjects with erectile dysfunction. Int J Impot Res 2015; **27:** 95.

270. Skoumal R, Chen J, Kula K et al: Efficacy and treatment satisfaction with on-demand tadalafil (Cialis) in men with erectile dysfunction. Eur Urol 2004; **46:** 362.
271. Sommer F, Klotz T and Engelmann U: Improved spontaneous erectile function in men with mild-to-moderate arteriogenic erectile dysfunction treated with a nightly dose of sildenafil for one year: a randomized trial. Asian J Androl 2007; **9:** 134.
272. Sperling H, Debruyne F, Boermans A et al: The POTENT I randomized trial: efficacy and safety of an orodispersible vardenafil formulation for the treatment of erectile dysfunction. J Sex Med 2010; **7:** 1497.
273. Sperling H, Schneider T and Hanisch JU: Acceptance of therapy in vardenafil-treated patients with erectile dysfunction (ACTIVE): a noninterventional study in Germany. Int J Impot Res 2010; **22:** 61.
274. Staab A, Tillmann C, Forgue ST et al: Population dose-response model for tadalafil in the treatment of male erectile dysfunction. Pharm Res 2004; **21:** 1463.
275. Steers W, Guay AT, Leriche A et al: Assessment of the efficacy and safety of Viagra (sildenafil citrate) in men with erectile dysfunction during long-term treatment. Int J Impot Res 2001; **13:** 261.
276. Steidle CP, McCullough AR, Kaminetsky JC et al: Early sildenafil dose optimization and personalized instruction improves the frequency, flexibility, and success of sexual intercourse in men with erectile dysfunction. Int J Impot Res 2007; **19:** 154.
277. Stief C, Porst H, Saenz De Tejada I et al: Sustained efficacy and tolerability with vardenafil over 2 years of treatment in men with erectile dysfunction. Int J Clin Pract 2004; **58:** 230.
278. Stroberg P, Murphy A and Costigan T: Switching patients with erectile dysfunction from sildenafil citrate to tadalafil: results of a European multicenter, open-label study of patient preference. Clin Ther 2003; **25:** 2724.
279. Sunwoo S, Kim YS, Cho BL et al: Post-marketing surveillance study of the safety and efficacy of sildenafil prescribed in primary care to erectile dysfunction patients. Int J Impot Res 2005; **17:** 71.
280. Tan HM, Chin CM, Chua CB et al: Efficacy and tolerability of vardenafil in Asian men with erectile dysfunction. Asian J Androl 2008; **10:** 495.
281. Tan HM, Moh CL, Mendoza JB et al: Asian sildenafil efficacy and safety study (ASSESS-1): a double-blind, placebo-controlled, flexible-dose study of oral sildenafil in Malaysian, Singaporean, and Filipino men with erectile dysfunction. The ASSESS-1 study group. Urology 2000; **56:** 635.
282. Tang WH, Zhuang XJ, Ma LL et al: Effect of sildenafil on erectile dysfunction and improvement in the quality of sexual life in China: a multi-center study. Int J Clin Exp Med 2015; **8:** 11539.
283. Taylor J, Baldo OB, Storey A et al: Differences in side-effect duration and related bother levels between phosphodiesterase type 5 inhibitors. BJU Int 2009; **103:** 1392.
284. Tolra JR, Campana JM, Ciutat LF et al: Prospective, randomized, open-label, fixed-dose, crossover study to establish preference of patients with erectile dysfunction after taking the three PDE-5 inhibitors. J Sex Med 2006; **3:** 901.
285. Tsujimura A, Yamanaka M, Takahashi T et al: The clinical studies of sildenafil for the ageing male. Int J Androl 2002; **25:** 28.
286. Valiquette L, Montorsi F and Auerbach S: Vardenafil demonstrates first-dose success and reliability of penetration and maintenance of erection in men with erectile dysfunction - RELY -II. Can Urol Assoc J 2008; **2:** 187.
287. Valiquette L, Young JM, Moncada I et al: Sustained efficacy and safety of vardenafil for treatment of erectile dysfunction: a randomized, double-blind, placebo-controlled study. Mayo Clin Proc 2005; **80:** 1291.
288. Van Ahlen H, Zumbe J, Stauch K et al: The real -life safety and efficacy of vardenafil (REALISE) study: results in men from Europe and overseas with erectile dysfunction and cardiovascular or metabolic conditions. J Sex Med 2010; **7:** 3161.
289. Virag R: Indications and early results of sildenafil (Viagra) in erectile dysfunction. Urology 1999; **54:** 1073.
290. von Keitz A, Rajfer J, Segal S et al: A multicenter, randomized, double-blind, crossover study to evaluate patient preference between tadalafil and sildenafil. Eur Urol 2004; **45:** 499.
291. Wagner G, Montorsi F, Auerbach S et al: Sildenafil citrate (Viagra) improves erectile function in elderly patients with erectile dysfunction: a subgroup analysis. J Gerontol A Biol Sci Med Sci 2001; **56:** M113.
292. Wijitsettakul U and Pempongkosol S: The efficacy and safety of on-demand elonza; a generic product of sildenafil in Thai men with erectile dysfunction. J Med Assoc Thai 2013; **96:** 683.
293. Yang Y, Liu R, Jiang H et al: Association between dosage frequency and the treatment outcomes of sildenafil in young and middle-aged men with erectile dysfunction: a Chinese, multicenter, observational study. Urology 2015; **86:** 62.
294. Yip WC, Chiang HS, Mendoza JB et al: Efficacy and safety of on demand tadalafil in the treatment of East and Southeast Asian men with erectile dysfunction: a randomized double-blind, parallel, placebo-controlled clinical study. Asian J Androl 2006; **8:** 685.
295. Young JM, Bennett C, Gilhooly P et al: Efficacy and safety of sildenafil citrate (Viagra) in black and Hispanic American men. Urology 2002; **60:** 39.

296. Zhang K, Xu B, Liu D et al: Sildenafil improves erectile hardness in Chinese men with erectile dysfunction: a real-life study analyzed on age stratification. Urology 2014; **83:** 831.
297. Zhao C, Kim SW, Yang DY et al: Efficacy and safety of avanafil for treating erectile dysfunction: results of a multicentre, randomized, double-blind, placebo-controlled trial. BJU Int 2012; **110:** 1801.
298. Zumbe J, Porst H, Sommer F et al: Comparable efficacy of once-daily versus on-demand vardenafil in men with mild-to-moderate erectile dysfunction: findings of the restore study. Eur Urol 2008; **54:** 204.
299. Park HJ, Kim SW, Kim JJ et al: A randomized, placebo-controlled, double-blind, multi-center therapeutic confirmatory study to evaluate the safety and efficacy of avanafil in Korean patients with erectile dysfunction. J Korean Med Sci 2017; **32:** 1016.
300. Li HJ, Bai WJ, Dai YT et al: An analysis of treatment preferences and sexual quality of life outcomes in female partners of Chinese men with erectile dysfunction. Asian J Androl 2016; **18:** 773.
301. Bai WJ, Li HJ, Jin JJ et al: A randomized clinical trial investigating treatment choice in Chinese men receiving sildenafil citrate and tadalafil for treating erectile dysfunction. Asian J Androl 2017; **19:** 500.
302. Capogrosso P, Ventimiglia E, Boeri L et al: Time of onset of vardenafil orodispersible tablet in a real-life setting - looking beyond randomized clinical trials. Expert Rev Clin Pharmacol 2017; **10:** 339.
303. Karabakan M, Keskin E, Akdemir S et al: Effect of tadalafil 5mg daily treatment on the ejaculatory times, lower urinary tract symptoms and erectile function in patients with erectile dysfunction. Int Braz J Urol 2017; **43:** 317.
304. Gong B, Ma M, Xie W et al: Direct comparison of tadalafil with sildenafil for the treatment of erectile dysfunction: a systematic review and meta-analysis. Int Urol Nephrol 2017; **49**: 1731.
305. Bekkering GE, Abou-Setta AM and Kleijnen J: The application of quantitative methods for identifying and exploring the presence of bias in systematic reviews: PDE-5 inhibitors for erectile dysfunction. Int J Impot Res 2008; **20:** 264.
306. Berner MM, Kriston L and Harms A: Efficacy of PDE-5-inhibitors for erectile dysfunction. A comparative meta-analysis of fixed-dose regimen randomized controlled trials administering the International Index of Erectile Function in broad-spectrum populations. Int J Impot Res 2006; **18:** 229.
307. Chen L, Staubli SE, Schneider MP et al: Phosphodiesterase 5 inhibitors for the treatment of erectile dysfunction: a trade-off network meta-analysis. Eur Urol 2015; **68:** 674.
308. Tsertsvadze A, Fink HA, Yazdi F et al: Oral phosphodiesterase-5 inhibitors and hormonal treatments for erectile dysfunction: a systematic review and meta-analysis. Ann Intern Med 2009; **151:** 650.
309. Tsertsvadze A, Yazdi F, Fink HA et al: Oral sildenafil citrate (Viagra) for erectile dysfunction: a systematic review and meta-analysis of harms. Urology 2009; **74:** 831.
310. Yuan J, Zhang R, Yang Z et al: Comparative effectiveness and safety of oral phosphodiesterase type 5 inhibitors for erectile dysfunction: a systematic review and network meta-analysis. Eur Urol 2013; **63:** 902.
311. Yuan JQ, Mao C, Yang ZY et al: A meta-regression evaluating the effectiveness and prognostic factors of oral phosphodiesterase type 5 inhibitors for the treatment of erectile dysfunction. Asian J Androl 2016; **18:** 60.
312. Burls A, Gold L and Clark W: Systematic review of randomised controlled trials of sildenafil (Viagra) in the treatment of male erectile dysfunction. Br J Gen Pract 2001; **51:** 1004.
313. Fink HA, Mac Donald R, Rutks IR et al: Sildenafil for male erectile dysfunction: a systematic review and meta-analysis. Arch Intern Med 2002; **162:** 1349.
314. Kriston L, Harms A and Berner MM: A meta-regression analysis of treatment effect modifiers in trials with flexible-dose oral sildenafil for erectile dysfunction in broad-spectrum populations. Int J Impot Res 2006; **18:** 559.
315. Moore RA, Edwards JE and McQuay HJ: Sildenafil (Viagra) for male erectile dysfunction: a meta-analysis of clinical trial reports. BMC Urol 2002; **2:** 6.
316. Peng Z, Yang L, Dong Q et al: Efficacy and safety of tadalafil once-a-day versus tadalafil on -demand in patients with erectile dysfunction: a systematic review and meta-analyses. Urol Int 2017; **99**: 343.
317. Markou S, Perimenis P, Gyftopoulos K et al: Vardenafil (Levitra) for erectile dysfunction: a systematic review and meta-analysis of clinical trial reports. Int J Impot Res 2004; **16:** 470.
318. Cui YS, Li N, Zong HT et al: Avanafil for male erectile dysfunction: a systematic review and meta-analysis. Asian J Androl 2014; **16:** 472.
319. Wang H, Yuan J, Hu X et al: The effectiveness and safety of avanafil for erectile dysfunction: a systematic review and meta-analysis. Curr Med Res Opin 2014; **30:** 1565.
320. Behrend L, Vibe-Petersen J and Perrild H: Sildenafil in the treatment of erectile dysfunction in men with diabetes: demand, efficacy and patient satisfaction. Int J Impot Res 2005; **17:** 264.
321. Blonde L: Sildenafil citrate for erectile dysfunction in men with diabetes and cardiovascular risk factors: a retrospective analysis of pooled data from placebo-controlled trials. Curr Med Res Opin 2006; **22:** 2111.
322. Boulton AJ, Selam JL, Sweeney M et al: Sildenafil citrate for the treatment of erectile dysfunction in men with type 2 diabetes mellitus. Diabetologia 2001; **44:** 1296.

323. Burnett AL, Strong TD, Trock BJ et al: Serum biomarker measurements of endothelial function and oxidative stress after daily dosing of sildenafil in type 2 diabetic men with erectile dysfunction. J Urol 2009; **181:** 245.
324. Buvat J, van Ahlen H, Schmitt H et al: Efficacy and safety of two dosing regimens of tadalafil and patterns of sexual activity in men with diabetes mellitus and erectile dysfunction: scheduled use vs. on-demand regimen evaluation (SURE) study in 14 European countries. J Sex Med 2006; **3:** 512.
325. Chen Y, Cui S, Lin H et al: Losartan improves erectile dysfunction in diabetic patients: a clinical trial. Int J Impot Res 2012; **24:** 217.
326. Deyoung L, Chung E, Kovac JR et al: Daily use of sildenafil improves endothelial function in men with type 2 diabetes. J Androl 2012; **33:** 176.
327. El-Sakka AI: Efficacy of sildenafil citrate in treatment of erectile dysfunction: effect of type 2 diabetes. Eur Urol 2004; **46:** 503.
328. El-Sakka AI, Anis T, Khadr N et al: Sildenafil for erectile dysfunction in the Middle East: observational analysis of patients with diabetes and/or hypertension treated in the clinical practice setting. J Int Med Res 2011; **39:** 558.
329. Fonseca V, Seftel A, Denne J et al: Impact of diabetes mellitus on the severity of erectile dysfunction and response to treatment: analysis of data from tadalafil clinical trials. Diabetologia 2004; **47:** 1914.
330. Gentile V, Vicini P, Prigiotti G et al: Preliminary observations on the use of propionyl-L-carnitine in combination with sildenafil in patients with erectile dysfunction and diabetes. Curr Med Res Opin 2004; **20:** 1377.
331. Goldstein I, Jones LA, Belkoff LH et al: Avanafil for the treatment of erectile dysfunction: a multicenter, randomized, double-blind study in men with diabetes mellitus. Mayo Clin Proc 2012; **87:** 843.
332. Goldstein I, Young JM, Fischer J et al: Vardenafil, a new phosphodiesterase type 5 inhibitor, in the treatment of erectile dysfunction in men with diabetes: a multicenter double-blind placebo-controlled fixed-dose study. Diabetes Care 2003; **26:** 777.
333. Grover-Paez F, Villegas Rivera G and Guillen Ortiz R: Sildenafil citrate diminishes microalbuminuria and the percentage of A1c in male patients with type 2 diabetes. Diabetes Res Clin Pract 2007; **78:** 136.
334. Hatzichristou D, Gambla M, Rubio-Aurioles E et al: Efficacy of tadalafil once daily in men with diabetes mellitus and erectile dysfunction. Diabet Med 2008; **25:** 138.
335. Ishii N, Nagao K, Fujikawa K et al: Vardenafil 20-mg demonstrated superior efficacy to 10-mg in Japanese men with diabetes mellitus suffering from erectile dysfunction. Int J Urol 2006; **13:** 1066.
336. Kirilmaz U, Guzel O, Aslan Y et al: The effect of lifestyle modification and glycemic control on the efficiency of sildenafil citrate in patients with erectile dysfunction due to type-2 diabetes mellitus. Aging Male 2015; **18:** 244.
337. Lee JW, Park HJ and Park NC: Serum high-sensitivity C-reactive protein levels and response to 5 mg tadalafil once daily in patients with erectile dysfunction and diabetes. Korean J Urol 2013; **54:** 858.
338. Hamidi Madani A, Asadolahzade A, Mokhtari G et al: Assessment of the efficacy of combination therapy with folic acid and tadalafil for the management of erectile dysfunction in men with type 2 diabetes mellitus. J Sex Med 2013; **10:** 1146.
339. Morano S, Mandosi E, Fallarino M et al: Antioxidant treatment associated with sildenafil reduces monocyte activation and markers of endothelial damage in patients with diabetic erectile dysfunction: a double-blind, placebo-controlled study. Eur Urol 2007; **52:** 1768.
340. Ng KK, Lim HC, Ng FC et al: The use of sildenafil in patients with erectile dysfunction in relation to diabetes mellitus--a study of 1,511 patients. Singapore Med J 2002; **43:** 387.
341. Perimenis P, Markou S, Gyftopoulos K et al: Switching from long-term treatment with self-injections to oral sildenafil in diabetic patients with severe erectile dysfunction. Eur Urol 2002; **41:** 387.
342. Popovic S, Nale D, Dabetic M et al: Effect of tadalafil on erectile dysfunction in male patients with diabetes mellitus. Vojnosanit Pregl 2007; **64:** 399.
343. Price DE, Gingell JC, Gepi-Attee S et al: Sildenafil: Study of a novel oral treatment for erectile dysfunction in diabetic men. Diabet Med 1998; **15:** 821.
344. Rendell MS, Rajfer J, Wicker PA et al: Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial. Sildenafil Diabetes Study Group. JAMA 1999; **281:** 421.
345. Saenz de Tejada I, Anglin G, Knight JR et al: Effects of tadalafil on erectile dysfunction in men with diabetes. Diabetes Care 2002; **25:** 2159.
346. Safarinejad MR: Oral sildenafil in the treatment of erectile dysfunction in diabetic men: a randomized double-blind and placebo-controlled study. J Diabetes Complications 2004; **18:** 205.
347. Santi D, Granata AR, Guidi A et al: Six months of daily treatment with vardenafil improves parameters of endothelial inflammation and of hypogonadism in male patients with type 2 diabetes and erectile dysfunction: a randomized, double-blind, prospective trial. Eur J Endocrinol 2016; **174:** 513.
348. Stuckey BG, Jadzinsky MN, Murphy LJ et al: Sildenafil citrate for treatment of erectile dysfunction in men with type 1 diabetes: results of a randomized controlled trial. Diabetes Care 2003; **26:** 279.

349. Zamorano-Leon JJ, Olivier C, de Las Heras N et al: Vardenafil improves penile erection in type 2 diabetes mellitus patients with erectile dysfunction: role of tropomyosin. J Sex Med 2013; **10:** 3110.
350. Ziegler D, Merfort F, Van Ahlen H et al: Efficacy and safety of flexible-dose vardenafil in men with type 1 diabetes and erectile dysfunction. J Sex Med 2006; **3:** 883.
351. Maresca L, D'Agostino M, Castaldo L et al: Exercise training improves erectile dysfunction (ED) in patients with metabolic syndrome on phosphodiesterase-5 (PDE-5) inhibitors. Monaldi Arch Chest Dis 2013; **80:** 177.
352. Schneider T, Gleissner J, Merfort F et al: Efficacy and safety of vardenafil for the treatment of erectile dysfunction in men with metabolic syndrome: results of a randomized, placebo-controlled trial. J Sex Med 2011; **8:** 2904.
353. Shabsigh R and Mattern A: REVITALISE: a large observational study assessing the safety and effectiveness of vardenafil in men with erectile dysfunction and metabolic syndrome. Sex Med 2016; **4**: e135.
354. Suetomi T, Kawai K, Hinotsu S et al: Negative impact of metabolic syndrome on the responsiveness to sildenafil in Japanese men. J Sex Med 2008; **5:** 1443.
355. Dadkhah F, Safarinejad MR, Asgari MA et al: Atorvastatin improves the response to sildenafil in hypercholesterolemic men with erectile dysfunction not initially responsive to sildenafil. Int J Impot Res 2010; **22:** 51.
356. Miner M, Gilderman L, Bailen J et al: Vardenafil in men with stable statin therapy and dyslipidemia. J Sex Med 2008; **5:** 1455.
357. Miner MM, Barnes A and Janning S: Efficacy of phosphodiesterase type 5 inhibitor treatment in men with erectile dysfunction and dyslipidemia: a post hoc analysis of the vardenafil statin study. J Sex Med 2010; **7:** 1937.
358. Albuquerque DC, Miziara LJ, Saraiva JF et al: Efficacy, safety and tolerability of sildenafil in Brazilian hypertensive patients on multiple antihypertensive drugs. Int Braz J Urol 2005; **31:** 342.
359. Aranda P, Ruilope LM, Calvo C et al: Erectile dysfunction in essential arterial hypertension and effects of sildenafil: results of a Spanish national study. Am J Hypertens 2004; **17:** 139.
360. Kloner RA, Brown M, Prisant LM et al: Effect of sildenafil in patients with erectile dysfunction taking antihypertensive therapy. Sildenafil Study Group. Am J Hypertens 2001; **14:** 70.
361. Kloner RA, Sadovsky R, Johnson EG et al: Efficacy of tadalafil in the treatment of erectile dysfunction in hypertensive men on concomitant thiazide diuretic therapy. Int J Impot Res 2005; **17:** 450.
362. Park HJ, Park NC, Shim HB et al: An open-label, multicenter, flexible dose study to evaluate the efficacy and safety of Viagra (sildenafil citrate) in Korean men with erectile dysfunction and arterial hypertension who are taking antihypertensive agents. J Sex Med 2008; **5:** 2405.
363. Pickering TG, Shepherd AM, Puddey I et al: Sildenafil citrate for erectile dysfunction in men receiving multiple antihypertensive agents: a randomized controlled trial. Am J Hypertens 2004; **17:** 1135.
364. van Ahlen H, Wahle K, Kupper W et al: Safety and efficacy of vardenafil, a selective phosphodiesterase 5 inhibitor, in patients with erectile dysfunction and arterial hypertension treated with multiple antihypertensives. J Sex Med 2005; **2:** 856.
365. Freitas D, Athanazio R, Almeida D et al: Sildenafil improves quality of life in men with heart failure and erectile dysfunction. Int J Impot Res 2006; **18:** 210.
366. Katz SD, Parker JD, Glasser DB et al: Efficacy and safety of sildenafil citrate in men with erectile dysfunction and chronic heart failure. Am J Cardiol 2005; **95:** 36.
367. Webster LJ, Michelakis ED, Davis T et al: Use of sildenafil for safe improvement of erectile function and quality of life in men with New York Heart Association classes II and III congestive heart failure: a prospective, placebo -controlled, double-blind crossover trial. Arch Intern Med 2004; **164:** 514.
368. Conti CR, Pepine CJ and Sweeney M: Efficacy and safety of sildenafil citrate in the treatment of erectile dysfunction in patients with ischemic heart disease. Am J Cardiol 1999; **83:** 29c.
369. DeBusk RF, Pepine CJ, Glasser DB et al: Efficacy and safety of sildenafil citrate in men with erectile dysfunction and stable coronary artery disease. Am J Cardiol 2004; **93:** 147.
370. Bocchio M, Pelliccione F, Mihalca R et al: Treatment of erectile dysfunction reduces psychological distress. Int J Androl 2009; **32:** 74.
371. Buranakitjaroen P, Mangklabruks A, Leungwattanakij S et al: Efficacy and safety of sildenafil in Asian males with erectile dysfunction and cardiovascular risk. J Med Assoc Thai 2007; **90:** 1100.
372. Olsson AM and Persson CA: Efficacy and safety of sildenafil citrate for the treatment of erectile dysfunction in men with cardiovascular disease. Int J Clin Pract 2001; **55:** 171.
373. Rubio-Aurioles E, Porst H, Eardley I et al: Comparing vardenafil and sildenafil in the treatment of men with erectile dysfunction and risk factors for cardiovascular disease: a randomized, double-blind, pooled crossover study. J Sex Med 2006; **3:** 1037.
374. Vicari E, Malaguarnera M, La Vignera S et al: Efficacy and limits of sildenafil citrate in patients with arterial erectile dysfunction: role of peripheral arterial disease and cardiovascular comorbidities. Asian J Androl 2008; **10:** 847.
375. Abolyosr A, Elsagheer GA, Abdel-Kader MS et al: Evaluation of the effect of sildenafil and/or doxazosin on benign prostatic hyperplasia-related lower urinary tract symptoms and erectile dysfunction. Urol Ann 2013; **5:** 237.

