# Canadian Urological Association guideline: Erectile dysfunction

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**Cite as:** Domes T, Najafabadi BT, Roberts M, et al. Canadian Urological Association guideline: Erectile dysfunction. *Can Urol Assoc J* 2021 August 17; Epub ahead of print. http://dx.doi.org/10.5489/cuaj.7572

Published online August 17, 2021

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## Abstract

Erectile dysfunction (ED) impacts the wellness and quality of life of millions of Canadians. An evaluation focused on the identification of reversible and irreversible underlying factors is recommended for patients presenting with ED. Through a shared decision-making model framework, the goal of ED treatment is to improve functional outcomes and enhance sexual satisfaction while minimizing adverse effects associated with treatment. Given that ED is assessed and treated by multiple different types of health practitioners, the purpose of this guideline is to provide the best available evidence to facilitate care delivery through a Canadian lens. After a narrative review of ED assessment and treatment for general

readership, five key clinical questions relating to priority areas of ED are assessed using the GRADE and Evidence to Decision making frameworks.

## Introduction

Erectile dysfunction (ED) is the inability to achieve or maintain an erection sufficient for satisfactory sexual performance. Penile erection requires a complex integration between vascular, neural and endocrine systems leading to adequate arterial dilatation, trabecular smooth muscle relaxation, and activation of the corporal veno-occlusive mechanism[1].

ED is highly prevalent, with both the Canadian Study of Erectile Dysfunction[2] and the Massachusetts Male Aging Study (MMAS)[3] reporting high rates of men experiencing ED with a higher prevalence and severity associated with aging. For example, in the MMAS approximately 40% of men in their 40's experienced ED of varying degrees of severity and the prevalence of ED increases about 10% per decade. Additionally, as a man ages, the proportion of men with a higher severity of ED increases. In the MMAS, the prevalence of severe ED tripled from 5% in men in their 40's to 15% in men in their 70's.

ED can be categorized as organic, psychogenic or mixed based on the patient's history and examination findings. Organic ED is typically classified by its underlying pathophysiological mechanism(s) which include vasculogenic (most common), neurogenic, structural, and hormonal causes.[1] Psychogenic ED can be generalized or situational and may be related to a history of psychosocial stress, performance anxiety and mental illness[4].

There are many modifiable and non-modifiable risk factors associated with primarily vasculogenic ED including advancing age, diabetes mellitus, dyslipidemia, hypertension, obesity, metabolic syndrome, sedentary lifestyle, and smoking.[5-7] There is a large body of evidence suggesting that ED and cardiovascular and cerebrovascular diseases share the same risk factor profile and that ED may serve as an early warning sign for the future development of vascular events in some populations[5, 8]. In spite of this established link, some studies have demonstrated that ED is not an independent risk predictor of future vascular events and that established risk predictors, such as the Framingham risk score, are superior[9, 10]. Therefore, it remains controversial whether a diagnosis of ED alone should initiate a more thorough cardiovascular evaluation. Patient factors such as age, ED severity and duration and the presence of other cardiovascular risk factors should guide clinicians when deciding if further investigations or optimization of cardiovascular health is required, in collaboration with other health care providers. [5, 8, 11-13].

ED is common after trauma (pelvic trauma and penile fracture), surgery (pelvic, penile and urethral) and radiation therapy[14-18]. Specifically, the Prostate Cancer Outcome Study[19] reported 78.8% of post-prostatectomy patients not having erections firm enough for intercourse two years after surgery compared to 60.8% of men having ED two years following

prostate radiotherapy. After 15 years from the time of treatment, the prevalence of ED increases further to 87% post-prostatectomy and 94% post-radiiotherapy.[19] ED is also frequently associated with other urological conditions such as lower urinary tract symptoms/benign prostatic hyperplasia [20] and chronic prostatitis/chronic pelvic pain syndrome[21].

The impacts of ED go beyond the physical loss of function and the inability of having sexual intercourse. ED has a significant impact on the psychosocial health, wellbeing and quality life for both the patient and their partner[22, 23] and can negatively impact relationships[24]. It is critical for the clinician to be aware of these potential negative effects on the couple. Including the partner during ED assessment and treatment has been shown to improve patient outcomes[25, 26].

## Methods

A guideline panel of 10 members including male sexual health, urology, and guideline methodology experts was established. The goal of the panel was to address relevant and priority issues and questions surrounding current ED practice and to produce an impactful document for learners and practitioners.

The guideline panel met and generated a broad list of topics and clinical questions relating to ED. In addition, each panel member selected and surveyed two community urologists practicing in their region in order to generate a second list of clinical questions that were felt to be relevant to the practice of a general urologist. Thirty questions were compiled and the panel selected the five most important questions through individual ratings based on perceived topic priority, identified practice variation and expected feasibility of answering the question (Appendix). These 5 questions were addressed systematically using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and the Evidence to Decision (EtD) framework[27, 28].