376. Choi H, Kim JH, Shim JS et al: Comparison of the efficacy and safety of 5-mg once-daily versus 5-mg alternate-day tadalafil in men with erectile dysfunction and lower urinary tract symptoms. Int J Impot Res 2015; **27:** 33.
377. Egerdie RB, Auerbach S, Roehrborn CG et al: Tadalafil 2.5 or 5 mg administered once daily for 12 weeks in men with both erectile dysfunction and signs and symptoms of benign prostatic hyperplasia: results of a randomized, placebo-controlled, double-blind study. J Sex Med 2012; **9:** 271.
378. Eryildirim B, Aktas A, Kuyumcuoglu U et al: The effectiveness of sildenafil citrate in patients with erectile dysfunction and lower urinary system symptoms and the significance of asymptomatic inflammatory prostatitis. Int J Impot Res 2010; **22:** 349.
379. Giuliano F, Oelke M, Jungwirth A et al: Tadalafil once daily improves ejaculatory function, erectile function, and sexual satisfaction in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia and erectile dysfunction: results from a randomized, placebo- and tamsulosin-controlled, 12-week double-blind study. J Sex Med 2013; **10:** 857.
380. Jin Z, Zhang ZC, Liu JH et al: An open, comparative, multicentre clinical study of combined oral therapy with sildenafil and doxazosin GITS for treating Chinese patients with erectile dysfunction and lower urinary tract symptoms secondary to benign prostatic hyperplasia. Asian J Androl 2011; **13:** 630.
381. Kaplan SA, Gonzalez RR and Te AE: Combination of alfuzosin and sildenafil is superior to monotherapy in treating lower urinary tract symptoms and erectile dysfunction. Eur Urol 2007; **51:** 1717.
382. Lee JY, Park SY, Jeong TY et al: Combined tadalafil and alpha-blocker therapy for benign prostatic hyperplasia in patients with erectile dysfunction: a multicenter, prospective study. J Androl 2012; **33:** 397.
383. Liguori G, Trombetta C, De Giorgi G et al: Efficacy and safety of combined oral therapy with tadalafil and alfuzosin: an integrated approach to the management of patients with lower urinary tract symptoms and erectile dysfunction. Preliminary report. J Sex Med 2009; **6:** 544.
384. McVary KT, Kaufman J, Young JM et al: Sildenafil citrate improves erectile function: a randomised double-blind trial with open-label extension. Int J Clin Pract 2007; **61:** 1843.
385. McVary KT, Monnig W, Camps JL, Jr. et al: Sildenafil citrate improves erectile function and urinary symptoms in men with erectile dysfunction and lower urinary tract symptoms associated with benign prostatic hyperplasia: a randomized, double-blind trial. J Urol 2007; **177:** 1071.
386. Mulhall JP, Guhring P, Parker M et al: Assessment of the impact of sildenafil citrate on lower urinary tract symptoms in men with erectile dysfunction. J Sex Med 2006; **3:** 662.
387. Porst H, McVary KT, Montorsi F et al: Effects of once-daily tadalafil on erectile function in men with erectile dysfunction and signs and symptoms of benign prostatic hyperplasia. Eur Urol 2009; **56:** 727.
388. Porst H, Roehrborn CG, Secrest RJ et al: Effects of tadalafil on lower urinary tract symptoms secondary to benign prostatic hyperplasia and on erectile dysfunction in sexually active men with both conditions: analyses of pooled data from four randomized, placebo-controlled tadalafil clinical studies. J Sex Med 2013; **10:** 2044.
389. Tuncel A, Nalcacioglu V, Ener K et al: Sildenafil citrate and tamsulosin combination is not superior to monotherapy in treating lower urinary tract symptoms and erectile dysfunction. World J Urol 2010; **28:** 17.
390. Maselli G, Bergamasco L, Silvestri V et al: Tadalafil versus solifenacin for persistent storage symptoms after prostate surgery in patients with erectile dysfunction: a prospective randomized study. Int J Urol 2011; **18:** 515.
391. Yu H, Wu H and Rao D: Analysis of the therapeutic effect of tadalafil on male ED after transurethral resection of prostate. Int J Impot Res 2012; **24:** 147.
392. Perimenis P, Karkoulias K, Markou S et al: Erectile dysfunction in men with obstructive sleep apnea syndrome: a randomized study of the efficacy of sildenafil and continuous positive airway pressure. Int J Impot Res 2004; **16:** 256.
393. Perimenis P, Konstantinopoulos A, Karkoulias K et al: Sildenafil combined with continuous positive airway pressure for treatment of erectile dysfunction in men with obstructive sleep apnea. Int Urol Nephrol 2007; **39:** 547.
394. Condorelli RA, Calogero AE, Di Mauro M et al: Effects of tadalafil treatment combined with physical activity in patients with low onset hypogonadism: results from a not-randomized single arm phase 2 study. Aging Male 2016**; 3:** 155.
395. Kennedy SH, Dugre H and Defoy I: A multicenter, double-blind, placebo-controlled study of sildenafil citrate in Canadian men with erectile dysfunction and untreated symptoms of depression, in the absence of major depressive disorder. Int Clin Psychopharmacol 2011; **26:** 151.
396. Rosen R, Shabsigh R, Berber M et al: Efficacy and tolerability of vardenafil in men with mild depression and erectile dysfunction: the depression-related improvement with vardenafil for erectile response study. Am J Psychiatry 2006; **163:** 79.
397. Seidman SN, Roose SP, Menza MA et al: Treatment of erectile dysfunction in men with depressive symptoms: results of a placebo-controlled trial with sildenafil citrate. Am J Psychiatry 2001; **158:** 1623.
398. Aizenberg D, Weizman A and Barak Y: Sildenafil for selective serotonin reuptake inhibitor-induced erectile dysfunction in elderly male depressed patients. J Sex Marital Ther 2003; **29:** 297.

399. Evliyaoglu Y, Yelsel K, Kobaner M et al: Efficacy and tolerability of tadalafil for treatment of erectile dysfunction in men taking serotonin reuptake inhibitors. Urology 2011; **77:** 1137.
400. Fava M, Nurnberg HG, Seidman SN et al: Efficacy and safety of sildenafil in men with serotonergic antidepressant-associated erectile dysfunction: results from a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2006; **67:** 240.
401. Nurnberg HG, Fava M, Gelenberg AJ et al: Open-label sildenafil treatment of partial and non-responders to double-blind treatment in men with antidepressant-associated sexual dysfunction. Int J Impot Res 2007; **19:** 167.
402. Nurnberg HG, Gelenberg A, Hargreave TB et al: Efficacy of sildenafil citrate for the treatment of erectile dysfunction in men taking serotonin reuptake inhibitors. Am J Psychiatry 2001; **158:** 1926.
403. Nurnberg HG, Hensley PL, Gelenberg AJ et al: Treatment of antidepressant-associated sexual dysfunction with sildenafil: a randomized controlled trial. JAMA 2003; **289:** 56.
404. Segraves RT, Lee J, Stevenson R et al: Tadalafil for treatment of erectile dysfunction in men on antidepressants. J Clin Psychopharmacol 2007; **27:** 62.
405. Tignol J, Furlan PM, Gomez-Beneyto M et al: Efficacy of sildenafil citrate (Viagra) for the treatment of erectile dysfunction in men in remission from depression. Int Clin Psychopharmacol 2004; **19:** 191.
406. Karami H, Hassanzadeh-Hadad A and Fallah-Karkan M: Comparing monotherapy with tadalafil or tamsulosin and their combination therapy in men with benign prostatic hyperplasia: a randomized clinical trial. Urol J 2016; **13:** 2920.
407. Ozcan L, Polat EC, Kocaaslan R et al: Effects of taking tadalafil 5 mg once daily on erectile function and total testosterone levels in patients with metabolic syndrome. Andrologia 2017; **49**: e12751.
408. Lee LK, Goren A, Boytsov NN et al: Treatment satisfaction among men with concurrent benign prostatic hyperplasia and erectile dysfunction treated with tadalafil or other phosphodiesterase type-5 inhibitor combinations. Patient Prefer Adherence 2016; **10:** 1205.
409. Bolat MS, Ozer I, Cinar O et al: The efficacy of low-dose tadalafil in patients undergoing hemodialysis with end-stage renal disease. Ren Fail 2017; **39:** 582.
410. Azab S, Aoud H and Nabil N: The correlation between high sensitivity C-reactive protein and erectile dysfunction patients with hypertension treated with vardenafil. Int J Impot Res 2017; **29:** 82.
411. Ohl DA, Carlsson M, Stecher VJ et al: Efficacy and safety of sildenafil in men with sexual dysfunction and spinal cord injury. Sex Med Rev 2017; **5**: 521.
412. Bannowsky A, Schulze H, van der Horst C et al: Recovery of erectile function after nerve-sparing radical prostatectomy: improvement with nightly low-dose sildenafil. BJU Int 2008; **101:** 1279.
413. Bannowsky A, van Ahlen H and Loch T: Increasing the dose of vardenafil on a daily basis does not improve erectile function after unilateral nerve-sparing radical prostatectomy. J Sex Med 2012; **9:** 1448.
414. Blander DS, Sanchez-Ortiz RF, Wein AJ et al: Efficacy of sildenafil in erectile dysfunction after radical prostatectomy. Int J Impot Res 2000; **12:** 165.
415. Briganti A, Di Trapani E, Abdollah F et al: Choosing the best candidates for penile rehabilitation after bilateral nerve-sparing radical prostatectomy. J Sex Med 2012; **9:** 608.
416. Brock G, Nehra A, Lipshultz LI et al: Safety and efficacy of vardenafil for the treatment of men with erectile dysfunction after radical retropubic prostatectomy. J Urol 2003; **170:** 1278.
417. Canat L, Guner B, Gurbuz C et al: Effects of three-times-per-week versus on-demand tadalafil treatment on erectile function and continence recovery following bilateral nerve sparing radical prostatectomy: results of a prospective, randomized, and single-center study. Kaohsiung J Med Sci 2015; **31:** 90.
418. Cathala N, Mombet A, Sanchez-Salas R et al: Evaluation of erectile function after laparoscopic radical prostatectomy in a single center. Can J Urol 2012; **19:** 6328.
419. Cavallini G, Modenini F, Vitali G et al: Acetyl-L-carnitine plus propionyl-L-carnitine improve efficacy of sildenafil in treatment of erectile dysfunction after bilateral nerve-sparing radical retropubic prostatectomy. Urology 2005; **66:** 1080.
420. Feng MI, Huang S, Kaptein J et al: Effect of sildenafil citrate on post-radical prostatectomy erectile dysfunction. J Urol 2000; **164:** 1935.
421. Hirik E, Bozkurt A, Karabakan M et al: Results of tadalafil treatment in patients following an open nerve-sparing radical prostatectomy. Arch Ital Urol Androl 2016; **88:** 4.
422. Hubanks JM, Umbreit EC, Karnes RJ et al: Open radical retropubic prostatectomy using high anterior release of the levator fascia and constant haptic feedback in bilateral neurovascular bundle preservation plus early postoperative phosphodiesterase type 5 inhibition: a contemporary series. Eur Urol 2012; **61:** 878.
423. Kim DJ, Hawksworth DJ, Hurwitz LM et al: A prospective, randomized, placebo-controlled trial of on-demand vs. nightly sildenafil citrate as assessed by Rigiscan and the International Index of Erectile Function. Andrology 2016; **4:** 27.

424. Kimura M, Caso JR, Banez LL et al: Predicting participation in and successful outcome of a penile rehabilitation programme using a phosphodiesterase type 5 inhibitor with a vacuum erection device after radical prostatectomy. BJU Int 2012; **110:** E931.
425. Lee IH, Sadetsky N, Carroll PR et al: The impact of treatment choice for localized prostate cancer on response to phosphodiesterase inhibitors. J Urol 2008; **179:** 1072.
426. Lowentritt BH, Scardino PT, Miles BJ et al: Sildenafil citrate after radical retropubic prostatectomy. J Urol 1999; **162:** 1614.
427. McCullough AR, Hellstrom WG, Wang R et al: Recovery of erectile function after nerve sparing radical prostatectomy and penile rehabilitation with nightly intraurethral alprostadil versus sildenafil citrate. J Urol 2010; **183:** 2451.
428. Megas G, Papadopoulos G, Stathouros G et al: Comparison of efficacy and satisfaction profile, between penile prosthesis implantation and oral PDE5 inhibitor tadalafil therapy, in men with nerve-sparing radical prostatectomy erectile dysfunction. BJU Int 2013; **112:** E169.
429. Montorsi F, Brock G, Lee J et al: Effect of nightly versus on-demand vardenafil on recovery of erectile function in men following bilateral nerve-sparing radical prostatectomy. Eur Urol 2008; **54:** 924.
430. Montorsi F, Brock G, Stolzenburg JU et al: Effects of tadalafil treatment on erectile function recovery following bilateral nerve-sparing radical prostatectomy: a randomised placebo-controlled study (REACTT). Eur Urol 2014; **65:** 587.
431. Patel HR, Ilo D, Shah N et al: Effects of tadalafil treatment after bilateral nerve-sparing radical prostatectomy: quality of life, psychosocial outcomes, and treatment satisfaction results from a randomized, placebo-controlled phase IV study. BMC Urol 2015; **15:** 31.
432. Montorsi F, Nathan HP, McCullough A et al: Tadalafil in the treatment of erectile dysfunction following bilateral nerve sparing radical retropubic prostatectomy: a randomized, double-blind, placebo controlled trial. J Urol 2004; **172:** 1036.
433. Mulhall JP, Burnett AL, Wang R et al: A phase 3, placebo controlled study of the safety and efficacy of avanafil for the treatment of erectile dysfunction after nerve sparing radical prostatectomy. J Urol 2013; **189:** 2229.
434. Nakano Y, Miyake H, Chiba K et al: Impact of penile rehabilitation with low-dose vardenafil on recovery of erectile function in Japanese men following nerve-sparing radical prostatectomy. Asian J Androl 2014; **16:** 892.
435. Nehra A, Grantmyre J, Nadel A et al: Vardenafil improved patient satisfaction with erectile hardness, orgasmic function and sexual experience in men with erectile dysfunction following nerve sparing radical prostatectomy. J Urol 2005; **173:** 2067.
436. Ogura K, Ichioka K, Terada N et al: Role of sildenafil citrate in treatment of erectile dysfunction after radical retropubic prostatectomy. Int J Urol 2004; **11:** 159.
437. Pace G, Del Rosso A and Vicentini C: Penile rehabilitation therapy following radical prostatectomy. Disabil Rehabil 2010; **32:** 1204.
438. Padma-Nathan H, McCullough AR, Levine LA et al: Randomized, double-blind, placebo-controlled study of postoperative nightly sildenafil citrate for the prevention of erectile dysfunction after bilateral nerve-sparing radical prostatectomy. Int J Impot Res 2008; **20:** 479.
439. Pavlovich CP, Levinson AW, Su LM et al: Nightly vs on-demand sildenafil for penile rehabilitation after minimally invasive nerve-sparing radical prostatectomy: results of a randomized double-blind trial with placebo. BJU Int 2013; **112:** 844.
440. Raina R, Agarwal A, Allamaneni SS et al: Sildenafil citrate and vacuum constriction device combination enhances sexual satisfaction in erectile dysfunction after radical prostatectomy. Urology 2005; **65:** 360.
441. Raina R, Lakin MM, Agarwal A et al: Long-term intracavernous therapy responders can potentially switch to sildenafil citrate after radical prostatectomy. Urology 2004; **63:** 532.
442. Raina R, Lakin MM, Agarwal A et al: Efficacy and factors associated with successful outcome of sildenafil citrate use for erectile dysfunction after radical prostatectomy. Urology 2004; **63:** 960.
443. Raina R, Lakin MM, Agarwal A et al: Long-term effect of sildenafil citrate on erectile dysfunction after radical prostatectomy: 3-year follow-up. Urology 2003; **62:** 110.
444. Seo YE, Kim SD, Kim TH et al: The efficacy and safety of tadalafil 5 mg once daily in the treatment of erectile dysfunction after robot-assisted laparoscopic radical prostatectomy: 1-year follow-up. Korean J Urol 2014; **55:** 112.
445. Zagaja GP, Mhoon DA, Aikens JE et al: Sildenafil in the treatment of erectile dysfunction after radical prostatectomy. Urology 2000; **56:** 631.
446. Zippe CD, Jhaveri FM, Klein EA et al: Role of Viagra after radical prostatectomy. Urology 2000; **55:** 241.
447. Zippe CD, Kedia AW, Kedia K et al: Treatment of erectile dysfunction after radical prostatectomy with sildenafil citrate (Viagra). Urology 1998; **52:** 963.
448. Watkins Bruner D, James JL, Bryan CJ et al: Randomized, double-blinded, placebo-controlled crossover trial of treating erectile dysfunction with sildenafil after radiotherapy and short-term androgen deprivation therapy: results of RTOG 0215. J Sex Med 2011; **8:** 1228.
449. Harrington C, Campbell G, Wynne C et al: Randomised, placebo-controlled, crossover trial of sildenafil citrate in the treatment of erectile dysfunction following external beam radiation treatment of prostate cancer. J Med Imaging Radiat Oncol 2010; **54:** 224.

450. Ilic D, Hindson B, Duchesne G et al: A randomised, double-blind, placebo-controlled trial of nightly sildenafil citrate to preserve erectile function after radiation treatment for prostate cancer. J Med Imaging Radiat Oncol 2013; **57:** 81.
451. Incrocci L, Hop WC and Slob AK: Efficacy of sildenafil in an open-label study as a continuation of a double-blind study in the treatment of erectile dysfunction after radiotherapy for prostate cancer. Urology 2003; **62:** 116.
452. Incrocci L, Koper PC, Hop WC et al: Sildenafil citrate (Viagra) and erectile dysfunction following external beam radiotherapy for prostate cancer: a randomized, double-blind, placebo-controlled, cross-over study. Int J Radiat Oncol Biol Phys 2001; **51:** 1190.
453. Incrocci L, Slagter C, Slob AK et al: A randomized, double-blind, placebo-controlled, cross-over study to assess the efficacy of tadalafil (Cialis) in the treatment of erectile dysfunction following three-dimensional conformal external-beam radiotherapy for prostatic carcinoma. Int J Radiat Oncol Biol Phys 2006; **66:** 439.
454. Incrocci L, Slob AK and Hop WC: Tadalafil (Cialis) and erectile dysfunction after radiotherapy for prostate cancer: an open-label extension of a blinded trial. Urology 2007; **70:** 1190.
455. Kedia S, Zippe CD, Agarwal A et al: Treatment of erectile dysfunction with sildenafil citrate (Viagra) after radiation therapy for prostate cancer. Urology 1999; **54:** 308.
456. Merrick GS, Butler WM, Lief JH et al: Efficacy of sildenafil citrate in prostate brachytherapy patients with erectile dysfunction. Urology 1999; **53:** 1112.
457. Ohebshalom M, Parker M, Guhring P et al: The efficacy of sildenafil citrate following radiation therapy for prostate cancer: temporal considerations. J Urol 2005; **174:** 258.
458. Pahlajani G, Raina R, Jones JS et al: Early intervention with phosphodiesterase-5 inhibitors after prostate brachytherapy improves subsequent erectile function. BJU Int 2010; **106:** 1524.
459. Pisansky TM, Pugh SL, Greenberg RE et al: Tadalafil for prevention of erectile dysfunction after radiotherapy for prostate cancer: the radiation therapy oncology group [0831] randomized clinical trial. JAMA 2014; **311:** 1300.
460. Potters L, Torre T, Fearn PA et al: Potency after permanent prostate brachytherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2001; **50:** 1235.
461. Raina R, Agarwal A, Goyal KK et al: Long-term potency after iodine-125 radiotherapy for prostate cancer and role of sildenafil citrate. Urology 2003; **62:** 1103.
462. Ricardi U, Gontero P, Ciammella P et al: Efficacy and safety of tadalafil 20 mg on demand vs. tadalafil 5 mg once-a-day in the treatment of post-radiotherapy erectile dysfunction in prostate cancer men: a randomized phase II trial. J Sex Med 2010; **7:** 2851.
463. Schiff JD, Bar-Chama N, Cesaretti J et al: Early use of a phosphodiesterase inhibitor after brachytherapy restores and preserves erectile function. BJU Int 2006; **98:** 1255.
464. Shemtov OM, Radomski SB and Crook J: Success of sildenafil for erectile dysfunction in men treated with brachytherapy or external beam radiation for prostate cancer. Can J Urol 2004; **11:** 2450.
465. Teloken PE, Ohebshalom M, Mohideen N et al: Analysis of the impact of androgen deprivation therapy on sildenafil citrate response following radiation therapy for prostate cancer. J Urol 2007; **178:** 2521.
466. Teloken PE, Parker M, Mohideen N et al: Predictors of response to sildenafil citrate following radiation therapy for prostate cancer. J Sex Med 2009; **6:** 1135.
467. Valicenti RK, Choi E, Chen C et al: Sildenafil citrate effectively reverses sexual dysfunction induced by three-dimensional conformal radiation therapy. Urology 2001; **57:** 769.
468. Weber DC, Bieri S, Kurtz JM et al: Prospective pilot study of sildenafil for treatment of postradiotherapy erectile dysfunction in patients with prostate cancer. J Clin Oncol 1999; **17:** 3444.
469. Zelefsky MJ, McKee AB, Lee H et al: Efficacy of oral sildenafil in patients with erectile dysfunction after radiotherapy for carcinoma of the prostate. Urology 1999; **53:** 775.
470. Zelefsky MJ, Shasha D, Branco RD et al: Prophylactic sildenafil citrate improves select aspects of sexual function in men treated with radiotherapy for prostate cancer. J Urol 2014; **192:** 868.
471. Chen J, Mabjeesh NJ, Greenstein A et al: Clinical efficacy of sildenafil in patients on chronic dialysis. J Urol 2001; **165:** 819.
472. Hyodo T, Ishida H, Masui N et al: Kidney disease quality of life of Japanese dialysis patients who desire administration of sildenafil and the treatment of erectile dysfunction using sildenafil. Ther Apher Dial 2004; **8:** 340.
473. Rosas SE, Wasserstein A, Kobrin S et al: Preliminary observations of sildenafil treatment for erectile dysfunction in dialysis patients. Am J Kidney Dis 2001; **37:** 134.
474. Seibel I, Poli De Figueiredo CE, Teloken C et al: Efficacy of oral sildenafil in hemodialysis patients with erectile dysfunction. J Am Soc Nephrol 2002; **13:** 2770.
475. Tas A, Ersoy A, Ersoy C et al: Efficacy of sildenafil in male dialysis patients with erectile dysfunction unresponsive to erythropoietin and/or testosterone treatments. Int J Impot Res 2006; **18:** 61.
476. Turk S, Karalezli G, Tonbul HZ et al: Erectile dysfunction and the effects of sildenafil treatment in patients on haemodialysis and continuous ambulatory peritoneal dialysis. Nephrol Dial Transplant 2001; **16:** 1818.

477. Turk S, Solak Y, Kan S et al: Effects of sildenafil and vardenafil on erectile dysfunction and health-related quality of life in haemodialysis patients: a prospective randomized crossover study. Nephrol Dial Transplant 2010; **25:** 3729.
478. YenicerioGlu Y, Kefi A, Aslan G et al: Efficacy and safety of sildenafil for treating erectile dysfunction in patients on dialysis. BJU Int 2002; **90:** 442.
479. Barrou B, Cuzin B, Malavaud B et al: Early experience with sildenafil for the treatment of erectile dysfunction in renal transplant recipients. Nephrol Dial Transplant 2003; **18:** 411.
480. Demir E, Balal M, Paydas S et al: Efficacy and safety of vardenafil in renal transplant recipients with erectile dysfunction. Transplant Proc 2006; **38:** 1379.
481. Prieto Castro RM, Anglada Curado FJ, Regueiro Lopez JC et al: Treatment with sildenafil citrate in renal transplant patients with erectile dysfunction. BJU Int 2001; **88:** 241.
482. Russo D, Musone D, Alteri V et al: Erectile dysfunction in kidney transplanted patients: efficacy of sildenafil. J Nephrol 2004; **17:** 291.
483. Sharma RK, Prasad N, Gupta A et al: Treatment of erectile dysfunction with sildenafil citrate in renal allograft recipients: a randomized, double -blind, placebo-controlled, crossover trial. Am J Kidney Dis 2006; **48:** 128.
484. Zhang Y, Guan DL, Ou TW et al: Sildenafil citrate treatment for erectile dysfunction after kidney transplantation. Transplant Proc 2005; **37:** 2100.
485. Derry FA, Dinsmore WW, Fraser M et al: Efficacy and safety of oral sildenafil (Viagra) in men with erectile dysfunction caused by spinal cord injury. Neurology 1998; **51:** 1629.
486. Ergin S, Gunduz B, Ugurlu H et al: A placebo-controlled, multicenter, randomized, double-blind, flexible-dose, two-way crossover study to evaluate the efficacy and safety of sildenafil in men with traumatic spinal cord injury and erectile dysfunction. J Spinal Cord Med 2008; **31:** 522.
487. Gans WH, Zaslau S, Wheeler S et al: Efficacy and safety of oral sildenafil in men with erectile dysfunction and spinal cord injury. J Spinal Cord Med 2001; **24:** 35.
488. Giuliano F, Hultling C, El Mashy WS et al: Sildenafil citrate (Viagra®): a novel oral treatment for erectile dysfunction caused by traumatic spinal cord injury. Int J Clin Pract Suppl. 1999**; 102**: 30.
489. Giuliano F, Rubio-Aurioles E, Kennelly M et al: Efficacy and safety of vardenafil in men with erectile dysfunction caused by spinal cord injury. Neurology 2006; **66:** 210.
490. Giuliano F, Sanchez-Ramos A, Lochner-Ernst D et al: Efficacy and safety of tadalafil in men with erectile dysfunction following spinal cord injury. Arch Neurol 2007; **64:** 1584.
491. Khorrami MH, Javid A, Moshtaghi D et al: Sildenafil efficacy in erectile dysfunction secondary to spinal cord injury depends on the level of cord injuries. Int J Androl 2010; **33:** 861.
492. Kimoto Y, Sakamoto S, Fujikawa K et al: Up-titration of vardena fi l dose from 10 mg to 20 mg improved erectile function in men with spinal cord injury. Int J Urol 2006; **13:** 1428.
493. Lombardi G, Macchiarella A, Cecconi F et al: Ten years of phosphodiesterase type 5 inhibitors in spinal cord injured patients. J Sex Med 2009; **6:** 1248.
494. Manou BK, van Tam PN, Sesay M et al: Effect of sildenafil on erectile dysfunction in spinal cord injured patients. Ghana Med J 2009; **43:** 132.
495. Maytom MC, Derry FA, Dinsmore WW et al: A two-part pilot study of sildenafil (Viagra) in men with erectile dysfunction caused by spinal cord injury. Spinal Cord 1999; **37:** 110.
496. Moemen MN, Fahmy I, AbdelAal M et al: Erectile dysfunction in spinal cord-injured men: different treatment options. Int J Impot Res 2008; **20:** 181.
497. Sanchez Ramos A, Vidal J, Jauregui ML et al: Efficacy, safety and predictive factors of therapeutic success with sildenafil for erectile dysfunction in patients with different spinal cord injuries. Spinal Cord 2001; **39:** 637.
498. Soler JM, Previnaire JG, Denys P et al: Phosphodiesterase inhibitors in the treatment of erectile dysfunction in spinal cord-injured men. Spinal Cord 2007; **45:** 169.
499. Tuzgen S, Karamehmetoglu SS, Karacan I et al: Use of sildenafil in the treatment of erectile dysfunction in patients with spinal cord injury. Neurosurgery Quarterly 2006; **16:** 40.
500. Miller NR and Arnold AC: Current concepts in the diagnosis, pathogenesis and management of nonarteritic anterior ischaemic optic neuropathy. Eye (Lond) 2015; **29:** 65.
501. Lee MS, Grossman D, Arnold AC et al: Incidence of nonarteritic anterior ischemic optic neuropathy: increased risk among diabetic patients. Ophthalmology 2011; **118:** 959.
502. Zotz RB, Finger C, Scharf RE et al: Associations between thrombophilic risk factors and determinants of atherosclerosis and inflammation in patients with non-arteritic anterior ischaemic optic neuropathy. Hamostaseologie 2016; **36:** 46.
503. Campbell UB, Walker AM, Gaffney M et al: Acute nonarteritic anterior ischemic optic neuropathy and exposure to phosphodiesterase type 5 inhibitors. J Sex Med 2015; **12:** 139.
504. Margo CE and French DD: Ischemic optic neuropathy in male veterans prescribed phosphodiesterase-5 inhibitors. Am J Ophthalmol 2007; **143:** 538.
505. Flahavan EM, Li H, Gupte-Singh K et al: Prospective case-crossover study investigating the possible association between nonarteritic anterior ischemic optic neuropathy and phosphodiesterase type 5 inhibitor exposure. Urology 2017; **105:** 76.
506. Pomeranz HD: The relationship between phosphodiesterase-5 inhibitors and nonarteritic anterior ischemic optic neuropathy. J Neuroophthalmol 2016; **36:** 193.

507. Li WQ, Qureshi AA, Robinson KC et al: Sildenafil use and increased risk of incident melanoma in US men: a prospective cohort study. JAMA Intern Med 2014; **174:** 964.
508. Loeb S, Folkvaljon Y, Lambe M et al: Use of phosphodiesterase type 5 inhibitors for erectile dysfunction and risk of malignant melanoma. JAMA 2015; **313:** 2449.
509. Lian Y, Yin H, Pollak MN et al: Phosphodiesterase type 5 inhibitors and the risk of melanoma skin cancer. Eur Urol 2016; **70:** 808.
510. Pottegard A, Schmidt SA, Olesen AB et al: Use of sildenafil or other phosphodiesterase inhibitors and risk of melanoma. Br J Cancer 2016; **115:** 895.
511. Matthews A, Langan SM, Douglas IJ et al: Phosphodiesterase type 5 inhibitors and risk of malignant melanoma: matched cohort study using primary care data from the UK clinical practice research datalink. PLoS Med 2016; **13:** e1002037.
512. Hill AB: The environment and disease: association or causation? Proc R Soc Med 1965; **58:** 295.
513. Michl U, Molfenter F, Graefen M et al: Use of phosphodiesterase type 5 inhibitors may adversely impact biochemical recurrence after radical prostatectomy. J Urol 2015; **193:** 479.
514. Gallina A, Bianchi M, Gandaglia G et al: A detailed analysis of the association between postoperative phosphodiesterase type 5 inhibitor use and the risk of biochemical recurrence after radical prostatectomy. Eur Urol 2015; **68:** 750.
515. Loeb S, Folkvaljon Y, Robinson D et al: Phosphodiesterase type 5 inhibitor use and disease recurrence after prostate cancer treatment. Eur Urol 2016; **70:** 824.
516. Jamnagerwalla J, Howard LE, Vidal AC et al: The association between phosphodiesterase type 5 inhibitors and prostate cancer: results from the REDUCE study. J Urol 2016; **196**: 715.
517. Atiemo HO, Szostak MJ and Sklar GN: Salvage of sildenafil failures referred from primary care physicians. J Urol 2003; **170:** 2356.
518. Jiann BP, Yu CC, Su CC et al: Rechallenge prior sildenafil nonresponders. Int J Impot Res 2004; **16:** 64.
519. Hatzichristou D, Moysidis K, Apostolidis A et al: Sildenafil failures may be due to inadequate patient instructions and follow-up: a study on 100 non-responders. Eur Urol 2005; **47:** 518.
520. Gruenwald I, Shenfeld O, Chen J et al: Positive effect of counseling and dose adjustment in patients with erectile dysfunction who failed treatment with sildenafil. Eur Urol 2006; **50:** 134.
521. Kim ED, Seftel AD, Goldfischer ER et al: A return to normal erectile function with tadalafil once daily after an incomplete response to as-needed PDE5 inhibitor therapy. J Sex Med 2013; **11**: 820.
522. Carson CC, Hatzichristou DG, Carrier S et al: Erectile response with vardenafil in sildenafil nonresponders: a multicentre, double-blind, 12-week, flexible-dose, placebo-controlled erectile dysfunction clinical trial. BJU Int 2004; **94:** 1301.
523. Brisson TE, Broderick GA, Thiel DD et al: Vardenafil rescue rates of sildenafil nonresponders: objective assessment of 327 patients with erectile dysfunction. Urology 2006; **68:** 397.
524. Ozgur BC, Gonenc F and Yazicioglu AH: Sildenafil or vardenafil nonresponders' erectile response to tadalafil. Urol J 2009; **6:** 267.
525. Wespes E, Rammal A and Garbar C: Sildenafil non-responders: haemodynamic and morphometric studies. Eur Urol 2005; **48:** 136.
526. Salonia A, Adaikan G, Buvat J et al: Sexual rehabilitation after treatment for prostate cancer-part 2: recommendations from the Fourth International Consultation for Sexual Medicine (ICSM 2015). J Sex Med 2017; **14:** 297.
527. Salonia A, Adaikan G, Buvat J et al: Sexual rehabilitation after treatment for prostate cancer-part 1: recommendations from the fourth international consultation for sexual medicine (ICSM 2015). J Sex Med 2017; **14:** 285.
528. Sopko NA and Burnett AL: Erection rehabilitation following prostatectomy - current strategies and future directions. Nat Rev Urol 2016; **13:** 216.
529. Basal S, Wambi C, Acikel C et al: Optimal strategy for penile rehabilitation after robot-assisted radical prostatectomy based on preoperative erectile function. BJU Int 2013; **111:** 658.
530. Fode M, Serefoglu EC, Albersen M et al: Sexuality following radical prostatectomy: is restoration of erectile function enough? Sex Med Rev 2017; **5:** 110.
531. Walz J, Epstein JI, Ganzer R et al: A critical analysis of the current knowledge of surgical anatomy of the prostate related to optimisation of cancer control and preservation of continence and erection in candidates for radical prostatectomy: an update. Eur Urol 2016; **70:** 301.
532. Nguyen LN, Head L, Witiuk K et al: The risks and benefits of cavernous neurovascular bundle sparing during radical prostatectomy: a systematic review and meta-analysis. J Urol 2017; **198**: 760.
533. Schover LR, Fouladi RT, Warneke CL et al: The use of treatments for erectile dysfunction among survivors of prostate carcinoma. Cancer 2002; **95:** 2397.
534. Donovan KA, Walker LM, Wassersug RJ et al: Psychological effects of androgen-deprivation therapy on men with prostate cancer and their partners. Cancer 2015; **121:** 4286.
535. Nelson CJ and Kenowitz J: Communication and intimacy-enhancing interventions for men diagnosed with prostate cancer and their partners. J Sex Med 2013; **10 Suppl 1:** 127.

536. Tal R, Alphs HH, Krebs P et al: Erectile function recovery rate after radical prostatectomy: a meta-analysis. J Sex Med 2009; **6:** 2538.
537. al-Abany M, Steineck G, Agren Cronqvist AK et al: Improving the preservation of erectile function after external beam radiation therapy for prostate cancer. Radiother Oncol 2000; **57:** 201.
538. van der Wielen GJ, van Putten WL and Incrocci L: Sexual function after three-dimensional conformal radiotherapy for prostate cancer: results from a dose-escalation trial. Int J Radiat Oncol Biol Phys 2007; **68:** 479.
539. Burnett AL, Aus G, Canby-Hagino ED et al: Erectile function outcome reporting after clinically localized prostate cancer treatment. J Urol 2007; **178:** 597.
540. Ficarra V, Novara G, Ahlering TE et al: Systematic review and meta-analysis of studies reporting potency rates after robot-assisted radical prostatectomy. Eur Urol 2012; **62:** 418.
541. Rabbani F, Schiff J, Piecuch M et al: Time course of recovery of erectile function after radical retropubic prostatectomy: does anyone recover after 2 years? J Sex Med 2010; **7:** 3984.
542. Nelson CJ, Scardino PT, Eastham JA et al: Back to baseline: erectile function recovery after radical prostatectomy from the patients' perspective. J Sex Med 2013; **10:** 1636.
543. Litwin MS, Flanders SC, Pasta DJ et al: Sexual function and bother after radical prostatectomy or radiation for prostate cancer: multivariate quality-of-life analysis from CaPSURE. Cancer of the Prostate Strategic Urologic Research Endeavor. Urology 1999; **54:** 503.
544. Mahmood J, Shamah AA, Creed TM et al: Radiation-induced erectile dysfunction: recent advances and future directions. Adv Radiat Oncol 2016; **1:** 161.
545. Mulhall JP, Bella AJ, Briganti A et al: Erectile function rehabilitation in the radical prostatectomy patient. J Sex Med 2010; **7:** 1687.
546. Burnett AL and Lue TF: Neuromodulatory therapy to improve erectile function recovery outcomes after pelvic surgery. J Urol 2006; **176:** 882.
547. Weyne E, Castiglione F, Van der Aa F et al: Landmarks in erectile function recovery after radical prostatectomy. Nat Rev Urol 2015; **12:** 289.
548. Ryu JK, Suh JK and Burnett AL: Research in pharmacotherapy for erectile dysfunction. Transl Androl Urol 2017; **6:** 207.
549. Segal RL, Bivalacqua TJ and Burnett AL: Current penile-rehabilitation strategies: clinical evidence. Arab J Urol 2013; **11:** 230.
550. Sadovsky R, Basson R, Krychman M et al: Cancer and sexual problems. J Sex Med 2010; **7:** 349.
551. Walker LM, Wassersug RJ and Robinson JW: Psychosocial perspectives on sexual recovery after prostate cancer treatment. Nat Rev Urol 2015; **12:** 167.
552. Salonia A, Burnett AL, Graefen M et al: Prevention and management of postprostatectomy sexual dysfunctions part 2: recovery and preservation of erectile function, sexual desire, and orgasmic function. Eur Urol 2012; **62:** 273.
553. Aversa A, Isidori AM, Spera G et al: Androgens improve cavernous vasodilation and response to sildenafil in patients with erectile dysfunction. Clin Endocrinol (Oxf) 2003; **58:** 632.
554. Buvat J, Montorsi F, Maggi M et al: Hypogonadal men nonresponders to the PDE5 inhibitor tadalafil benefit from normalization of testosterone levels with a 1% hydroalcoholic testosterone gel in the treatment of erectile dysfunction (TADTEST study). J Sex Med 2011; **8:** 284.
555. Shabsigh R, Kaufman JM, Steidle C et al: Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. J Urol 2004; **172:** 658.
556. Spitzer M, Basaria S, Travison TG et al: Effect of testosterone replacement on response to sildenafil citrate in men with erectile dysfunction: a parallel, randomized trial. Ann Intern Med 2012; **157:** 681.
557. Shamloul R, Ghanem H, Fahmy I et al: Testosterone therapy can enhance erectile function response to sildenafil in patients with PADAM: a pilot study. J Sex Med 2005; **2:** 559.
558. Kalinchenko SY, Kozlov GI, Gontcharov NP et al: Oral testosterone undecanoate reverses erectile dysfunction associated with diabetes mellitus in patients failing on sildenafil citrate therapy alone. Aging Male 2003; **6:** 94.
559. Rosenthal BD, May NR, Metro MJ et al: Adjunctive use of Androgel (testosterone gel) with sildenafil to treat erectile dysfunction in men with acquired androgen deficiency syndrome after failure using sildenafil alone. Urology 2006; **67:** 571.
560. Yassin AA, Saad F and Diede HE: Testosterone and erectile function in hypogonadal men unresponsive to tadalafil: results from an open-label uncontrolled study. Andrologia 2006; **38:** 61.
561. Hwang TI, Chen HE, Tsai TF et al: Combined use of androgen and sildenafil for hypogonadal patients unresponsive to sildenafil alone. Int J Impot Res 2006; **18:** 400.
562. Kim JW, Oh MM, Park MG et al: Combination therapy of testosterone enanthate and tadalafil on PDE5 inhibitor non-reponders with severe and intermediate testosterone deficiency. Int J Impot Res 2013; **25:** 29.
563. Alhathal N, Elshal AM and Carrier S: Synergetic effect of testosterone and phophodiesterase-5 inhibitors in hypogonadal men with erectile dysfunction: a systematic review. Can Urol Assoc J 2012; **6:** 269.
564. Corona G, Isidori AM, Buvat J et al: Testosterone supplementation and sexual function: a meta-analysis study. J Sex Med 2014; **11:** 1577.

565. Bolona ER, Uraga MV, Haddad RM et al: Testosterone use in men with sexual dysfunction: a systematic review and meta-analysis of randomized placebo-controlled trials. Mayo Clin Proc 2007; **82:** 20.
566. Huo S, Scialli AR, McGarvey S et al: Treatment of men for "low testosterone:" a systematic review. PLoS One 2016; **11:** e0162480.
567. Algeffari M, Jayasena CN, MacKeith P et al: Testosterone therapy for sexual dysfunction in men with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Diabet Med 2018; **35:** 195.
568. al-Juburi AZ and O'Donnell PD: Synergist erection system: clinical experience. Urology 1990; **35:** 304.
569. Aloui R, Iwaz J, Kokkidis MJ et al: A new vacuum device as alternative treatment for impotence. Br J Urol 1992; **70:** 652.
570. Asopa R and Williams G: Use of the "correctaid" device in the management of impotence. Br J Urol 1989; **63:** 546.
571. Baltaci S, Aydos K, Kosar A et al: Treating erectile dysfunction with a vacuum tumescence device: a retrospective analysis of acceptance and satisfaction. Br J Urol 1995; **76:** 757.
572. Blackard CE, Borkon WD, Lima JS et al: Use of vacuum tumescence device for impotence secondary to venous leakage. Urology 1993; **41:** 225.
573. Bosshardt RJ, Farwerk R, Sikora R et al: Objective measurement of the effectiveness, therapeutic success and dynamic mechanisms of the vacuum device. Br J Urol 1995; **75:** 786.
574. Broderick GA, Allen G and McClure RD: Vacuum tumescence devices: the role of papaverine in the selection of patients. J Urol 1991; **145:** 284.
575. Cookson MS and Nadig PW: Long-term results with vacuum constriction device. J Urol 1993; **149:** 290.
576. Derouet H, Caspari D, Rohde V et al: Treatment of erectile dysfunction with external vacuum devices. Andrologia 1999; **31 Suppl 1:** 89.
577. Dutta TC and Eid JF: Vacuum constriction devices for erectile dysfunction: a long-term, prospective study of patients with mild, moderate, and severe dysfunction. Urology 1999; **54:** 891.
578. Earle CM, Seah M, Coulden SE et al: The use of the vacuum erection device in the management of erectile impotence. Int J Impot Res 1996; **8:** 237.
579. el-Bahrawy M, el-Baz MA, Emam A et al: Noninvasive vacuum constriction device in the management of erectile dysfunction. Int Urol Nephrol 1995; **27:** 331.
580. Gilbert HW and Gingell JC: Vacuum constriction devices: second-line conservative treatment for impotence. Br J Urol 1992; **70:** 81.
581. Gould JE, Switters DM, Broderick GA et al: External vacuum devices: a clinical comparison with pharmacologic erections. World J Urol 1992; **10:** 68.
582. Kaplan FJ, Levitt NS, Stevens PJ et al: Non-invasive management of organic impotence. S Afr Med J 1995; **85:** 276.
583. Khayyamfar F, Forootan SK, Ghasemi H et al: Evaluating the efficacy of vacuum constrictive device and causes of its failure in impotent patients. Urol J 2013; **10:** 1072.
584. Kolettis PN, Lakin MM, Montague DK et al: Efficacy of the vacuum constriction device in patients with corporeal venous occlusive dysfunction. Urology 1995; **46:** 856.
585. Korenman SG and Viosca SP: Use of a vacuum tumescence device in the management of impotence in men with a history of penile implant or severe pelvic disease. J Am Geriatr Soc 1992; **40:** 61.
586. Korenman SG, Viosca SP, Kaiser FE et al: Use of a vacuum tumescence device in the management of impotence. J Am Geriatr Soc 1990; **38:** 217.
587. Lewis RW and Witherington R: External vacuum therapy for erectile dysfunction: use and results. World J Urol 1997; **15:** 78.
588. Meinhardt W, Lycklama a Nijeholt AA, Kropman RF et al: The negative pressure device for erectile disorders: when does it fail? J Urol 1993; **149:** 1285.
589. Moul JW and McLeod DG: Negative pressure devices in the explanted penile prosthesis population. J Urol 1989; **142:** 729.
590. Nadig PW, Ware JC and Blumoff R: Noninvasive device to produce and maintain an erection-like state. Urology 1986; **27:** 126.
591. Opsomer RJ, Wese FX, De Groote P et al: The external vacuum device in the management of erectile dysfunction. Acta Urol Belg 1997; **65:** 13.
592. Segenreich E, Israilov SR, Shmueli J et al: Vacuum therapy combined with psychotherapy for management of severe erectile dysfunction. Eur Urol 1995; **28:** 47.
593. Sidi AA, Becher EF, Zhang G et al: Patient acceptance of and satisfaction with an external negative pressure device for impotence. J Urol 1990; **144:** 1154.
594. Sidi AA and Lewis JH: Clinical trial of a simplified vacuum erection device for impotence treatment. Urology 1992; **39:** 526.
595. Turner LA, Althof SE, Levine SB et al: External vacuum devices in the treatment of erectile dysfunction: a one-year study of sexual and psychosocial impact. J Sex Marital Ther 1991; **17:** 81.
596. Turner LA, Althof SE, Levine SB et al: Treating erectile dysfunction with external vacuum devices: impact upon sexual, psychological and marital functioning. J Urol 1990; **144:** 79.
597. van Thillo EL and Delaere KP: The vacuum erection device. A noninvasive treatment for impotence. Acta Urol Belg 1992; **60:** 9.
598. Villeneuve R, Corcos J and Carmel M: Assisted erection follow-up with couples. J Sex Marital Ther 1991; **17:** 94.

599. Vrijhof HJ and Delaere KP: Vacuum constriction devices in erectile dysfunction: acceptance and effectiveness in patients with impotence of organic or mixed aetiology. Br J Urol 1994; **74:** 102.
600. Willard BA: An assessment of a vacuum constriction device in treating erectile dysfunction. Urol Nurs 1998; **18:** 33.
601. Witherington R: Vacuum constriction device for management of erectile impotence. J Urol 1989; **141:** 320.
602. Arauz-Pacheco C, Basco M, Ramirez LC et al: Treatment of diabetic impotence with a vacuum device: efficacy and effects on psychological status. Am J Med Sci 1992; **303:** 281.
603. Bodansky HJ: Treatment of male erectile dysfunction using the active vacuum assist device. Diabet Med 1994; **11:** 410.
604. Famuyiwa OO, Al-Jasser SJ, Ahmad AS et al: Experience with the vacuum-enhanced tumescence erecaid system in the treatment of erectile impotence among diabetic patients in Saudi Arabia. Practical Diabetes 1992; **9:** 141.
605. Israilov S, Shmuely J, Niv E et al: Evaluation of a progressive treatment program for erectile dysfunction in patients with diabetes mellitus. Int J Impot Res 2005; **17:** 431.
606. Pajovic B, Dimitrovski A, Fatic N et al: Vacuum erection device in treatment of organic erectile dysfunction and penile vascular differences between patients with DM type I and DM type II. Aging Male 2017; **20:** 49.
607. Price DE, Cooksey G, Jehu D et al: The management of impotence in diabetic men by vacuum tumescence therapy. Diabet Med 1991; **8:** 964.
608. Sun L, Peng FL, Yu ZL et al: Combined sildenafil with vacuum erection device therapy in the management of diabetic men with erectile dysfunction after failure of first-line sildenafil monotherapy. Int J Urol 2014; **21:** 1263.
609. Engel JD: Effect on sexual function of a vacuum erection device post-prostatectomy. Can J Urol 2011; **18:** 5721.
610. Nason GJ, McNamara F, Twyford M et al: Efficacy of vacuum erectile devices (VEDs) after radical prostatectomy: the initial Irish experience of a dedicated VED clinic. Int J Impot Res 2016; **6**: 205.
611. Raina R, Agarwal A, Ausmundson S et al: Early use of vacuum constriction device following radical prostatectomy facilitates early sexual activity and potentially earlier return of erectile function. Int J Impot Res 2006; **18:** 77.
612. Denil J, Ohl DA and Smythe C: Vacuum erection device in spinal cord injured men: patient and partner satisfaction. Arch Phys Med Rehabil 1996; **77:** 750.
613. Heller L, Aloni R, Keren O et al: Vacuum tumescence constriction therapy for neuropathic impotence. Int J Adolesc Med Health 1994; **7:** 255.
614. Lloyd EE, Toth LL and Perkash I: Vacuum tumescence: an option for spinal cord injured males with erectile dysfunction. SCI Nurs 1989; **6:** 25.
615. Seckin B, Atmaca I, Ozgok Y et al: External vacuum device therapy for spinal cord injured males with erectile dysfunction. Int Urol Nephrol 1996; **28:** 235.
616. Watanabe T, Chancellor MB, Rivas DA et al: Epidemiology of current treatment for sexual dysfunction in spinal cord injured men in the USA model spinal cord injury centers. J Spinal Cord Med 1996; **19:** 186.
617. Zasler ND and Katz PG: Synergist erection system in the management of impotence secondary to spinal cord injury. Arch Phys Med Rehabil 1989; **70:** 712.
618. Chen J, Mabjeesh NJ and Greenstein A: Sildenafil versus the vacuum erection device: patient preference. J Urol 2001; **166:** 1779.
619. Canguven O, Bailen J, Fredriksson W et al: Combination of vacuum erection device and PDE5 inhibitors as salvage therapy in PDE5 inhibitor nonresponders with erectile dysfunction. J Sex Med 2009; **6:** 2561.
620. Kohler TS, Pedro R, Hendlin K et al: A pilot study on the early use of the vacuum erection device after radical retropubic prostatectomy. BJU Int 2007; **100:** 858.
621. Brison D, Seftel A and Sadeghi-Nejad H: The resurgence of the vacuum erection device (VED) for treatment of erectile dysfunction. J Sex Med 2013; **10:** 1124.
622. Padma-Nathan H, Hellstrom WJ, Kaiser FE et al: Treatment of men with erectile dysfunction with transurethral alprostadil. Medicated Urethral System for Erection (MUSE) Study Group. N Engl J Med 1997; **336:** 1.
623. Williams G, Abbou CC, Amar ET et al: Efficacy and safety of transurethral alprostadil therapy in men with erectile dysfunction. MUSE Study Group. Br J Urol 1998; **81:** 889.
624. Shokeir AA, Alserafi MA and Mutabagani H: Intracavernosal versus intraurethral alprostadil: a prospective randomized study. BJU Int 1999; **83:** 812.
625. Shabsigh R, Padma-Nathan H, Gittleman M et al: Intracavernous alprostadil alfadex is more efficacious, better tolerated, and preferred over intraurethral alprostadil plus optional actis: a comparative, randomized, crossover, multicenter study. Urology 2000; **55:** 109.
626. Chiang HS, Wen TC and Liang JF: Titration study of MUSE (Medicated Urethral System for Erection) in erectile dysfunction. J Formos Med Assoc 2000; **99:** 926.
627. Ekman P, Sjogren L, Englund G et al: Optimizing the therapeutic approach of transurethral alprostadil. BJU Int 2000; **86:** 68.
628. Guay AT, Perez JB, Velasquez E et al: Clinical experience with intraurethral alprostadil (MUSE) in the treatment of men with erectile dysfunction. A retrospective study. Medicated urethral system for erection. Eur Urol 2000; **38:** 671.
629. Jaffe JS, Antell MR, Greenstein M et al: Use of intraurethral alprostadil in patients not responding to sildenafil citrate. Urology 2004; **63:** 951.

630. Khan MA, Raistrick M, Mikhailidis DP et al: MUSE: clinical experience. Curr Med Res Opin 2002; **18:** 64.
631. Kim SC, Ahn TY, Choi HK et al: Multicenter study of the treatment of erectile dysfunction with transurethral alprostadil (MUSE) in Korea. Int J Impot Res 2000; **12:** 97.
632. Kongkanand A, Ratana-Olarn K, Wuddhikarn S et al: Evaluation of transurethal alprostadil for safety and efficacy in men with erectile dysfunction. J Med Assoc Thai 2002; **85:** 223.
633. Mulhall JP, Jahoda AE, Ahmed A et al: Analysis of the consistency of intraurethral prostaglandin E1 (MUSE) during at-home use. Urology 2001; **58:** 262.
634. Garrido Abad P, Sinues Ojas B, Martinez Blazquez L et al: Safety and efficacy of intraurethral alprostadil in patients with erectile dysfunction refractory to treatment using phosphodiesterase-5 inhibitors. Actas Urol Esp 2015; **39:** 635.
635. Pangkahila WI: Evaluation of transurethral application of alprostadil for erectile dysfunction in Indonesians. Asian J Androl 2000; **2:** 233.
636. Shabsigh R, Padma-Nathan H, Gittleman M et al: Intracavernous alprostadil alfadex (EDEX/ VIRIDAL) is effective and safe in patients with erectile dysfunction after failing sildenafil (Viagra). Urology 2000; **55:** 477.
637. Hatzichristou DG, Apostolidis A, Tzortzis V et al: Sildenafil versus intracavernous injection therapy: efficacy and preference in patients on intracavernous injection for more than 1 year. J Urol 2000; **164:** 1197.
638. al-Juburi AZ and O'Donnell PD: Follow up outcome of intracavernous papaverine. J Ark Med Soc 1990; **86:** 383.
639. Alexandre B, Lemaire A, Desvaux P et al: Intracavernous injections of prostaglandin E1 for erectile dysfunction: patient satisfaction and quality of sex life on long-term treatment. J Sex Med 2007; **4:** 426.
640. Althof SE, Turner LA, Levine SB et al: Intracavernosal injection in the treatment of impotence: a prospective study of sexual, psychological, and marital functioning. J Sex Marital Ther 1987; **13:** 155.
641. Althof SE, Turner LA, Levine SB et al: Sexual, psychological, and marital impact of self-injection of papaverine and phentolamine: a long-term prospective study. J Sex Marital Ther 1991; **17:** 101.
642. Armstrong DK, Convery A and Dinsmore WW: Intracavernosal papaverine and phentolamine for the medical management of erectile dysfunction in a genitourinary clinic. Int J STD AIDS 1993; **4:** 214.
643. Armstrong DK, Convery A and Dinsmore WW: Prostaglandin E1 in the medical management of erectile dysfunction in a genito-urinary medicine clinic. Ulster Med J 1994; **63:** 18.
644. Armstrong DK, Convery AG and Dinsmore WW: Reasons for patient drop-out from an intracavernous auto-injection programme for erectile dysfunction. Br J Urol 1994; **74:** 99.
645. Bahren W, Scherb W, Gall H et al: Effects of intracavernosal pharmacotherapy on self-esteem, performance anxiety and partnership in patients with chronic erectile dysfunction. Eur Urol 1989; **16:** 175.
646. Baniel J, Israilov S, Engelstein D et al: Three-year outcome of a progressive treatment program for erectile dysfunction with intracavernous injections of vasoactive drugs. Urology 2000; **56:** 647.
647. Baum N, Randrup E, Junot D et al: Prostaglandin E1 versus sex therapy in the management of psychogenic erectile dysfunction. Int J Impot Res 2000; **12:** 191.
648. Bennett AH, Carpenter AJ and Barada JH: An improved vasoactive drug combination for a pharmacological erection program. J Urol 1991; **146:** 1564.
649. Beretta G, Zanollo A, Ascani L et al: Prostaglandin E1 in the therapy of erectile deficiency. Acta Eur Fertil 1989; **20:** 305.
650. Brindley GS: Maintenance treatment of erectile impotence by cavernosal unstriated muscle relaxant injection. Br J Psychiatry 1986; **149:** 210.
651. Brock G, Tu LM and Linet OI: Return of spontaneous erection during long-term intracavernosal alprostadil (CAVERJECT) treatment. Urology 2001; **57:** 536.
652. Brown SL, Haas CA, Koehler M et al: Hepatotoxicity related to intracavernous pharmacotherapy with papaverine. Urology 1998; **52:** 844.
653. Buvat J, Costa P, Morlier D et al: Double-blind multicenter study comparing alprostadil alpha-cyclodextrin with moxisylyte chlorhydrate in patients with chronic erectile dysfunction. J Urol 1998; **159:** 116.
654. Buvat J, Lemaire A and Herbaut-Buvat M: Intracavernous pharmacotherapy: comparison of moxisylyte and prostaglandin E1. Int J Impot Res 1996; **8:** 41.
655. Canale D, Giorgi PM, Lencioni R et al: Long-term intracavernous self-injection with prostaglandin E1 for the treatment of erectile dysfunction. Int J Androl 1996; **19:** 28.
656. Casabe A, Bechara A, Cheliz G et al: Drop-out reasons and complications in self-injection therapy with a triple vasoactive drug mixture in sexual erectile dysfunction. Int J Impot Res 1998; **10:** 5.
657. Chen J, Godschalk M, Katz PG et al: The lowest effective dose of prostaglandin E1 as treatment for erectile dysfunction. J Urol 1995; **153:** 80.
658. Chen J, Godschalk MF, Katz PG et al: Incidence of penile pain after injection of a new formulation of prostaglandin E1. J Urol 1995; **154:** 77.
659. Chen RN, Lakin MM, Montague DK et al: Penile scarring with intracavernous injection therapy using prostaglandin E1: a risk factor analysis. J Urol 1996; **155:** 138.
660. Chew KK, Stuckey BG, Earle CM et al: Penile fibrosis in intracavernosal prostaglandin E1 injection therapy for erectile dysfunction. Int J Impot Res 1997; **9:** 225.

661. Chiang HS, Wen TC, Wu CC et al: Intracavernous self-injection therapy for the treatment of erectile dysfunction. J Formos Med Assoc 1992; **91:** 898.
662. Coombs PG, Heck M, Guhring P et al: A review of outcomes of an intracavernosal injection therapy programme. BJU Int 2012; **110:** 1787.
663. Cooper AJ: Evaluation of I-C papaverine in patients with psychogenic and organic impotence. Can J Psychiatry 1991; **36:** 574.
664. de la Taille A, Delmas V, Amar E et al: Reasons of dropout from short- and long-term self-injection therapy for impotence. Eur Urol 1999; **35:** 312.
665. Dhabuwala CB, Kerkar P, Bhutwala A et al: Intracavernous papaverine in the management of psychogenic impotence. Arch Androl 1990; **24:** 185.
666. Dinsmore WW: Medical treatment of impotence with papaverine and phentolamine intracavernosal injection. Ulster Med J 1990; **59:** 174.
667. Dinsmore WW, Gingell C, Hackett G et al: Treating men with predominantly nonpsychogenic erectile dysfunction with intracavernosal vasoactive intestinal polypeptide and phentolamine mesylate in a novel auto-injector system: a multicentre double-blind placebo-controlled study. BJU Int 1999; **83:** 274.
668. El-Sakka AI: Intracavernosal prostaglandin E1 self vs office injection therapy in patients with erectile dysfunction. Int J Impot Res 2006; **18:** 180.
669. The long-term safety of alprostadil (prostaglandin-E1) in patients with erectile dysfunction. The European Alprostadil Study Group. Br J Urol 1998; **82:** 538.
670. Flynn RJ and Williams G: Long-term follow-up of patients with erectile dysfunction commenced on self injection with intracavernosal papaverine with or without phentolamine. Br J Urol 1996; **78:** 628.
671. Gall H, Sparwasser C, Bahren W et al: Long-term results of corpus cavernosum autoinjection therapy for chronic erectile dysfunction. Andrologia 1992; **24:** 285.
672. Gerber GS and Levine LA: Pharmacological erection program using prostaglandin E1. J Urol 1991; **146:** 786.
673. Gerstenberg TC, Metz P, Ottesen B et al: Intracavernous self-injection with vasoactive intestinal polypeptide and phentolamine in the management of erectile failure. J Urol 1992; **147:** 1277.
674. Girdley FM, Bruskewitz RC, Feyzi J et al: Intracavernous self-injection for impotence: a long-term therapeutic option? Experience in 78 patients. J Urol 1988; **140:** 972.
675. Godschalk M, Gheorghiu D, Chen J et al: Long-term efficacy of a new formulation of prostaglandin E1 as treatment for erectile failure. J Urol 1996; **155:** 915.
676. Godschalk MF, Chen J, Katz PG et al: Prostaglandin E1 as treatment for erectile failure in elderly men. J Am Geriatr Soc 1994; **42:** 1263.
677. Godschalk MF, Chen J, Katz PG et al: Treatment of erectile failure with prostaglandin E1: a double-blind, placebo-controlled, dose-response study. J Urol 1994; **151:** 1530.
678. Govier FE, McClure RD, Weissman RM et al: Experience with triple-drug therapy in a pharmacological erection program. J Urol 1993; **150:** 1822.
679. Gupta R, Kirschen J, Barrow RC et al: Predictors of success and risk factors for attrition in the use of intracavernous injection. J Urol 1997; **157:** 1681.
680. Hattat H, Ozkara H, Akkus E et al: Our experience with pharmacological erection treatment of erectile dysfunction. J Androl 1994; **15 Suppl:** 47s.
681. Hauck EW, Altinkilic BM, Schroeder-Printzen I et al: Prostaglandin E1 long-term self-injection programme for treatment of erectile dysfunction--a follow-up of at least 5 years. Andrologia 1999; **31 Suppl 1:** 99.
682. He L, Wen J, Jiang X et al: Long-term efficacy and safety of self-intracavernous injection of prostaglandin E1 for treatment of erectile dysfunction in China. Andrologia 2011; **43:** 208.
683. Hirsch IH, Schanne FJ, Carsello J et al: Sequential penile ultrasound monitoring of patients treated with chronic intracavernous prostaglandin E1. Urology 1995; **45:** 1037.
684. Hollander JB, Gonzalez J and Norman T: Patient satisfaction with pharmacologic erection program. Urology 1992; **39:** 439.
685. Hsiao W, Bennett N, Guhring P et al: Satisfaction profiles in men using intracavernosal injection therapy. J Sex Med 2011; **8:** 512.
686. Irwin MB and Kata EJ: High attrition rate with intracavernous injection of prostaglandin E1 for impotency. Urology 1994; **43:** 84.
687. Ismail M, Abbott L and Hirsch IH: Experience with intracavernous PGE-1 in the treatment of erectile dysfunction: dose considerations and efficacy. Int J Impot Res 1997; **9:** 39.
688. Janosko EO: Intracavernous self-injection of papaverine and regitine for the treatment of organic impotence. N C Med J 1986; **47:** 305.
689. Kaplan SA, Reis RB, Kohn IJ et al: Combination therapy using oral alpha-blockers and intracavernosal injection in men with erectile dysfunction. Urology 1998; **52:** 739.
690. Kerfoot WW and Carson CC: Pharmacologically induced erections among geriatric men. J Urol 1991; **146:** 1022.
691. Khan MM and Khwaja M: Open label study of intracavernous injection of alpostadil alphadex in the treatment of erectile dysfunction. Journal of Postgraduate Medical Institute 2005; **19:** 52.
692. Kirkeby HJ and Johannesen NL: Pharmacologically induced prolonged erections produced by papaverine. Follow-up of injection therapy. Scand J Urol Nephrol Suppl 1989; **125:** 97.

693. Kunelius P and Lukkarinen O: Intracavernous self-injection of prostaglandin E1 in the treatment of erectile dysfunction. Int J Impot Res 1999; **11:** 21.
694. Lakin MM, Montague DK, VanderBrug Medendorp S et al: Intracavernous injection therapy: analysis of results and complications. J Urol 1990; **143:** 1138.
695. Lehmann K, Casella R, Blochlinger A et al: Reasons for discontinuing intracavernous injection therapy with prostaglandin E1 (alprostadil). Urology 1999; **53:** 397.
696. Levine SB, Althof SE, Turner LA et al: Side effects of self-administration of intracavernous papaverine and phentolamine for the treatment of impotence. J Urol 1989; **141:** 54.
697. Linet OI and Ogrinc FG: Efficacy and safety of intracavernosal alprostadil in men with erectile dysfunction. The Alprostadil Study Group. N Engl J Med 1996; **334:** 873.
698. Willke RJ, Glick HA, McCarron TJ et al: Quality of life effects of alprostadil therapy for erectile dysfunction. J Urol 1997; **157:** 2124.
699. Lloyd LK and Richards JS: Intracavernous pharmacotherapy for management of erectile dysfunction in spinal cord injury. Paraplegia 1989; **27:** 457.
700. Lundberg L, Olsson JO and Kihl B: Long-term experience of self-injection therapy with prostaglandin E1 for erectile dysfunction. Scand J Urol Nephrol 1996; **30:** 395.
701. Meinhardt W, de la Fuente RB, Lycklama a Nijeholt AA et al: Prostaglandin E1 with phentolamine for the treatment of erectile dysfunction. Int J Impot Res 1996; **8:** 5.
702. Meinhardt W, Lycklama a Nijeholt AA, Kropman RF et al: Comparison of a mixture of papaverine, phentolamine and prostaglandin E1 with other intracavernous injections. Eur Urol 1994; **26:** 319.
703. Moemen MN, Hamed HA, Kamel, II et al: Clinical and sonographic assessment of the side effects of intracavernous injection of vasoactive substances. Int J Impot Res 2004; **16:** 143.
704. Montorsi F, Guazzoni G, Bergamaschi F et al: Effectiveness and safety of multidrug intracavernous therapy for vasculogenic impotence. Urology 1993; **42:** 554.
705. Montorsi F, Guazzoni G, Bergamaschi F et al: Four-drug intracavernous therapy for impotence due to corporeal veno-occlusive dysfunction. J Urol 1993; **149:** 1291.
706. Mulhall JP, Jahoda AE, Cairney M et al: The causes of patient dropout from penile self-injection therapy for impotence. J Urol 1999; **162:** 1291.
707. Nellans RE, Ellis LR and Kramer-Levien D: Pharmacological erection: diagnosis and treatment applications in 69 patients. J Urol 1987; **138:** 52.
708. Nelson RP: Injections of papaverine and regitine into the corpora cavernosa for erectile dysfunction: clinical results in 60 patients. South Med J 1989; **82:** 26.
709. Nisen H: Cavernous auto-injection therapy with prostaglandin E1. Ann Chir Gynaecol Suppl 1993; **206:** 69.
710. Pagliarulo A, Ludovico GM, Cirillo-Marucco E et al: Compliance to longterm vasoactive intracavernous therapy. Int J Impot Res 1996; **8:** 63.
711. Perimenis P, Athanasopoulos A, Geramoutsos I et al: The incidence of pharmacologically induced priapism in the diagnostic and therapeutic management of 685 men with erectile dysfunction. Urol Int 2001; **66:** 27.
712. Perimenis P, Gyftopoulos K, Athanasopoulos A et al: Diabetic impotence treated by intracavernosal injections: high treatment compliance and increasing dosage of vaso-active drugs. Eur Urol 2001; **40:** 398.
713. Pery M, Rosenberger A, Kaftori JK et al: Intracorporeal calcifications after self-injection of papaverine. Radiology 1990; **176:** 81.
714. Porst H, Buvat J, Meuleman E et al: Intracavernous alprostadil alfadex--an effective and well tolerated treatment for erectile dysfunction. Results of a long-term European study. Int J Impot Res 1998; **10:** 225.
715. Porst H, van Ahlen H, Block T et al: Intracavernous self-injection of prostaglandin E1 in the therapy of erectile dysfunction. Vasa Suppl 1989; **28:** 50.
716. Puppo P, De Rose AF, Pittaluga P et al: Diagnosis of male impotence after intracavernous papaverine test. Eur Urol 1988; **15:** 213.
717. Purvis K, Egdetveit I and Christiansen E: Intracavernosal therapy for erectile failure--impact of treatment and reasons for drop-out and dissatisfaction. Int J Impot Res 1999; **11:** 287.
718. Rabbani KJ, Tauqeer F and Rabbani R: Prostaglandin E1 for the medical management of erectile dysfunction. Pak J Med Health Sci 2010; **4:** 512.
719. Robinette MA and Moffat MJ: Intracorporal injection of papaverine and phentolamine in the management of impotence. Br J Urol 1986; **58:** 692.
720. Robinson PK: An observational study of prostaglandin E1: comparing trial and maintenance dose. Urol Nurs 1994; **14:** 76.
721. Rowland DL, Boedhoe HS, Dohle G et al: Intracavernosal self-injection therapy in men with erectile dysfunction: satisfaction and attrition in 119 patients. Int J Impot Res 1999; **11:** 145.
722. Ruutu M, Lindstrom BL, Virtanen J et al: Intracavernous self-injection for erectile failure. Eur Urol 1988; **15:** 96.
723. Sandhu D, Curless E, Dean J et al: A double blind, placebo controlled study of intracavernosal vasoactive intestinal polypeptide and phenotolamine mesylate in a novel auto-injector for the treatment of non-psychogenic erectile dysfunction. Int J Impot Res 1999; **11:** 91.

724. Schramek P, Dorninger R, Waldhauser M et al: Prostaglandin E1 in erectile dysfunction. Efficiency and incidence of priapism. Br J Urol 1990; **65:** 68.
725. Sexton WJ, Benedict JF and Jarow JP: Comparison of long-term outcomes of penile prostheses and intracavernosal injection therapy. J Urol 1998; **159:** 811.
726. Shah PJ, Dinsmore W, Oakes RA et al: Injection therapy for the treatment of erectile dysfunction: a comparison between alprostadil and a combination of vasoactive intestinal polypeptide and phentolamine mesilate. Curr Med Res Opin 2007; **23:** 2577.
727. Sidi AA, Reddy PK and Chen KK: Patient acceptance of and satisfaction with vasoactive intracavernous pharmacotherapy for impotence. J Urol 1988; **140:** 293.
728. Soderdahl DW, Thrasher JB and Hansberry KL: Intracavernosal drug-induced erection therapy versus external vacuum devices in the treatment of erectile dysfunction. Br J Urol 1997; **79:** 952.
729. Sparwasser C, Drescher P, Pust RA et al: Long-term results of therapy with intracavernousal injections and penile venous surgery in chronic erectile dysfunction. Scand J Urol Nephrol Suppl 1994; **157:** 107.
730. Stackl W, Hasun R and Marberger M: Intracavernous injection of prostaglandin E1 in impotent men. J Urol 1988; **140:** 66.
731. Stief CG, Gall H, Scherb W et al: Mid-term results of autoinjection therapy for erectile dysfunction. Urology 1988; **31:** 483.
732. Sundaram CP, Thomas W, Pryor LE et al: Long-term follow-up of patients receiving injection therapy for erectile dysfunction. Urology 1997; **49:** 932.
733. Sung HH, Ahn JS, Kim JJ et al: The role of intracavernosal injection therapy and the reasons of withdrawal from therapy in patients with erectile dysfunction in the era of PDE5 inhibitors. Andrology 2014; **2:** 45.
734. Torok A, Szekely J and Gotz F: Papaverine-induced erection. Int Urol Nephrol 1989; **21:** 195.
735. Turner LA, Althof SE, Levine SB et al: Twelve-month comparison of two treatments for erectile dysfunction: self-injection versus external vacuum devices. Urology 1992; **39:** 139.
736. Turner LA, Althof SE, Levine SB et al: Self-injection of papaverine and phentolamine in the treatment of psychogenic impotence. J Sex Marital Ther 1989; **15:** 163.
737. Valdevenito R and Melman A: Intracavernous self-injection pharmacotherapy program: analysis of results and complications. Int J Impot Res 1994; **6:** 81.
738. van der Windt F, Dohle GR, van der Tak J et al: Intracavernosal injection therapy with and without sexological counselling in men with erectile dysfunction. BJU Int 2002; **89:** 901.
739. Virag R, Shoukry K, Floresco J et al: Intracavernous self-injection of vasoactive drugs in the treatment of impotence: 8-year experience with 615 cases. J Urol 1991; **145:** 287.
740. Watters GR, Keogh EJ, Earle CM et al: Experience in the management of erectile dysfunction using the intracavernosal self-injection of vasoactive drugs. J Urol 1988; **140:** 1417.
741. Weidner W, Schroeder-Printzen I, Fischer C et al: Experience in the treatment of erectile dysfunction using the intracavernosal self-injection of papaverine: results of a prospective study after a median follow-up of 42 months involving 135 patients and 10766 injections. World J Urol 1992; **10:** 179.
742. Weiss JN, Badlani GH, Ravalli R et al: Reasons for high drop-out rate with self-injection therapy for impotence. Int J Impot Res 1994; **6:** 171.
743. Williams G, Mulcahy MJ and Kiely EA: Impotence: treatment by autoinjection of vasoactive drugs. Br Med J (Clin Res Ed) 1987; **295:** 595.
744. Wu CC, Xue ZY, Apichat K et al: The use of alprostadil sterile powder in a home self-injection study of Asian men with erectile dysfunction. Clin Ther 1996; **18:** 256.
745. Bell DS, Cutter GR, Hayne VB et al: Factors predicting efficacy of phentolamine-papaverine intracorporeal injection for treatment of erectile dysfunction in diabetic male. Urology 1992; **40:** 36.
746. Heaton JP, Lording D, Liu SN et al: Intracavernosal alprostadil is effective for the treatment of erectile dysfunction in diabetic men. Int J Impot Res 2001; **13:** 317.
747. Montorsi F, Guazzoni G, Bergamaschi F et al: Clinical reliability of multi-drug intracavernous vasoactive pharmacotherapy for diabetic impotence. Acta Diabetol 1994; **31:** 1.
748. Perimenis P, Konstantinopoulos A, Perimeni PP et al: Long-term treatment with intracavernosal injections in diabetic men with erectile dysfunction. Asian J Androl 2006; **8:** 219.
749. Tsai YS, Lin JS and Lin YM: Safety and efficacy of alprostadil sterile powder (s. Po., CAVERJECT) in diabetic patients with erectile dysfunction. Eur Urol 2000; **38:** 177.
750. Israilov S, Niv E, Livne PM et al: Intracavernous injections for erectile dysfunction in patients with cardiovascular diseases and failure or contraindications for sildenafil citrate. Int J Impot Res 2002; **14:** 38.
751. Albaugh JA and Ferrans CE: Impact of penile injections on men with erectile dysfunction after prostatectomy. Urol Nurs 2010; **30:** 64.
752. Claro Jde A, de Aboim JE, Maringolo M et al: Intracavernous injection in the treatment of erectile dysfunction after radical prostatectomy: an observational study. Sao Paulo Med J 2001; **119:** 135.
753. Dennis RL and McDougal WS: Pharmacological treatment of erectile dysfunction after radical prostatectomy. J Urol 1988; **139:** 775.

754. Domes T, Chung E, DeYoung L et al: Clinical outcomes of intracavernosal injection in postprostatectomy patients: a single-center experience. Urology 2012; **79:** 150.
755. Gontero P, Fontana F, Bagnasacco A et al: Is there an optimal time for intracavernous prostaglandin E1 rehabilitation following nonnerve sparing radical prostatectomy? Results from a hemodynamic prospective study. J Urol 2003; **169:** 2166.
756. Montorsi F, Guazzoni G, Strambi LF et al: Recovery of spontaneous erectile function after nerve-sparing radical retropubic prostatectomy with and without early intracavernous injections of alprostadil: results of a prospective, randomized trial. J Urol 1997; **158:** 1408.
757. Mydlo JH, Viterbo R and Crispen P: Use of combined intracorporal injection and a phosphodiesterase-5 inhibitor therapy for men with a suboptimal response to sildenafil and/or vardenafil monotherapy after radical retropubic prostatectomy. BJU Int 2005; **95:** 843.
758. Prabhu V, Alukal JP, Laze J et al: Long-term satisfaction and predictors of use of intracorporeal injections for post-prostatectomy erectile dysfunction. J Urol 2013; **189:** 238.
759. Raina R, Lakin MM, Thukral M et al: Long-term efficacy and compliance of intracorporeal (IC) injection for erectile dysfunction following radical prostatectomy: SHIM (IIEF-5) analysis. Int J Impot Res 2003; **15:** 318.
760. Yiou R, Bütow Z, Parisot J et al: Is it worth continuing sexual rehabilitation after radical prostatectomy with intracavernous injection of alprostadil for more than 1 year? Sex Med 2015; **3:** 42.
761. Yiou R, Cunin P, de la Taille A et al: Sexual rehabilitation and penile pain associated with intracavernous alprostadil after radical prostatectomy. J Sex Med 2011; **8:** 575.
762. Mansi MK, Alkhudair WK and Huraib S: Treatment of erectile dysfunction after kidney transplantation with intracavernosal self-injection of prostaglandin E1. J Urol 1998; **159:** 1927.
763. Beretta G, Zanollo A, Fanciullacci F et al: Intracavernous injection of papaverine in paraplegic males. Acta Eur Fertil 1986; **17:** 283.
764. Bodner DR, Leffler B and Frost F: The role of intracavernous injection of vasoactive medications for the restoration of erection in spinal cord injured males: a three year follow up. Paraplegia 1992; **30:** 118.
765. Chao R and Clowers DE: Experience with intracavernosal tri-mixture for the management of neurogenic erectile dysfunction. Arch Phys Med Rehabil 1994; **75:** 276.
766. Earle CM, Keogh EJ, Ker JK et al: The role of intracavernosal vasoactive agents to overcome impotence due to spinal cord injury. Paraplegia 1992; **30:** 273.
767. Hirsch IH, Smith RL, Chancellor MB et al: Use of intracavernous injection of prostaglandin E1 for neuropathic erectile dysfunction. Paraplegia 1994; **32:** 661.
768. Kapoor VK, Chahal AS, Jyoti SP et al: Intracavernous papaverine for impotence in spinal cord injured patients. Paraplegia 1993; **31:** 675.
769. Sidi AA, Cameron JS, Dykstra DD et al: Vasoactive intracavernous pharmacotherapy for the treatment of erectile impotence in men with spinal cord injury. J Urol 1987; **138:** 539.
770. Tang SF, Chu NK and Wong MK: Intracavernous injection of prostaglandin E1 in spinal cord injured patients with erectile dysfunction. A preliminary report. Paraplegia 1995; **33:** 731.
771. Zaslau S, Nicolis C, Galea G et al: A simplified pharmacologic erection program for patients with spinal cord injury. J Spinal Cord Med 1999; **22:** 303.
772. Derouet H, Meeth M and Bewermeier H: Experience with a papaverine/phentolamine/ prostaglandin E1-mixture in non-responders to autoinjection therapy. Aktuelle Urologie 1996; **5**: 271.
773. Akdemir F, Okulu E and Kayigil O: Long-term outcomes of AMS Spectra® penile prosthesis implantation and satisfaction rates. Int J Impot Res 2017; **5:** 184.
774. Casabe AR, Sarotto N, Gutierrez C et al: Satisfaction assessment with malleable prosthetic implant of Spectra (AMS) and Genesis (Coloplast) models. Int J Impot Res 2016; **28:** 228.
775. Akin-Olugbade O, Parker M, Guhring P et al: Determinants of patient satisfaction following penile prosthesis surgery. J Sex Med 2006; **3:** 743.
776. Al-Najar A, Naumann CM, Kaufmann S et al: Should being aged over 70 years hinder penile prosthesis implantation? BJU Int 2009; **104:** 834.
777. Altunkol A, Erçil H, Şener NC et al: Clinical evaluation of outcomes of penile prosthesis implantation and partner satisfaction. Erciyes Tip Dergisi 2014; **36:** 148.
778. Anafarta K, Safak M, Beduk Y et al: Clinical experience with inflatable and malleable penile implants in 104 patients. Urol Int 1996; **56:** 100.
779. Bae JH, Song PH, Kim HT et al: Assessment of erectile and ejaculatory function after penile prosthesis implantation. Korean J Urol 2010; **51:** 202.
780. Bettocchi C, Palumbo F, Spilotros M et al: Patient and partner satisfaction after AMS inflatable penile prosthesis implant. J Sex Med 2010; **7:** 304.
781. Borges F, Hakim L and Kline C: Surgical technique to maintain penile length after insertion of an inflatable penile prosthesis via infrapubic approach. J Sex Med 2006; **3:** 550.
782. Bozkurt IH, Arslan B, Kozacioglu Z et al: Does the etiology affect the outcome and satisfaction rates of penile prosthesis implantation surgery? Kaohsiung J Med Sci 2014; **30:** 570.
783. Bozkurt IH, Arslan B, Yonguc T et al: Patient and partner outcome of inflatable and semi-rigid penile prosthesis in a single institution. Int Braz J Urol 2015; **41:** 535.

784. Brinkman MJ, Henry GD, Wilson SK et al: A survey of patients with inflatable penile prostheses for satisfaction. J Urol 2005; **174:** 253.
785. Cakan M, Demirel F, Karabacak O et al: Risk factors for penile prosthetic infection. Int Urol Nephrol 2003; **35:** 209.
786. Carson CC, Mulcahy JJ and Govier FE: Efficacy, safety and patient satisfaction outcomes of the AMS 700CX inflatable penile prosthesis: results of a long-term multicenter study. AMS 700CX Study Group. J Urol 2000; **164:** 376.
787. Carson CC 3rd, Mulcahy JJ and Harsch MR: Long-term infection outcomes after original antibiotic impregnated inflatable penile prosthesis implants: up to 7.7 years of followup. J Urol 2011; **185:** 614.
788. Carvalheira A, Santana R and Pereira NM: Why are men satisfied or dissatisfied with penile implants? A mixed method study on satisfaction with penile prosthesis implantation. J Sex Med 2015; **12:** 2474.
789. Chiang HS, Liao CH and Chang ML: Benefits of antibiotic-impregnated inflatable penile prosthesis (InhibiZone®) in patients at high risk of infection in Taiwan. Urological Science 2016; **27:** 144.
790. Chiang HS, Wu CC and Wen TC: 10 years of experience with penile prosthesis implantation in Taiwanese patients. J Urol 2000; **163:** 476.
791. Chin CM, Jacinto HA and Lim PHC: Penile implant surgery - review of local series. Asian Journal of Surgery 1999; **22:** 402.
792. Deuk Choi Y, Jin Choi Y, Hwan Kim J et al: Mechanical reliability of the AMS 700CXM inflatable penile prosthesis for the treatment of male erectile dysfunction. J Urol 2001; **165:** 822.
793. Chung E, Solomon M, Deyoung L et al: Clinical outcomes and patient satisfaction rates among elderly male aged ≥75 years with inflatable penile prosthesis implant for medically refractory erectile dysfunction. World J Urol 2013; **1:** 173.
794. Chung E, Van CT, Wilson I et al: Penile prosthesis implantation for the treatment for male erectile dysfunction: clinical outcomes and lessons learnt after 955 procedures. World J Urol 2013; **31:** 591.
795. Daitch JA, Angermeier KW, Lakin MM et al: Long-term mechanical reliability of AMS 700 series inflatable penile prostheses: Comparison of CX/CXM and Ultrex cylinders. J Urol 1997; **158:** 1400.
796. Dhabuwala C, Sheth S and Zamzow B: Infection rates of ifampin/gentamicin-coated Titan Coloplast penile implants. Comparison with Inhibizone-impregnated AMS penile implants. J Sex Med 2011; **8:** 315.
797. Dhar NB, Angermeier KW and Montague DK: Long-term mechanical reliability of AMS 700CX/ CXM inflatable penile prosthesis. J Urol 2006; **176:** 2599.
798. Dorflinger T and Bruskewitz R: AMS malleable penile prosthesis. Urology 1986; **28:** 480.
799. Droggin D, Shabsigh R and Anastasiadis AG: Antibiotic coating reduces penile prosthesis infection. J Sex Med 2005; **2:** 565.
800. Earle CM, Watters GR, Tulloch AG et al: Complications associated with penile implants used to treat impotence. Aust N Z J Surg 1989; **59:** 959.
801. Eid JF, Wilson SK, Cleves M et al: Coated implants and "no touch" surgical technique decreases risk of infection in inflatable penile prosthesis implantation to 0.46%. Urology 2012; **79:** 1310.
802. Enemchukwu EA, Kaufman MR, Whittam BM et al: Comparative revision rates of inflatable penile prostheses using woven Dacron® fabric cylinders. J Urol 2013; **190:** 2189.
803. Fathy A, Shamloul R, AbdelRahim A et al: Experience with Tube (Promedon) malleable penile implant. Urol Int 2007; **79:** 244.
804. Fein RL: GFS Mark II inflatable penile prosthesis: four-year clinical study. Urology 1994; **43:** 209.
805. Ferguson KH and Cespedes RD: Prospective long-term results and quality-of-life assessment after DURA-II penile prosthesis placement. Urology 2003; **61:** 437.
806. Furlow WL, Goldwasser B and Gundian JC: Implantation of model AMS 700 penile prosthesis: long-term results. J Urol 1988; **139:** 741.
807. Knoll LD, Furlow WL and Motley RC: Clinical experience implanting an inflatable penile prosthesis with controlled-expansion cylinder. Urology 1990; **36:** 502.
808. Garber BB and Marcus SM: Does surgical approach affect the incidence of inflatable penile prosthesis infection? Urology 1998; **52:** 291.
809. Garber BB: Inflatable penile prosthesis: results of 150 cases. Br J Urol 1996; **78:** 933.
810. Garber BB: Outpatient inflatable penile prosthesis insertion. Urology 1997; **49:** 600.
811. Garber BB: Inflatable penile prosthesis: site-specific malfunction analysis. Int J Impot Res 2003; **15:** 22.
812. Gentile G, Franceschelli A, Massenio P et al: Patient's satisfaction after 2-piece inflatable penile prosthesis implantation: an Italian multicentric study. Arch Ital Urol Androl 2016; **88:** 1.
813. Goldstein I, Bertero EB, Kaufman JM et al: Early experience with the first pre-connected 3-piece inflatable penile prosthesis: the Mentor Alpha-1. J Urol 1993; **150:** 1814.
814. Goldstein I, Newman L, Baum N et al: Safety and efficacy outcome of Mentor Alpha-1 inflatable penile prosthesis implantation for impotence treatment. J Urol 1997; **157:** 833.
815. Grewal S, Vetter J, Brandes SB et al: A population-based analysis of contemporary rates of reoperation for penile prosthesis procedures. Urology 2014; **84:** 112.

816. Henry GD, Brinkman MJ, Mead SF et al: A survey of patients with inflatable penile prostheses: assessment of timing and frequency of intercourse and analysis of implant durability. J Sex Med 2012; **9:** 1715.
817. Henry GD, Carrion R, Jennermann C et al: Prospective evaluation of postoperative penile rehabilitation: penile length/girth maintenance 1 year following Coloplast Titan inflatable penile prosthesis. J Sex Med 2015; **12:** 1298.
818. Hollenbeck BK, Miller DC and Ohl DA: The utility of lockout valve reservoirs in preventing autoinflation in penile prostheses. Int Urol Nephrol 2002; **34:** 379.
819. Holloway FB and Farah RN: Intermediate term assessment of the reliability, function and patient satisfaction with the AMS700 Ultrex penile prosthesis. J Urol 1997; **157:** 1687.
820. Jarow JP: Risk factors for penile prosthetic infection. J Urol 1996; **156:** 402.
821. Jensen JB, Larsen EH, Kirkeby HJ et al: Clinical experience with the Mentor Alpha-1 inflatable penile prosthesis: report on 65 patients. Scand J Urol Nephrol 2005; **39:** 69.
822. Jensen JB, Madsen SS, Larsen EH et al: Patient and partner satisfaction with the Mentor Alpha-1 inflatable penile prosthesis. Scand J Urol Nephrol 2005; **39:** 66.
823. Ji YS, Ko YH, Song PH et al: Long-term survival and patient satisfaction with inflatable penile prosthesis for the treatment of erectile dysfunction. Korean J Urol 2015; **56:** 461.
824. Kilicarslan H, Kaynak Y, Gokcen K et al: Comparison of patient satisfaction rates for the malleable and two piece-inflatable penile prostheses. Turk J Urol 2014; **40:** 207.
825. Kim DS, Yang KM, Chung HJ et al: AMS 700CX/CXM inflatable penile prosthesis has high mechanical reliability at long-term follow-up. J Sex Med 2010; **7:** 2602.
826. Kucuk EV, Tahra A, Bindayi A et al: Erectile dysfunction patients are more satisfied with penile prosthesis implantation compared with tadalafil and intracavernosal injection treatments. Andrology 2016; **4**: 952.
827. Lacy J, Walker J, Gupta S et al: Risk factors for removal or revision of penile prostheses in the veteran population. Urology 2016; **98**: 189.
828. Levine LA, Estrada CR and Morgentaler A: Mechanical reliability and safety of, and patient satisfaction with the Ambicor inflatable penile prosthesis: results of a 2 center study. J Urol 2001; **166:** 932.
829. Liberman SN, Gomella LG and Hirsch IH: Experience with the Ultrex and Ultrex Plus inflatable penile prosthesis: new implantation techniques and surgical outcome. Int J Impot Res 1998; **10:** 175.
830. Lin AN: Implantation of penile prosthesis: Clinical experience with 105 cases. Asian J Surg 1989; **12:** 125.
831. Lindeborg L, Fode M, Fahrenkrug L et al: Satisfaction and complications with the Titan® one-touch release penile implant. Scand J Urol 2014; **48:** 105.
832. Lledo-Garcia E, Jara-Rascon J, Moncada Iribarren I et al: Penile prosthesis first and replacement surgeries: analysis of patient and partner satisfaction. J Sex Med 2015; **12:** 1646.
833. Lotan Y, Roehrborn CG, McConnell JD et al: Factors influencing the outcomes of penile prosthesis surgery at a teaching institution. Urology 2003; **62:** 918.
834. Lubensky JD: Outpatient 3-piece inflatable penile prosthesis. J Urol 1991; **145:** 1176.
835. Lux M, Reyes-Vallejo L, Morgentaler A et al: Outcomes and satisfaction rates for the redesigned 2-piece penile prosthesis. J Urol 2007; **177:** 262.
836. Lynch MJ, Scott GM, Inglis JA et al: Reducing the loss of implants following penile prosthetic surgery. Br J Urol 1994; **73:** 423.
837. Malloy TR, Wein AJ and Carpiniello VL: Reliability of AMS 700 inflatable penile prosthesis. Urology 1986; **28:** 385.
838. Manning M, Martinez FJ, Alken P et al: Spontaneous tumescence after implantation of three-piece hydraulic penile prostheses: a short-term experience. Int J Impot Res 2003; **15:** 152.
839. Mansi MK: Penile prosthesis: long-term follow up. Saudi Med J 1996; **17:** 365.
840. McLaren RH and Barrett DM: Patient and partner satisfaction with the AMS 700 penile prosthesis. J Urol 1992; **147:** 62.
841. Merrill DC: Clinical experience with the mentor inflatable penile prosthesis in 301 patients. J Urol 1988; **140:** 1424.
842. Milbank AJ, Montague DK, Angermeier KW et al: Mechanical failure of the American Medical Systems Ultrex inflatable penile prosthesis: before and after 1993 structural modification. J Urol 2002; **167:** 2502.
843. Minervini A, Ralph DJ and Pryor JP: Outcome of penile prosthesis implantation for treating erectile dysfunction: experience with 504 procedures. BJU Int 2006; **97:** 129.
844. Miranda-Sousa A, Keating M, Moreira S et al: Concomitant ventral phalloplasty during penile implant surgery: a novel procedure that optimizes patient satisfaction and their perception of phallic length after penile implant surgery. J Sex Med 2007; **4:** 1494.
845. Mirheydar H, Zhou T, Chang DC et al: Reoperation rates for penile prosthetic surgery. J Sex Med 2016; **13:** 129.
846. Moncada I, Martinez-Salamanca JI, Jara J et al: Inflatable penile prosthesis implantation without corporeal dilation: a cavernous tissue sparing technique. J Urol 2010; **183:** 1123.
847. Montorsi F, Rigatti P, Carmignani G et al: AMS three-piece inflatable implants for erectile dysfunction: a long-term multi-institutional study in 200 consecutive patients. Eur Urol 2000; **37:** 50.
848. Gittens P, Moskovic DJ, Avila D, Jr. et al: Favorable female sexual function is associated with patient satisfaction after inflatable penile prosthesis implantation. J Sex Med 2011; **8:** 1996.

849. Moul JW and McLeod DG: Experience with the AMS 600 malleable penile prosthesis. J Urol 1986; **135:** 929.
850. Mulhall JP, Ahmed A, Branch J et al: Serial assessment of efficacy and satisfaction profiles following penile prosthesis surgery. J Urol 2003; **169:** 1429.
851. Natali A, Olianas R and Fisch M: Penile implantation in Europe: successes and complications with 253 implants in Italy and Germany. J Sex Med 2008; **5:** 1503.
852. Negro CL, Paradiso M, Rocca A et al: Implantation of AMS 700 LGX penile prosthesis preserves penile length without the need for penile lengthening procedures. Asian J Androl 2016; **18:** 114.
853. Nickas ME, Kessler R and Kabalin JN: Long-term experience with controlled expansion cylinders in the AMS 700CX inflatable penile prosthesis and comparison with earlier versions of the Scott inflatable penile prosthesis. Urology 1994; **44:** 400.
854. Nukui F, Okamoto S, Nagata M et al: Complications and reimplantation of penile implants. Int J Urol 1997; **4:** 52.
855. Ohl DA, Brock G, Ralph D et al: Prospective evaluation of patient satisfaction, and surgeon and patient trainer assessment of the Coloplast Titan one touch release three-piece inflatable penile prosthesis. J Sex Med 2012; **9:** 2467.
856. Paranhos M, Andrade E, Antunes AA et al: Penile prosthesis implantation in an academic institution in Latin America. Int Braz J Urol 2010; **36:** 591.
857. Pescatori E, Alei G, Antonini G et al: INSIST-ED: Italian Society of Andrology registry on penile prosthesis surgery. First data analysis. Arch Ital Urol Androl 2016; **88:** 122.
858. Pozza D, Pozza M, Musy M et al: 500 penile prostheses implanted by a surgeon in Italy in the last 30 years. Arch Ital Urol Androl 2015; **87:** 216.
859. Randrup ER: Clinical experience with 180 inflatable penile prostheses. South Med J 1995; **88:** 47.
860. Randrup E, Wilson S, Mobley D et al: Clinical experience with Mentor Alpha I inflatable penile prosthesis. Report on 333 cases. Urology 1993; **42:** 305.
861. Rogers E and Murphy DM: Use of the AMS inflatable penile prosthesis in the management of erectile impotence. Ir Med J 1997; **90:** 105.
862. Salama N: Satisfaction with the malleable penile prosthesis among couples from the Middle East--is it different from that reported elsewhere? Int J Impot Res 2004; **16:** 175.
863. Salem EA, Wilson SK, Neeb A et al: Mechanical reliability of AMS 700 CX improved by parylene coating. J Sex Med 2009; **6:** 2615.
864. Saypol DC, Uhran CM and Stockman JC: Treatment of erectile failure with inflatable prostheses: three-year experience. N J Med 1987; **84:** 191.
865. Scarzella GI: Reliability of the AMS inflatable prostheses in 444 consecutive cases. Arch Ital Urol Androl 1993; **65:** 661.
866. Scarzella GI: Cylinder reliability of inflatable penile prosthesis. Experience with distensible and nondistensible cylinders in 325 patients. Urology 1988; **31:** 486.
867. Serefoglu EC, Mandava SH, Gokce A et al: Long -term revision rate due to infection in hydrophilic-coated inflatable penile prostheses: 11-year follow-up. J Sex Med 2012; **9:** 2182.
868. Sevinc C, Ozkaptan O, Balaban M et al: Outcome of penile prosthesis implantation: are malleable prostheses an appropriate treatment option in patients with erectile dysfunction caused by prior radical surgery? Asian J Androl 2016; **4**: 477.
869. Simsek A, Kucuktopcu O, Ozgor F et al: Self and partner satisfaction rates after 3 part inflatable penile prosthesis implantation. Arch Ital Urol Androl 2014; **86:** 219.
870. Song WD, Yuan YM, Cui WS et al: Penile prosthesis implantation in Chinese patients with severe erectile dysfunction: 10-year experience. Asian J Androl 2013; **15:** 658.
871. Tefilli MV, Dubocq F, Rajpurkar A et al: Assessment of psychosexual adjustment after insertion of inflatable penile prosthesis. Urology 1998; **52:** 1106.
872. Thomas AZ, Carrol R, Manecksha RP et al: Extended long term functional outcome of inflatable penile prosthesis in a single institution. Ir Med J 2011; **104:** 53.
873. Vakalopoulos I, Kampantais S, Ioannidis S et al: High patient satisfaction after inflatable penile prostheses implantation correlates with female partner satisfaction. J Sex Med 2013; **10:** 2774.
874. Vitarelli A, Divenuto L, Fortunato F et al: Long term patient satisfaction and quality of life with AMS700CX inflatable penile prosthesis. Arch Ital Urol Androl 2013; **85:** 133.
875. Whalen RK and Merrill DC: Patient satisfaction with mentor inflatable penile prosthesis. Urology 1991; **37:** 531.
876. Wilson SK and Delk JR, 2nd: Inflatable penile implant infection: predisposing factors and treatment suggestions. J Urol 1995; **153:** 659.
877. Wilson SK, Carson CC, Cleves MA et al: Quantifying risk of penile prosthesis infection with elevated glycosylated hemoglobin. J Urol 1998; **159:** 1537.
878. Wilson SK, Cleves MA and Delk JR 2nd: Comparison of mechanical reliability of original and enhanced Mentor Alpha I penile prosthesis. J Urol 1999; **162:** 715.
879. Wilson SK, Delk JR, Salem EA et al: Long-term survival of inflatable penile prostheses: single surgical group experience with 2,384 first-time implants spanning two decades. J Sex Med 2007; **4:** 1074.
880. Woodworth BE, Carson CC and Webster GD: Inflatable penile prosthesis: effect of device modification on functional longevity. Urology 1991; **38:** 533.
881. Zabar KJ, Ahmadi A and Jalal AA: Penile prosthesis implantation for the treatment of erectile dysfunction. Bahrain Medical Bulletin 2009; **31:** 2.

882. Zhu YC, Zhao JL, Wu YG et al: Clinical features and treatment options for Chinese patients with severe primary erectile dysfunction. Urology 2010; **76:** 387.
883. Antonini G, Busetto GM, De Berardinis E et al: Penile prosthesis implant for erectile dysfunction: a new minimally invasive infrapubic surgical technique. Arch Ital Urol Androl 2015; **87:** 322.
884. Menard J, Tremeaux JC, Faix A et al: Erectile function and sexual satisfaction before and after penile prosthesis implantation in radical prostatectomy patients: a comparison with patients with vasculogenic erectile dysfunction. J Sex Med 2011; **8:** 3479.
885. Kim YD, Yang SO, Lee JK et al: Usefulness of a malleable penile prosthesis in patients with a spinal cord injury. Int J Urol 2008; **15:** 919.
886. Kramer AC and Schweber A: Patient expectations prior to Coloplast Titan penile prosthesis implant predicts postoperative satisfaction. J Sex Med 2010; **7:** 2261.
887. Nehra A, Carson CC 3rd, Chapin AK et al: Long-term infection outcomes of 3-piece antibiotic impregnated penile prostheses used in replacement implant surgery. J Urol 2012; **188:** 899.
888. Mulcahy JJ and Carson CC 3rd: Long-term infection rates in diabetic patients implanted with antibiotic-impregnated versus nonimpregnated inflatable penile prostheses: 7-year outcomes. Eur Urol 2011; **60:** 167.
889. Christodoulidou M and Pearce I: Infection of penile prostheses in patients with diabetes mellitus. Surg Infect (Larchmt) 2016; **17:** 2.
890. Deveci S, Martin D, Parker M et al: Penile length alterations following penile prosthesis surgery. Eur Urol 2007; **51:** 1128.
891. Wang R, Howard GE, Hoang A et al: Prospective and long-term evaluation of erect penile length obtained with inflatable penile prosthesis to that induced by intracavernosal injection. Asian J Androl 2009; **11:** 411.
892. Levine LA and Rybak J: Traction therapy for men with shortened penis prior to penile prosthesis implantation: a pilot study. J Sex Med 2011; **8:** 2112.
893. Canguven O, Talib RA, Campbell J et al: Is the daily use of vacuum erection device for a month before penile prosthesis implantation beneficial? A randomized controlled trial. Andrology 2017; **5:** 103.
894. Pahlajani G, Raina R, Jones S et al: Vacuum erection devices revisited: its emerging role in the treatment of erectile dysfunction and early penile rehabilitation following prostate cancer therapy. J Sex Med 2012; **9:** 1182.
895. Tsambarlis PN, Chaus F and Levine LA: Successful placement of penile prostheses in men with severe corporal fibrosis following vacuum therapy protocol. J Sex Med 2017; **14:** 44.
896. Henry GD, Kansal NS, Callaway M et al: Centers of excellence concept and penile prostheses: an outcome analysis. J Urol 2009; **181:** 1264.
897. Hakky TS, Suber J, Henry G et al: Penile enhancement procedures with simultaneous penile prosthesis placement. Adv Urol 2012; **2012:** doi:10.1155/2012/314612.
898. Chew KK and Stuckey BG: Use of transurethral alprostadil (MUSE) (prostaglandin E1) for glans tumescence in a patient with penile prosthesis. Int J Impot Res 2000; **12:** 195.
899. Benevides MD and Carson CC: Intraurethral application of alprostadil in patients with failed inflatable penile prosthesis. J Urol 2000; **163:** 785.
900. Mulhall JP, Jahoda A, Aviv N et al: The impact of sildenafil citrate on sexual satisfaction profiles in men with a penile prosthesis in situ. BJU Int 2004; **93:** 97.
901. Pryor MB, Carrion R, Wang R et al: Patient satisfaction and penile morphology changes with postoperative penile rehabilitation 2 years after Coloplast Titan prosthesis. Asian J Androl 2016; **18:** 754.
902. Anafarta K, Aydos K and Yaman O: Is deep dorsal vein arterialization an alternative surgical approach to treat venogenic impotence? Urol Int 1997; **59:** 109.
903. Austoni E, Colombo F, Mantovani F et al: Venous surgery in erectile dysfunction: therapeutic strategy and results. Urol Int 1992; **49:** 63.
904. Balko A, Malhotra CM and Wincze JP: Deep-penile-vein arterialization for arterial and venous impotence. Arch Surg 1986; **121:** 774.
905. Cookson MS, Phillips DL, Huff ME et al: Analysis of microsurgical penile revascularization results by etiology of impotence. J Urol 1993; **149:** 1308.
906. Crespo E, Bove D, Farrell G et al: Revascularization of the cavernous body in vasculogenic sexual male impotence with a new microsurgical technique. Cardiovasc Res Cent Bull 1983; **22:** 29.
907. DePalma RG, Olding M, Yu GW et al: Vascular interventions for impotence: lessons learned. J Vasc Surg 1995; **21:** 576.
908. Frankovicova M and Thoma A: Microvascular treatment of impotence. Plast Reconstr Surg 1993; **91:** 99.
909. Grasso M, Lania C, Castelli M et al: Deep dorsal vein arterialization in vasculogenic impotence: our experience. Arch Ital Urol Nefrol Androl 1992; **64:** 309.
910. Hatzinger M, Seemann O, Grenacher L et al: Laparoscopy-assisted penile revascularization: a new method. J Endourol 1997; **11:** 269.
911. Janssen T, Sarramon JP, Rischmann P et al: Microsurgical arterio-arterial and arterio-venous penile revascularization in patients with pure arteriogenic impotence. Br J Urol 1994; **73:** 561.
912. Jarow JP and DeFranzo AJ: Long-term results of arterial bypass surgery for impotence secondary to segmental vascular disease. J Urol 1996; **156:** 982.

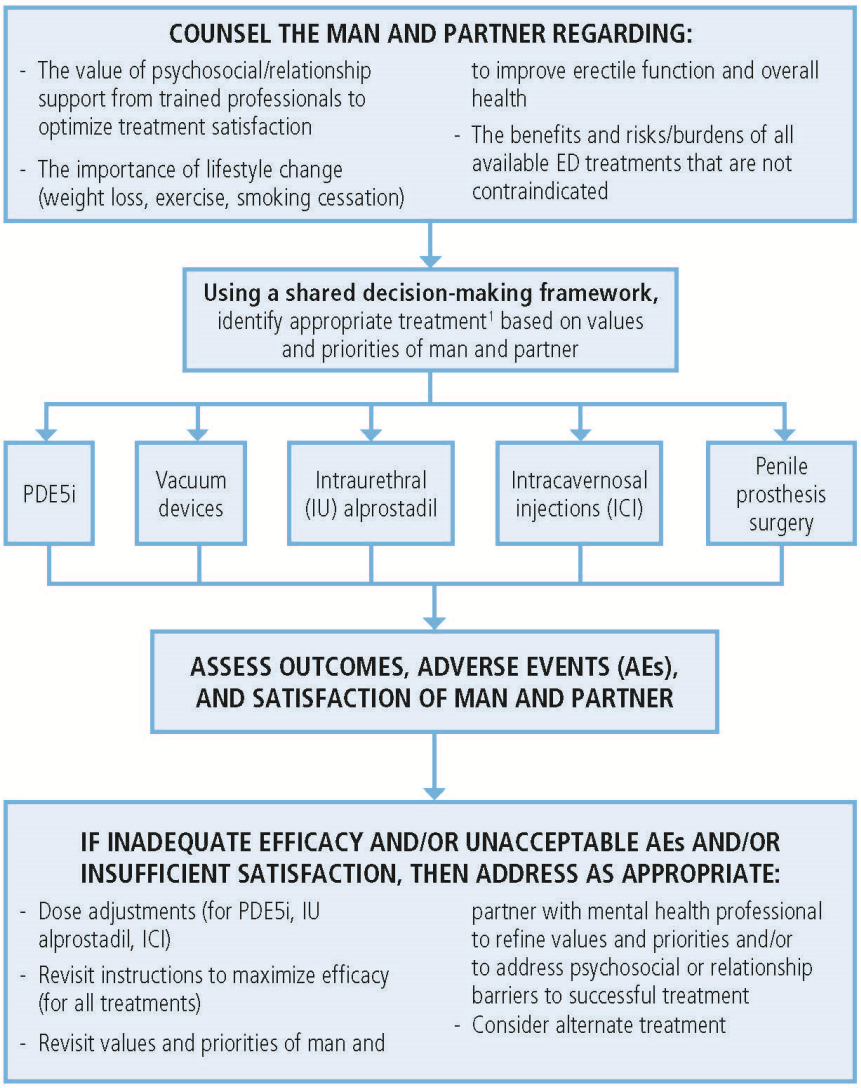
913. Kaufman JM, Kaufman JL and Fitch WP 3rd: Deep dorsal vein arterialization in arteriogenic impotence: use of the dorsal artery as a neoarterial source. Int J Impot Res 1995; **7:** 157.
914. Kawanishi Y, Kimura K, Nakanishi R et al: Penile revascularization surgery for arteriogenic erectile dysfunction: the long-term efficacy rate calculated by survival analysis. BJU Int 2004; **94:** 361.
915. Kayigil O, Agras K and Okulu E: Is deep dorsal vein arterialization effective in elderly patients? Int Urol Nephrol 2008; **40:** 125.
916. Kayigil O, Ahmed SI and Metin A: Deep dorsal vein arterialization in pure cavernoocclusive dysfunction. Eur Urol 2000; **37:** 345.
917. Kayigil O, Okulu E, Aldemir M et al: Penile revascularization in vasculogenic erectile dysfunction (ED): long-term follow-up. BJU Int 2012; **109:** 109.
918. Knoll LD: Penile dorsal vein arterialization in managing venogenic impotence. Tech Urol 1995; **1:** 157.
919. Lizza EF and Zorgniotti AW: Experience with the long-term effect of microsurgical penile revascularization. Int J Impot Res 1994; **6:** 145.
920. Lobelenz M, Junemann KP, Kohrmann KU et al: Penile revascularization in nonresponders to intracavernous injections using a modified microsurgical technique. Eur Urol 1992; **21:** 120.
921. Lukkarinen O, Tonttila P, Hellstrom P et al: Non-prosthetic surgery in the treatment of erectile dysfunction. A retrospective study of 45 impotent patients in the University of Oulu. Scand J Urol Nephrol 1998; **32:** 42.
922. Manning M, Junemann KP, Scheepe JR et al: Long-term followup and selection criteria for penile revascularization in erectile failure. J Urol 1998; **160:** 1680.
923. Melman A and Riccardi R, Jr.: The success of microsurgical penile revascularization in treating arteriogenic impotence. Int J Impot Res 1993; **5:** 47.
924. Michal V, Kramar R, Pospichal J et al: Arterial epigastricocavernous anastomosis for the treatment of sexual impotence. World J Surg 1977; **1:** 515.
925. Munarriz R, Uberoi J, Fantini G et al: Microvascular arterial bypass surgery: long-term outcomes using validated instruments. J Urol 2009; **182:** 643.
926. Sarramon JP, Bertrand N, Malavaud B et al: Microrevascularisation of the penis in vascular impotence. Int J Impot Res 1997; **9:** 127.
927. Sarramon JP, Malavaud B, Braud F et al: Evaluation of male sexual function by the International Index of Erectile Function after deep dorsal vein arterialization of the penis. J Urol 2001; **166:** 576.
928. Schramek P, Engelmann U and Kaufmann F: Microsurgical arteriovenous revascularization in the treatment of vasculogenic impotence. J Urol 1992; **147:** 1028.
929. Sohn M, Sikora R, Bohndorf K et al: Selective microsurgery in arteriogenic erectile failure. World J Urol 1990; **8:** 104.
930. Vardi Y, Gruenwald I, Gedalia U et al: Evaluation of penile revascularization for erectile dysfunction: a 10-year follow-up. Int J Impot Res 2004; **16:** 181.
931. Virag R and Bennett AH: Arterial and venous surgery for vasculogenic impotence: a combined French and American experience. Arch Ital Urol Nefrol Androl 1991; **63:** 95.
932. Wespes E, Corbusier A, Delcour C et al: Deep dorsal vein arterialisation in vascular impotence. Br J Urol 1989; **64:** 535.
933. Wespes E, Wildschutz T, Roumeguere T et al: The place of surgery for vascular impotence in the third millennium. J Urol 2003; **170:** 1284.
934. Zumbe J, Drawz G, Wiedemann A et al: Indications for penile revascularization and long-term results. Andrologia 1999; **31 Suppl 1:** 83.
935. Munarriz R: Penile microvascular arterial bypass surgery: indications, outcomes, and complications. ScientificWorldJournal 2010; **10:** 1556.
936. Dabaja AA, Teloken P and Mulhall JP: A critical analysis of candidacy for penile revascularization. J Sex Med 2014; **11:** 2327.
937. Afsar H, Metin A, Sozduyar N et al: Erectile dysfunction due to venous incompetence treated by dorsal vein ligation. Int Urol Nephrol 1992; **24:** 65.
938. Anafarta K, Beduk Y, Aydos K et al: Treatment of impotence due to venous leakage by resection of the deep dorsal vein of the penis. Urol Int 1992; **48:** 332.
939. Bar-Moshe O and Vandendris M: Surgical approach of venous leakage. Urol Int 1992; **49:** 19.
940. Berardinucci D, Morales A, Heaton JP et al: Surgical treatment of penile veno-occlusive dysfunction: is it justified? Urology 1996; **47:** 88.
941. Cakan M, Yalcinkaya F, Demirel F et al: Is dorsale penile vein ligation (DPVL) still a treatment option in veno-occlusive dysfunction? Int Urol Nephrol 2004; **36:** 381.
942. Cayan S: Primary penile venous leakage surgery with crural ligation in men with erectile dysfunction. J Urol 2008; **180:** 1056.
943. Chen SC, Hsieh CH, Hsu GL et al: The progression of the penile vein: could it be recurrent? J Androl 2005; **26:** 53.
944. Claes H and Baert L: Pelvic floor exercise versus surgery in the treatment of impotence. Br J Urol 1993; **71:** 52.
945. Claro Jde A, de Lima ML and Netto Junior N: Surgical treatment of veno-occlusive dysfunction: evaluation of short-term and long-term results. Rev Paul Med 1992; **110:** 280.
946. Flores S, Tal R, O'Brien K et al: Outcomes of crural ligation surgery for isolated crural venous leak. J Sex Med 2011; **8:** 3495.

947. Fowlis GA, Sidhu PS, Jager HR et al: Preliminary report--combined surgical and radiological penile vein occlusion for the management of impotence caused by venous-sinusoidal incompetence. Br J Urol 1994; **74:** 492.
948. Freedman AL, Costa Neto F, Mehringer CM et al: Long-term results of penile vein ligation for impotence from venous leakage. J Urol 1993; **149:** 1301.
949. Gilbert P, Sparwasser C, Beckert R et al: Venous surgery in erectile dysfunction. The role of dorsal-penile-vein ligation and spongiosolysis for impotence. Urol Int 1992; **49:** 40.
950. Hassan AA, Hassouna MM and Elhilali MM: Long -term results of penile venous ligation for corporeal venous occlusive dysfunction. Can J Surg 1995; **38:** 537.
951. Hirsch M, Lubetsky R, Goldman H et al: Dorsal vein sclerosis as a predictor of outcome in penile venous ligation surgery. J Urol 1993; **150:** 1810.
952. Hsu GL, Chen HS, Hsieh CH et al: Clinical experience of a refined penile venous stripping surgery procedure for patients with erectile dysfunction: is it a viable option? J Androl 2010; **31:** 271.
953. Hwang TI and Yang CR: Penile vein ligation for venogenic impotence. Eur Urol 1994; **26:** 46.
954. Katzenwadel A, Popken G and Wetterauer U: Penile venous surgery for cavernosal venous leakage: long-term results and retrospective studies. Urol Int 1993; **50:** 71.
955. Kerfoot WW, Carson CC, Donaldson JT et al: Investigation of vascular changes following penile vein ligation. J Urol 1994; **152:** 884.
956. Kim ED and McVary KT: Long-term results with penile vein ligation for venogenic impotence. J Urol 1995; **153:** 655.
957. Knoll LD, Furlow WL and Benson RC: Penile venous ligation surgery for the management of cavernosal venous leakage. Urol Int 1992; **49:** 33.
958. Kropman RF, Lycklama Nijeholt AAAB, Odink HF et al: Treatment of impotence caused by veno-occlusive dysfunction with detachable balloons and coils in combination with resection of the deep dorsal vein: comparison with resection of the deep dorsal vein only. World J Urol 1992; **10:** 226.
959. Lewis RW: Results of surgery for veno-occlusive disease. J Sex Marital Ther 1991; **17:** 129.
960. Lunglmayr G, Nachtigall M and Gindl K: Long-term results of deep dorsal penile vein transsection in venous impotence. Eur Urol 1988; **15:** 209.
961. McLoughlin J, Asopa R and Williams G: Surgical treatment of venous leakage: medium-term follow-up. Eur Urol 1993; **23:** 352.
962. Miwa Y, Shioyama R, Itou Y et al: Pelvic venoablation with ethanol for the treatment of erectile dysfunction due to veno-occlusive dysfunction. Urology 2001; **58:** 76.
963. Montague DK, Angermeier KW, Lakin MM et al: Penile venous ligation in 18 patients with 1 to 3 years of followup. J Urol 1993; **149:** 306.
964. Motiwala HG, Patel DD, Joshi SP et al: Experience with penile venous surgery. Urol Int 1993; **51:** 9.
965. Netto Jr NR, Cara A, Reinato JAS et al: Cavernosometry: corroboratory method to surgical treatment of impotence due to venous leakage. Urology 1990; **35:** 35.
966. Ng FC, Ruan XQ, Wong HT et al: Venous ligation for cavernous leak impotence--a report on 30 cases. Ann Acad Med Singapore 1995; **24:** 716.
967. Nikoobakht M, Saraji A and Meysamie A: Preoperative corporal biopsy as a predictor of postoperative results in venoocclusive erectile dysfunction. Urol J 2005; **2:** 160.
968. Parrott LH, Sholes AH, Rice JC et al: Penile vein dissection: a study of its long-term efficacy in impotence. World J Urol 1989; **7:** 169.
969. Petrou S and Lewis RW: Management of corporal veno-occlusive dysfunction. Urol Int 1992; **49:** 48.
970. Popken G, Katzenwadel A and Wetterauer U: Long-term results of dorsal penile vein ligation for symptomatic treatment of erectile dysfunction. Andrologia 1999; **31 Suppl 1:** 77.
971. Rossman B, Mieza M and Melman A: Penile vein ligation for corporeal incompetence: an evaluation of short-term and long-term results. J Urol 1990; **144:** 679.
972. Sasso F, Gulino G, Di Pinto A et al: Should venous surgery be still proposed or neglected? Int J Impot Res 1996; **8:** 25.
973. Sasso F, Gulino G, Weir J et al: Patient selection criteria in the surgical treatment of veno-occlusive dysfunction. J Urol 1999; **161:** 1145.
974. Schultheiss D, Truss MC, Becker AJ et al: Long-term results following dorsal penile vein ligation in 126 patients with veno-occlusive dysfunction. Int J Impot Res 1997; **9:** 205.
975. Stief CG, Djamilian M, Truss MC et al: Prognostic factors for the postoperative outcome of penile venous surgery for venogenic erectile dysfunction. J Urol 1994; **151:** 880.
976. Da Ros CT, Teloken C, Antonini CC et al: Long-term results of penile vein ligation for erectile dysfunction due to cavernovenous disease. Tech Urol 2000; **6:** 172.
977. Torok A, Szekely J, Mark B et al: Surgical treatment of impotence due to venous outflow. Int Urol Nephrol 1989; **21:** 485.
978. Treiber U and Gilbert P: Venous surgery in erectile dysfunction: a critical report on 116 patients. Urology 1989; **34:** 22.
979. Tsai TC, Hsu GL, Chen SC et al: Analysis of the results of reconstructive surgery for vasculogenic impotence. Taiwan Yi Xue Hui Za Zhi 1988; **87:** 182.
980. Vale JA, Feneley MR, Lees WR et al: Venous leak surgery: long-term follow-up of patients undergoing excision and ligation of the deep dorsal vein of the penis. Br J Urol 1995; **76:** 192.
981. Wagenknecht LV: New treatment of increased venous drainage in organic impotence: ligation of internal iliac veins. Eur Urol 1989; **16:** 172.

982. Weidner W, Weiske WH, Rudnick J et al: Venous surgery in veno-occlusive dysfunction: long-time results after deep dorsal vein resection. Urol Int 1992; **49:** 24.
983. Wespes E and Schulman CC: Venous leakage: surgical treatment of a curable cause of impotence. J Urol 1985; **133:** 796.
984. Wespes E, Moreira de Goes P, Sattar AA et al: Objective criteria in the long-term evaluation of penile venous surgery. J Urol 1994; **152:** 888.
985. Wespes E, Delcour C, Preserowitz L et al: Impotence due to corporeal veno-occlusive dysfunction: long-term follow-up of venous surgery. Eur Urol 1992; **21:** 115.
986. Williams G, Mulcahy MJ, Hartnell G et al: Diagnosis and treatment of venous leakage: a curable cause of impotence. Br J Urol 1988; **61:** 151.
987. Yu GW, Schwab FJ, Melograna FS et al: Preoperative and postoperative dynamic cavernosography and cavernosometry: objective assessment of venous ligation for impotence. J Urol 1992; **147:** 618.
988. Vardi Y, Appel B, Kilchevsky A et al: Does low intensity extracorporeal shock wave therapy have a physiological effect on erectile function? Short-term results of a randomized, double-blind, sham controlled study. J Urol 2012; **187:** 1769.
989. Srini VS, Reddy RK, Shultz T et al: Low intensity extracorporeal shockwave therapy for erectile dysfunction: a study in an Indian population. Can J Urol 2015; **22:** 7614.
990. Olsen AB, Persiani M, Boie S et al: Can low-intensity extracorporeal shockwave therapy improve erectile dysfunction? A prospective, randomized, double-blind, placebo-controlled study. Scand J Urol 2015; **49:** 329.
991. Kalyvianakis D and Hatzichristou D: Low-intensity shockwave therapy improves hemodynamic parameters in patients with vasculogenic erectile dysfunction: a triplex ultrasonography-based sham-controlled trial. J Sex Med 2017; **14:** 891.
992. Kitrey ND, Gruenwald I, Appel B et al: Penile low intensity shock wave treatment is able to shift PDE5i nonresponders to responders: a double-blind, sham controlled study. J Urol 2016; **195:** 1550.
993. Yee CH, Chan ES, Hou SS et al: Extracorporeal shockwave therapy in the treatment of erectile dysfunction: a prospective, randomized, double -blinded, placebo controlled study. Int J Urol 2014; **21:** 1041.
994. Fojecki GL, Tiessen S and Osther PJ: Effect of low-energy linear shockwave therapy on erectile dysfunction-a double-blinded, sham-controlled, randomized clinical trial. J Sex Med 2017; **14:** 106.
995. Clavijo RI, Kohn TP, Kohn JR et al: Effects of low-intensity extracorporeal shockwave therapy on erectile dysfunction: a systematic review and meta-analysis. J Sex Med 2017; **14:** 27.
996. Angulo JC, Arance I, de Las Heras MM et al: Efficacy of low-intensity shock wave therapy for erectile dysfunction: a systematic review and meta-analysis. Actas Urol Esp 2017; **41:** 479.
997. Lu Z, Lin G, Reed-Maldonado A et al: Low-intensity extracorporeal shock wave treatment improves erectile function: a systematic review and meta-analysis. Eur Urol 2017; **71:** 223.
998. Zou ZJ, Tang LY, Liu ZH et al: Short-term efficacy and safety of low-intensity extracorporeal shock wave therapy in erectile dysfunction: a systematic review and meta-analysis. Int Braz J Urol 2017; **43:** 805**.**
999. Bahk JY, Jung JH, Han H et al: Treatment of diabetic impotence with umbilical cord blood stem cell intracavernosal transplant: preliminary report of 7 cases. Exp Clin Transplant 2010; **8:** 150.
1000. Garber MG and Carlos, ND: Intracavernous administration of adipose stem cells: a new technique of treating erectile dysfunction in diabetic patient, preliminary report of 6 cases. MOJ Cell Sci Rep 2015; **1:** 00018**.**
1001. Yiou R, Hamidou L, Birebent B et al: Safety of intracavernous bone marrow-mononuclear cells for postradical prostatectomy erectile dysfunction: an open dose-escalation pilot study. Eur Urol 2016; **69:** 988.
1002. Haahr MK, Jensen CH, Toyserkani NM et al: Safety and potential effect of a single intracavernous injection of autologous adipose-derived regenerative cells in patients with erectile dysfunction following radical prostatectomy: an open-label phase I clinical trial. EBioMedicine 2016; **5:** 204.
1003. Levy JA, Marchand M, Iorio L et al: Determining the feasibility of managing erectile dysfunction in humans with placental-derived stem cells. J Am Osteopath Assoc 2016; **116:** e1.
1004. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
1005. https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html
1006. Carter HB, Albertsen PC, Barry MJ, et al. Early Detection of Prostate Cancer: AUA Guideline. J Urol 2013; **2**:419-426.
1007. Mulhall JP, Trost LW, Brannigan RE et al: Evaluation and Management of Testosterone Deficiency: AUA Guideline. J Urol 2018; doi 10.1016/j.juro.2018.03.115.

APPENDIX A

ERECTILE DYSFUNCTION ALGORITHM

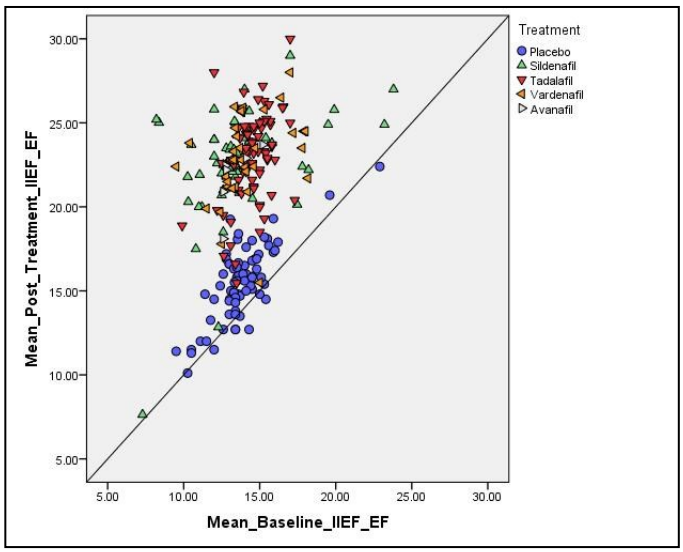


[1] For men with testosterone deficiency, defined as the presence of symptoms and signs and a total testosterone <300 ng/dl, counseling should emphasize that restoration of testosterone levels to theraputic levels is likely to increase efficacy of ED treatments other than prosthesis surgery.

APPENDIX B: Additional Tables and Plots

Appendix B1 -- Guideline Statement 8: PDE5i data

PDE5i have similar efficacy in the general ED population. Examination of data reported by trials that evaluated PDE5i revealed that these medications had similar efficacy among men in the general ED population, defined as men with a variety of underlying conditions that potentially contributed to ED symptoms. This pattern was evident when raw data were examined [see International Index of Erectile Function-Erectile Function (IIEF-EF) subscale table in guideline] as well as when the subset of data that could be meta-analyzed were pooled. The same patterns can be seen in the graph below that plots mean IIEF-EF baseline scores and mean post-treatment scores for each study by medication (symbols above the diagonal line reflect increased scores from baseline to post-treatment. Active treatment groups generally cluster above the placebo groups without clear separation among medications.**



**The symbol in the lower left corner is the active treatment arm of Zhang, Xu (2014). These men had severe ED and did not benefit from sildenafil treatment for one month, illustrating the importance of appropriate patient selection to maximize the possibility of successful treatment with the PDE5i medications.

Similar patterns are evident for other measures. Data from the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) are below; mean satisfaction scores (possible range 0 to 100) are similar across active medications (limited data available for tadalafil and vardenafil).

General ED Population: Post-Treatment EDITS Scores

Treatment	# study arms	Minimum	Maximum	Mean
Placebo	13	34.08	66.00	47.27
Sildenafil	21	30.70	96.00	71.40
Tadalafil	5	41.00	84.00	69.36
Vardenafil	3	37.50	74.07	59.06

The same pattern is evident for the Sexual Encounter Profile (SEP) question 2 ("Were you able to insert your penis into your partner's vagina?") and question 3 ("Did your erection last long enough for you to have successful intercourse?"). The percentages of men who respond "yes" are relatively similar across active medications (limited data are available for avanafil).

General ED Population: Post-Treatment SEP Questions 2 and 3
Percent "yes" responses

Treatment	Measure	# study arms	Minimum	Maximum	Mean
Placebo	SEP_Q2_post-treatment	40	24.00%	82.30%	52.94%
	SEP_Q3_post-treatment	51	20.00%	61.50%	34.62%
Sildenafil	SEP_Q2_post-treatment	10	4.00%	96.96%	71.40%
	SEP_Q3_post-treatment	21	4.10%	86.60%	70.49%
Tadalafil	SEP_Q2_post-treatment	50	56.00%	96.52%	78.00%
	SEP_Q3_post-treatment	59	37.00%	85.00%	66.64%
Vardenafil	SEP_Q2_post-treatment	27	65.90%	95.76%	83.20%
	SEP_Q3_post-treatment	31	53.50%	89.40%	74.56%
Avanafil	SEP_Q2_post-treatment	4	64.00%	80.20%	73.80%
	SEP_Q3_post-treatment	4	41.00%	66.60%	55.40%

A subgroup of studies used global assessment questions (GAQ 1 and 2) or global efficacy questions (GEQ 1 and 2). The phrasing of the questions differs, but essentially question 1 asks whether the study medication has improved erections and question 2 asks whether, if the treatment has improved a man's erections, has his ability to engage in sexual activity improved. These data are tabulated below. Again, there are no clear differences across medications (limited data for avanafil).

General ED Population: GEQ/GAQ Data by Treatment
Percent "yes" responses

Treatment	Measure	# study arms	Minimum	Maximum	Mean
Placebo	GEQ or GAQ Q1 post-treatment	55	6.00%	83.00%	29.85%
	GEQ or GAQ Q2 post-treatment	13	17.00%	94.00%	39.66%
Sildenafil	GEQ or GAQ Q1 post-treatment	50	56.00%	100.00%	81.94%
	GEQ or GAQ Q2 post-treatment	18	70.00%	100.00%	87.47%
Tadalafil	GEQ or GAQ Q1 post-treatment	42	20.00%	97.30%	78.19%
	GEQ or GAQ Q2 post-treatment	7	42.00%	97.00%	73.11%
Vardenafil	GEQ or GAQ Q1 post-treatment	31	36.00%	96.00%	82.15%
	GEQ or GAQ Q2 post-treatment	No studies			
Avanafil	GEQ or GAQ Q1 post-treatment	3	46.00%	61.60%	53.53%
	GEQ or GAQ Q2 post-treatment	1	89.00%	89.00%	89.00%

<u>Dose-response effects across PDE5i medications are small and non-linear</u> (i.e., doubling the dose does not double the effect). Higher doses may produce higher average effects but dose groups generally were not statistically significantly different unless comparing extremely low doses to extremely high doses. The magnitude of average increased effects with increased doses is small and often not clinically significant (e.g., a one or two point increase on the IIEF-EF). IIEF-EF data for trials of sildenafil, tadalafil, and vardenafil that used fixed doses are below (insufficient data for avanafil).

General ED Population: Baseline and Post-Treatment IIEF-EF Scores by Treatment and Dose (mg) For Fixed Dose Study Arms

Treatment	Dose (mg)	Measure	# study arms	Minimum	Maximum	Mean
Sildenafil	50.0	Mean IIEF-EF Baseline	5	12.20	18.21	13.98
		Mean IIEF-EF Post-Treatment	5	21.00	24.60	22.58
	100.0	Mean IIEF-EF Baseline	7	12.00	17.80	14.35
		Mean IIEF-EF Post-Treatment	7	20.84	29.00	23.84
Tadalafil	5.0	Mean IIEF-EF Baseline	12	13.10	15.80	14.27
		Mean IIEF-EF Post-Treatment	12	17.70	24.80	21.98
	10.0	Mean IIEF-EF Baseline	13	9.90	15.80	14.02
		Mean IIEF-EF Post-Treatment	13	15.46	26.40	21.28
	20.0	Mean IIEF-EF Baseline	32	12.00	17.30	14.84
		Mean IIEF-EF Post-Treatment	32	19.50	30.00	24.45
Vardenafil	5.0	Mean IIEF-EF Baseline	4	12.50	14.20	13.33
		Mean IIEF-EF Post-Treatment	3	17.80	22.36	20.35
	10.0	Mean IIEF-EF Baseline	14	12.40	18.00	14.60
		Mean IIEF-EF Post-Treatment	13	15.50	25.64	22.30
	20.0	Mean IIEF-EF Baseline	9	12.60	18.17	14.17
		Mean IIEF-EF Post-Treatment	7	21.20	28.00	23.88

<u>On demand dosing vs. daily dosing for tadalafil appears to produce the same level of efficacy</u>. Note that daily dosing trials generally used lower doses than did on demand trials. Trials of sildenafil and avanafil used only on demand dosing.

General ED Population: IIEF-EF Baseline and Post-Treatment Scores By Treatment Type and Dosing Frequency

Tx	Dosing	Measure	Study arms	Min	Max	Mean
Placebo	On demand	Mean IIEF-EF Baseline	68	9.50	22.90	13.66
		Mean IIEF-EF Post-Treatment	65	10.11	22.40	15.41
	Daily	Mean IIEF-EF Baseline	6	13.40	15.90	14.57
		Mean IIEF-EF Post-Treatment	6	14.60	19.30	16.17
Sildenafil	On demand	Mean IIEF-EF Baseline	65	7.29	23.80	13.61
		Mean IIEF-EF Post-Treatment	69	7.63	29.00	22.98
Tadalafil	On demand	Mean IIEF-EF Baseline	53	9.90	17.30	14.55
		Mean IIEF-EF Post-Treatment	52	15.46	30.00	23.01
	Daily	Mean IIEF-EF Baseline	16	12.64	15.80	14.18
		Mean IIEF-EF Post-Treatment	16	17.08	26.40	22.27
Vardenafil	On demand	Mean IIEF-EF Baseline	43	9.50	18.17	13.66
		Mean IIEF-EF Post-Treatment	33	17.80	28.00	23.11
	Daily	Mean IIEF-EF Baseline	2	17.80	17.90	17.85
		Mean IIEF-EF Post-Treatment	2	23.50	24.50	24.00
Avanafil	On demand	Mean IIEF-EF Baseline	6	12.60	15.20	13.34
		Mean IIEF-EF Post-Treatment	6	18.10	23.70	21.71

Adverse events. Data from trials that evaluated men from the general ED population are below.

General ED Population: Frequently-Reported Adverse Events (percent)					
Treatment	**Adverse Event**	**# study arms**	**Minimum**	**Maximum**	**Mean**
Placebo	Dyspepsia	66	0.00%	7.50%	1.15%
	Headache	82	0.00%	12.10%	4.05%
	Flushing	68	0.00%	9.40%	1.52%
	Back pain	30	0.00%	14.90%	2.18%
	Nasal congestion or rhinitis	51	0.00%	9.10%	1.35%
	Myalgia	21	0.00%	5.00%	0.97%
	Visual disturbance	28	0.00%	3.70%	0.60%
	Dizziness	20	0.00%	6.10%	1.29%
Sildenafil	Dyspepsia	81	0.00%	16.00%	4.81%
	Headache	103	0.00%	32.00%	11.15%
	Flushing	99	0.00%	45.80%	10.45%
	Back pain	15	0.00%	6.00%	2.07%
	Nasal congestion or rhinitis	70	0.00%	18.70%	3.80%
	Myalgia	14	0.00%	7.40%	2.11%
	Visual disturbance	56	0.00%	11.00%	3.59%
	Dizziness	31	0.00%	13.70%	2.68%
Tadalafil	Dyspepsia	62	0.00%	22.00%	5.57%
	Headache	70	1.00%	43.00%	8.89%
	Flushing	45	.30%	10.00%	3.55%
	Back pain	58	0.00%	16.10%	4.21%
	Nasal congestion or rhinitis	31	0.00%	8.60%	3.27%
	Myalgia	40	0.00%	9.70%	3.36%
	Visual disturbance	10	0.00%	3.33%	0.64%
	Dizziness	17	0.00%	6.20%	2.28%
Vardenafil	Dyspepsia	40	0.00%	9.00%	3.38%
	Headache	53	.70%	22.00%	10.80%
	Flushing	53	.10%	36.00%	8.98%
	Back pain	16	0.00%	3.10%	1.43%
	Nasal congestion or rhinitis	43	.10%	17.00%	5.52%
	Myalgia	2	0.00%	1.10%	0.55%
	Visual disturbance	13	0.00%	3.33%	1.55%
	Dizziness	11	.15%	2.90%	1.56%
Avanafil	Dyspepsia	2	0.00%	1.43%	0.72%
	Headache	6	4.29%	10.14%	6.87%
	Flushing	6	3.50%	13.00%	6.94%
	Back pain	4	1.50%	2.50%	2.10%
	Nasal congestion or rhinitis	6	.60%	4.30%	1.96%
	Myalgia	2	0.00%	0.00%	0.00%
	Visual disturbance	2	0.00%	1.43%	0.72%
	Dizziness	1	1.30%	1.30%	1.30%

Tadalafil was the only medication for which there were substantial on demand vs. daily dosing studies. Those data are below.

Tadalafil: Rates of Commonly-Reported Adverse Events (means)				
	# study arms	On demand	# study arms	Daily
Dyspepsia	42	6.10	17	4.21
Headache	48	10.62	19	4.59
Flushing	34	3.50	8	3.54
Back pain	40	4.44	15	3.81
Nasal conges-tion	25	3.38	6	2.83
Myalgia	23	3.87	14	2.59
Dizziness	12	2.75	5	1.14

Most AEs follow a dose-response pattern such that men in active treatment arms reported statistically significantly higher rates of AEs than did men in placebo arms and the percentage of men reporting a particular AE increased as dose increases. Within individual studies, however, the differences between dose groups were usually not statistically significantly different. Data from studies of men in the general ED population that administered medications at fixed doses (i.e., did not allow the patient to titrate dose up or down) are below.

General ED Population: Adverse Event Rates by Drug and Dose (mg)						
Treatment	Dose_ mg	Adverse Event	# study arms	Minimum	Maximum	Mean
Placebo	0	Dyspepsia	36	0.00%	3.70%	0.84%
		Headache	42	0.00%	8.50%	4.01%
		Flushing	32	0.00%	6.00%	1.21%
		Back pain	25	0.00%	14.90%	2.35%
		Nasal congestion or rhinitis	25	0.00%	9.10%	1.64%
		Myalgia	16	0.00%	4.00%	0.96%
		Visual disturbance	9	0.00%	2.00%	0.52%
		Dizziness	9	0.00%	6.10%	1.32%

General ED Population: Adverse Event Rates by Drug and Dose (mg)						
Treatment	**Dose_ mg**	**Adverse Event**	**# study arms**	**Minimum**	**Maximum**	**Mean**
Sildenafil	50	Dyspepsia	9	0.00%	11.00%	3.88%
		Headache	11	0.00%	21.00%	8.96%
		Flushing	11	0.00%	27.00%	9.72%
		Back pain	1	6.00%	6.00%	6.00%
		Nasal congestion or rhinitis	6	1.20%	3.00%	2.00%
		Myalgia	1	7.40%	7.40%	7.40%
		Visual disturbance	4	1.00%	6.00%	2.40%
		Dizziness	3	0.00%	2.30%	0.93%
	100	Dyspepsia	10	0.50%	16.00%	6.22%
		Headache	11	1.40%	32.00%	12.86%
		Flushing	11	1.70%	20.00%	11.00%
		Back pain	4	0.00%	0.80%	0.35%
		Nasal congestion or rhinitis	10	0.40%	11.00%	3.80%
		Myalgia	2	0.00%	0.00%	0.00%
		Visual disturbance	8	0.30%	11.00%	6.58%
		Dizziness	2	0.80%	1.70%	1.25%

General ED Population: Adverse Event Rates by Drug and Dose (mg)						
Treatment	**Dose_ mg**	**Adverse Event**	**# study arms**	**Minimum**	**Maximum**	**Mean**
Tadalafil	2.5	Dyspepsia	3	1.00%	4.20%	2.50%
		Headache	3	2.50%	7.00%	4.20%
		Flushing	1	1.00%	1.00%	1.00%
		Back pain	3	2.80%	5.20%	4.00%
		Nasal congestion or rhinitis	2	0.00%	5.00%	2.50%
		Myalgia	3	1.50%	4.20%	2.90%
		Visual disturbance	0	NR	NR	NR
		Dizziness	0	NR	NR	NR
	5	Dyspepsia	13	0.50%	9.00%	3.85%
		Headache	15	1.00%	11.00%	4.85%
		Flushing	7	0.80%	6.70%	3.81%
		Back pain	11	0.00%	6.80%	3.00%
		Nasal congestion or rhinitis	6	1.10%	4.10%	2.37%
		Myalgia	8	1.00%	4.40%	1.89%
		Visual disturbance	1	0.00%	0.00%	0.00%
		Dizziness	3	0.00%	2.40%	1.30%
	10	Dyspepsia	9	1.20%	11.40%	6.53%
		Headache	10	2.60%	16.70%	9.33%
		Flushing	4	3.00%	8.00%	4.90%
		Back pain	10	0.80%	10.80%	5.42%
		Nasal congestion or rhinitis	5	1.20%	8.00%	4.02%
		Myalgia	5	4.00%	9.20%	5.96%
		Visual disturbance	3	0.00%	2.50%	0.83%
		Dizziness	3	1.30%	4.60%	2.80%
	20	Dyspepsia	28	0.80%	22.00%	6.83%
		Headache	33	1.60%	43.00%	11.44%
		Flushing	27	0.30%	10.00%	3.76%
		Back pain	25	0.60%	16.10%	4.54%
		Nasal congestion or rhinitis	15	0.50%	8.60%	3.43%
		Myalgia	19	0.30%	9.70%	3.74%
		Visual disturbance	6	0.00%	3.33%	0.66%
		Dizziness	6	0.70%	6.20%	2.82%

General ED Population: Adverse Event Rates by Drug and Dose (mg)						
Treatment	**Dose_ mg**	**Adverse Event**	**# study arms**	**Minimum**	**Maximum**	**Mean**
Vardenafil	5	Dyspepsia	5	0.70%	2.00%	1.34%
		Headache	5	6.80%	11.00%	9.14%
		Flushing	5	5.00%	21.00%	9.70%
		Back pain	1	3.10%	3.10%	3.10%
		Nasal congestion or rhinitis	5	4.00%	9.00%	5.64%
		Myalgia	0	NR	NR	NR
		Visual disturbance	1	1.50%	1.50%	1.50%
		Dizziness	1	1.40%	1.40%	1.40%
	10	Dyspepsia	15	0.00%	6.60%	3.19%
		Headache	15	3.50%	22.00%	10.91%
		Flushing	15	1.30%	29.00%	9.31%
		Back pain	5	0.00%	3.10%	1.60%
		Nasal congestion or rhinitis	10	1.20%	14.00%	6.49%
		Myalgia	1	1.10%	1.10%	1.10%
		Visual disturbance	2	0.00%	2.00%	1.00%
		Dizziness	4	1.20%	2.90%	2.28%
	20	Dyspepsia	10	1.00%	9.00%	5.40%
		Headache	11	10.40%	22.00%	16.55%
		Flushing	11	3.00%	36.00%	13.17%
		Back pain	3	1.00%	1.70%	1.40%
		Nasal congestion or rhinitis	10	1.11%	17.00%	9.20%
		Myalgia	1	0.00%	0.00%	0.00%
		Visual disturbance	5	0.00%	3.33%	2.17%
		Dizziness	1	2.80%	2.80%	2.80%

When means for the general and four special populations (men with diabetes, with BPH/LUTS, post-RP, or post-RT) for which there are substantial data were examined, it appears that men post-RP and men post-RT reported substantially higher rates of AEs than did men in the general ED population. Whether men who have had prostate cancer treatment are more likely to experience AEs or are more likely to report AEs is not clear. Men post-RP reported higher rates of AEs in response to sildenafil than in response to other PDE5s. Men post-RT reported high rates of AEs across PDE5s and in placebo groups. The high rates of AEs reported by men in placebo groups suggest that men post-RT may have heightened sensitivity to body sensations and may have unmet needs for psychosocial support. These patterns can be seen in the table below (AEs for which there were 1 or 2 study arms are omitted); see cells in bold.

Common AEs by Treatment and Population (mean percentages)					
PLACEBO	**Gen Pop**	**Diabetes**	**BPH/LUTS**	**Post-RP**	**Post-RT**
Dyspepsia	1.15%	0.57%	0.40%	0.34%	**21.17%**
Headache	4.05%	3.12%	3.03%	3.74%	**9.28%**
Flushing	1.52%	0.86%	Insufficient data	0.00%	**4.78%**
Nasal congestion	1.35%	0.94%	Insufficient data	2.17%	**11.08%**
Visual disturbance	0.60%	0.68%	NR	Insufficient data	**7.50%**
Myalgia	0.97%	3.15%	Insufficient data	Insufficient data	Insufficient data
Dizziness	1.29%	NR	NR	Insufficient data	**6.78%**
SILDENAFIL	**Gen Pop**	**Diabetes**	**BPH/LUTS**	**Post-RP**	**Post-RT**
Dyspepsia	4.81%	7.57%	4.20%	**10.00%**	**21.14%**
Headache	11.15%	13.48%	7.53%	**16.55%**	**17.11%**
Flushing	10.45%	12.53%	3.54%	**16.24%**	**12.43%**
Nasal congestion	3.80%	3.77%	4.00%	**6.93%**	**9.48%**
Visual disturbance	3.59%	2.90%	NR	**5.67%**	**10.09%**
Myalgia	2.11%	Insufficient data	NR	NR	Insufficient data
Dizziness	2.68%	Insufficient data	Insufficient data	**8.63%**	**7.29%**
TADALAFIL	**Gen Pop**	**Diabetes**	**BPH/LUTS**	**Post-RP**	**Post-RT**
Dyspepsia	5.57%	7.94%	2.32%	4.11%	**16.95%**
Headache	8.89%	9.18%	3.07%	7.65%	**17.30%**
Flushing	3.55%	2.78%	1.85%	**9.56%**	**11.38%**
Nasal congestion	3.27%	2.28%	NR	Insufficient data	2.68%
Visual disturbance	0.64%	Insufficient data	NR	NR	NR
Myalgia	3.36%	3.27%	2.15%	4.66%	NR
Dizziness	2.28%	Insufficient data	Insufficient data	NR	Insufficient data
VARDENAFIL	**Gen Pop**	**Diabetes**	**BPH/LUTS**	**Post-RP**	**Post-RT**
Dyspepsia	3.38%	NR	no studies	4.14%	no studies
Headache	10.80%	7.41%	no studies	**15.29%**	no studies
Flushing	8.98%	8.69%	no studies	10.80%	no studies
Nasal congestion	5.52%	5.00%	no studies	19.00%	no studies
Visual disturbance	1.55%	NR	no studies	NR	no studies
Myalgia	0.55%	NR	no studies	NR	no studies
Dizziness	1.56%	NR	no studies	NR	no studies

Appendix B2 -- Guideline Statement 16: Intracavernosal injection (ICI) data

Commonly reported adverse events in extracted ICI studies:

Commonly Reported Adverse Events for ICI Medications					
Treatment		**# study arms**	**Min**	**Max**	**Mean**
ICI papaverine	Pain_with_injection	3	20.00%	71.00%	40.33%
	Injection_site_hematoma_or_inflammation	4	17.40%	27.40%	23.87%
	Penile_fibrosis_nodule_plaque	7	.00%	17.40%	9.88%
	Prolonged_painful_erection_percent	5	.00%	8.70%	4.92%
	Priapism_percent	5	.00%	15.20%	7.14%
ICI alprostadil	Pain_with_injection	22	.23%	73.00%	25.39%
	Pain_with_erection	5	1.10%	74.50%	24.32%
	Injection_site_hematoma_or_inflammation	17	.00%	36.00%	10.17%
	Penile_pain	4	4.60%	28.50%	12.77%
	Penile_fibrosis_nodule_plaque	24	.00%	23.30%	4.92%
	Penile_deviation_deformity	3	1.00%	9.30%	4.10%
	Prolonged_painful_erection_percent	15	.00%	43.00%	6.31%
	Priapism_percent	20	.00%	10.40%	1.78%
	Genital_pain_percent	3	.35%	47.00%	27.05%
	Local_bleeding_percent	4	1.00%	15.00%	6.97%
ICI papaverine + phentolamine	Pain_with_injection	6	.00%	78.00%	14.43%
	Injection_site_hematoma_or_inflammation	9	1.40%	38.30%	14.46%
	Penile_pain	5	1.80%	48.00%	14.06%
	Penile_bruising	7	5.00%	47.00%	22.14%
	Penile_fibrosis_nodule_plaque	15	.00%	57.00%	13.02%
	Penile_deviation_deformity	5	.00%	10.00%	3.72%
	Prolonged_painful_erection_percent	7	1.80%	16.70%	8.90%
	Priapism_percent	15	.00%	13.90%	5.50%
ICI papaverine + phentolamine + alprostadil	Pain_with_injection	4	.00%	3.50%	2.02%
	Injection_site_hematoma_or_inflammation	3	3.70%	20.70%	14.83%
	Penile_fibrosis_nodule_plaque	6	.00%	8.30%	4.53%
	Prolonged_painful_erection_percent	2	1.90%	3.70%	2.80%
	Priapism_percent	5	.50%	5.70%	3.15%
ICI papaverine + phentolamine + alprostadil + atropine	Pain_with_injection	3	.00%	.00%	.00%
	Injection_site_hematoma_or_inflammation	3	19.30%	31.10%	26.03%
	Penile_fibrosis_nodule_plaque	3	3.70%	9.60%	6.26%
	Priapism_percent	2	.00%	9.60%	4.80%

Appendix B3 -- Guideline Statement 18: Penile prosthesis data

Patient and partner satisfaction data:

Patient Satisfaction Rates with Prosthesis Surgery					
Prosthesis Type	**Prosthesis Subtype**	**# study arms**	**Minimum**	**Maximum**	**Mean**
Inflatable	AMS 700 Series	20	65.00%	97.30%	86.62%
	Coloplast Titan	4	70.00%	97.60%	85.65%
	Other models or multiple models or unspecified models	13	77.80%	96.40%	88.28%
Malleable	AMS Spectra malleable	2	72.20%	96.20%	84.20%
	AMS 600-650 series malleable	5	34.78%	82.50%	66.06%
	Other models or unspecified models	2	87.00%	90.40%	88.70%

Partner Satisfaction Rates with Prosthesis Surgery					
Prosthesis Type	**Prosthesis Subtype**	**# study arms**	**Minimum**	**Maximum**	**Mean**
Inflatable	AMS 700 Series	8	69.80%	96.00%	83.34%
	Other or Multiple or Unspecified Inflatable	7	76.00%	98.00%	88.24%
Malleable	AMS Spectra malleable	2	84.60%	94.30%	89.45%
	AMS 600-650 series malleable	2	57.00%	75.00%	66.00%

Appendix B4 -- Guideline Statement 21: Penile arterial reconstruction data

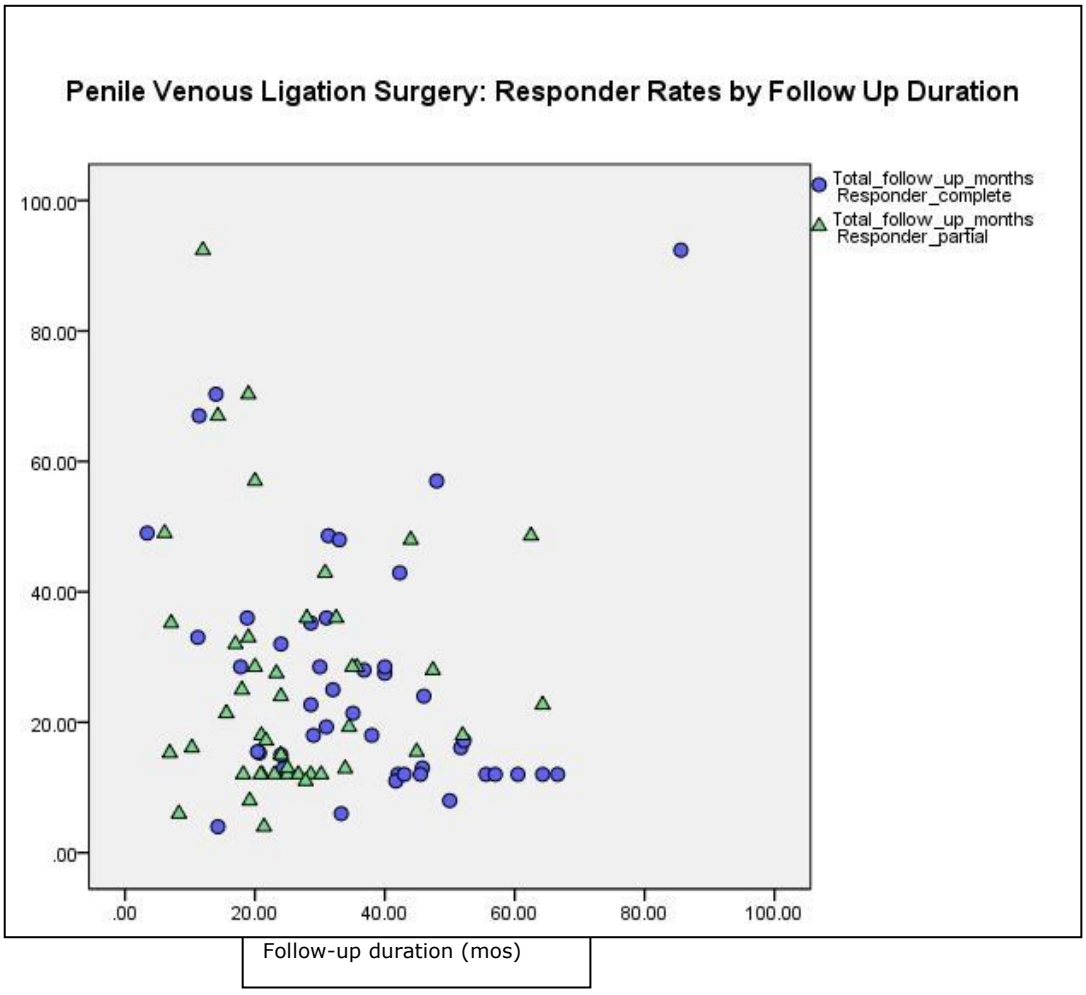
Complete, partial, and non-response rates to surgery. Below are those data; for studies that reported response rates at different durations post-surgery, the latest duration was used.

Arterial Reconstruction Studies: Responder Rates by Category				
Responder Category	**# study arms**	**Mean**	**Minimum**	**Maximum**
Responder_complete	32	49.69%	12.00%	81.60%
Responder_partial	25	26.72%	7.70%	53.30%
Nonresponder	28	26.83%	5.30%	59.10%

Appendix B5 -- Guideline Statement 22: Penile venous surgery data

Complete, partial, and non-response rates to surgery:

The pattern of declining positive response rates over time can be seen in the scatterplot below which plots complete and partial responder rates by follow-up duration. The exception to this trend is Hsu, Chen (2010) who reported that 85.6% of 167 Taiwanese men at 92.4 mos of follow-up were complete responders to venous ligation surgery[926]. These men had no comorbidities at the time of surgery. The procedure involved stripping and ligation of the deep dorsal, emissary, and cavernosal veins as well as ligation of the para-arterial veins; some men also had ligation of the crural veins.



Overall, there was considerable variability regarding response rates. Below are those data; for studies that reported response rates at different durations post-surgery, the latest duration was used.

Venous Ligation Studies: Responder Rates by Category				
Responder Category	**# study arms**	**Mean**	**Minimum**	**Maximum**
Responder_complete	59	38.83%	3.40%	85.60%
Responder_partial	46	25.73%	6.10%	64.30%
Nonresponder	55	41.07%	2.40%	90.50%

ABREVIATIONS

AE	Adverse events
AMSTAR	A measurement tool for the assessment of systematic reviews
AUA	American Urological Association
BPH	Benign prostatic hyperplasia
BMI	Body mass index
cGMP	Cyclic guanasine monophosphate
CVD	Cardiovascular disease
CCT	Controlled clinical trial
DRE	Digital rectal examination
DUS	Penile duplex ultrasound
EDV	End diastolic velocity
EPL	Erect penile length
ED	Erectile dysfunction
EDITS	Erectile dysfunction inventory of treatment satisfaction
EF	Erectile function
EHS	Erection hardness score
ESWT	Extracorporeal shock wave therapy
IRB	Institutional review board
IIEF	International index of erectile function
ICI	Intracavernosal injections
IU	Intraurethral
LUTS	Lower urinary tract symptoms
NAION	Nonarteritic anterior ischemic optic neuropathy
PSV	Peak systolic velocity
PD	Peyronie's disease
PED5i	Phosphodiesterase type 5 inhibitor
PRP	Platelet-rich plasma
PE	Premature ejaculation
QoL	Quality of life
RP	Radical prostatectomy
RT	Radiotherapy
RCT	Randomized controlled trial
RR	Relative risk
SIPA	Selective internal pudendal angiography
SEP	Sexual encounter profile
SHIM	Sexual health inventory for men
SEAR	Self-esteem and relationship questionnaire
SDM	Shared decision making
TD	Testosterone deficiency
VED	Vacuum erection device

Erectile Dysfunction Panel, Consultants, and Staff

Arthur L. Burnett, MD (Co-Chair)
The Johns Hopkins Hospital
Baltimore, MD

Ajay Nehra, MD (Co-Chair)
Massachusetts General Hospital
Boston, MA

Daniel J. Culkin, MD
University of Oklahoma
Oklahoma City, OK,

Lawrence Scott Hakim, MD
Cleveland Clinic
Weston, FL

Joel Heidelbaugh, M.D.
Univserity of Michigan
Ann Arbor, MI

Mohit Khera, MD
Baylor College of Medicine Medical Center
Houston, Texas

Kevin T. McVary, MD
Southern Illinois University
Springfield, IL

Martin M. Miner, MD
Men's Health Center; The Miriam Hospital
Providence, RI

Christian J. Nelson, PhD
Memorial Sloan Kettering Cancer Center
New York, NY

Hossein Sadeghi-Nejad, MD
Rutgers New Jersey Medical School
Hackensack, NJ

Allen D. Seftel, MD
Cooper University Hospital
Camden, NJ

Rodney Henry Breau, MD
Ottawa Hospital Research Institute
Ottawa, ON

Alan William Shindel, MD
University of California, San Francisco
San Francisco, CA

Patient Representative
Nick Condon

Consultant
Martha M. Faraday, PhD

Staff

Heddy Hubbard, Ph.D., MPH, RN, FAAN
Abid Khan, MHS, MPP
Erin Kirkby, MS
Nenellia Khachatourian Bronson, MA
Leila L. Rahimi, MHS
Brooke Bixler, MPH
Shalini Selvarajah, MD, MPH

Conflict of Interest Disclosures

Consultant or Advisor: Arthur Burnett: Auxilium, American Medical Systems, Coloplast, Pfizer, Astellas, Lilly, Genomic Health; **Mohit Khera**: Abbvie, Boston Scientific, ATYU Pharmaceuticals, Coloplast, Endo Pharmaceuticals; **Kevin McVary**: NeoTract, NxThera, Boston Scientific

Health Publishing: Arthur Burnett: VIVUS, Practical Reviews in Urology, European Urology, Urology Times, Journal of Sexual Medicine, Andrology, International Urology and Nephrology; **Mohit Khera**: Journal of Sexual Medicine; Hossein Sadeghi-Nejad: Journal of Sexual Medicine; **Alan Shindel:** Endotext.com

Investment Interest: Alan Shindel: Genomic Health

Leadership Position: Arthur Burnett: Reflexonic, The Center for Intimacy After Cancer Therapy; **Mohit Khera:** Sexual Medicine Society of North America; **Martin Miner:** American Society of Men's Health; **Christian Nelson:** Association of Peyronie's Disease Advocates; **Hossein Sadeghi-Nejad:** Sexual Medicine Society of North America; **Allen Seftel:** Journal of Urology, American Geriatrics Society, Mid-Atlantic Section of AUA, International Journal of Impotence Research; **Ajay Nehra:** International Society of Men's Health

Meeting Participant/Lecturer: Lawrence Hakim: ENDO Urology, Slate/Auxilium

Owner, Product Development: Allen Seftel: Patient Pocket, LLC

Scientific Study or Trial: Arthur Burnett: Medispec, Endo Pharmaceuticals, Acorda Therapeutics, National Institutes of Health; **Kevin McVary:** Astellas, NIDDK, Sophris; **Martin Miner:** Ichelxix; **Christian Nelson:** National Institutes of Health; **Allen Seftel:** Ixchelsis, Progenics

PEER REVIEWERS

We are grateful to the persons listed below who contributed to the Guideline by providing comments during the peer review process. Their reviews do not necessarily imply endorsement of the Guideline.

Peter C. Albertsen
Stanley Altof
Nelson Bennett
Pat Fulgham
David Ginsberg
James Eastham
Wellington Epaminondas
Jordan Dimitrakoff
Jason Hedges
Wayne Hellstrom
Tobias Kohler
Eric Labrode
Ronald Lewis
Mark Lindgren
Tom F. Lue
Brett Mellinger
Drogo Montague
Abraham Morgentaler
Ronald Morton
John Mulcahy
John P. Mulhall
Michael A. Perelman, Ph.D
Migeul Pineda, MD
Thomas Polascik
Jacob Rajfer
Roger E. Schultz
Ira Sharlip
Kirill Shiranov
Puneet Sindhwani
Thomas F. Stringer
Brantley Thrasher
Mark Traffas
Landon Trost
Darius Unwala
Run Wang
Steve Wilson
Stuart Wolf

DISCLAIMER

This document was written by the Erectile Dysfunction Guideline Panel of the American Urological Association Education and Research, Inc., which was created in 2016. The Practice Guidelines Committee (PGC) of the AUA selected the committee chair. Panel members were selected by the chair. Membership of the Panel included specialists in urology, family medicine, and psychology with specific expertise on this disorder. The mission of the Panel was to develop recommendations that are analysis-based or consensus-based, depending on Panel processes and available data, for optimal clinical practices in the treatment of muscle-invasive bladder cancer.

Funding of the Panel was provided by the AUA. Panel members received no remuneration for their work. Each member of the Panel provides an ongoing conflict of interest disclosure to the AUA.

While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases.

Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses (‘off label‘) that are not approved by the Food and Drug Administration (FDA), or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not in-tended to provide legal advice about use and misuse of these substances.

Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices.

For this reason, the AUA does not regard technologies or management which are too new to be addressed by this guideline as necessarily experimental or investigational.