The GRADE approach enabled the panel to appreciate the certainty in the evidence for each outcome, and overall, as very low, low, moderate, or high[29, 30]. The EtD framework assisted the panel in making clinical recommendations by considering desirable effects, undesirable effects, balance of the effects (net benefit), certainty in estimates of effect, patients' values and preferences, resources required, cost-effectiveness, equity, feasibility, and acceptability[31]. Summary of Findings (SoF) and EtD framework tables using the GRADEpro GTD application[32, 33] are available in the Appendix.

The panel chose improvements in erectile function (measured by the International Index of Erectile Function (IIEF)-EF score[34]) and quality of life as critical outcomes, and adverse events as an important outcome, to be collected during the literature review. The panel used the generally accepted minimal clinically important difference (MCID) of 4 in the IIEF-EF score as a significant improvement in erectile function, however the panel recognizes

the limitation that the MCID varies based on the baseline severity of ED (mild: 2; moderate: 5; severe: 7). [35].

Effect estimates were derived from studies contained in existing systematic reviews that addressed the five chosen clinical questions and by reproducing some of the review stages to ensure the most accurate effect estimates were calculated. These review steps included appraisal of the reviews, review of additional literature to locate any missing major trials, determining the risk of bias in the included studies, and performing the meta-analyses again.

Interpreting recommendations in the GRADE framework emphasizes the role of shared decision-making and patient values and preferences. In this framework, recommendations can be for or against and strong or conditional. A strong recommendation indicates that the panel believes that a significant majority of patients would choose the recommended course of action when aware of the available evidence. A conditional recommendation implies that the panel believes that most patients would want the recommended course of action, however a substantial proportion would not. For clinicians, this means that when a weak recommendation is made the "best" course of action will rely on elucidating patient values and preferences in a shared decision-making process.

## Background and narrative overview of ED

### *Patient assessment*

The cornerstone of the assessment of patients with ED is a detailed history and physical exam. Screening laboratory testing to rule out associated conditions should be considered for patients presenting with ED, depending on the clinical context. Specialized tests, including imaging, are of limited value and are not recommended except in special circumstances.

#### *History*

A detailed history should include medical and psychological co-morbidities, medications, substance use history (tobacco, alcohol, drugs), surgical and pelvic radiation history, a history of pelvic trauma, and previous treatments for sexual dysfunction. A detailed psychosocial and sexual history is key to a comprehensive assessment. While the underlying cause of ED is often multifactorial, key questions related to psychosocial factors and sexual history can point towards psychogenic and situational factors contributing to sexual dysfunction (Table 1). It has been hypothesized that excessive pornography use may contribute to sexual dysfunction during partnered sex[36], especially in younger patients with ED. However, this association is not clearly demonstrated in the empirical literature and requires further study[37, 38]. Comorbid sexual conditions such as premature ejaculation (PE), anorgasmia, low libido, and Peyronie's Disease (PD) should be identified in the initial assessment of any patients with ED, as the presence of these comorbid conditions will impact further assessment and management of ED.

*Assessment tools*
Validated questionnaires and assessment tools (Table 2) can be useful in the initial diagnosis and follow-up of ED patients, especially when evaluating a patient's response to treatment. While these assessment tools do not replace a detailed history and physical exam, they are cost-effective and non-threatening for patients to complete[39], however these tools have varying degrees of utility in clinical practice. These assessment tools were originally validated in the heterosexual population, however the IIEF has also been shown to be efficacious in the men who have sex with men (MSM) population.[40]

*Physical examination*
Physical examination is a helpful adjunct to assess a patient's overall body habitus, level of virilization and genital anatomy to identify any comorbid medical and/or sexual conditions[41]. Table 3 summarizes the key features of the physical examination for patients with ED.

*Laboratory testing*
In patients with either suspected vasculogenic or idiopathic ED, a baseline hemoglobin A1C, fasting glucose and lipid profile should be considered to rule out occult diabetes and dyslipidemia. Patients with symptoms associated with testosterone deficiency or failure of phosphodiesterase type-5 inhibitors (PDE5is) should consider having a morning serum total testosterone level drawn[41].

*Specialized testing*
Specialized testing, including nocturnal penile tumescence (NPT) and penile duplex ultrasound (PDU), is rarely required in the routine assessment of patients with ED. These tests can be used to differentiate between organic and non-organic causes of ED when the patient's history is conflicting and in medico-legal cases. NPT estimates nocturnal penile rigidity[42] and PDU measures arterial inflow (to assess arterial insufficiency) and venous outflow (to assess for venous leak) after the injection of a vasoactive substance[43]. Both tests provide little practical information beyond what can be obtained from a detailed history and should only be obtained in limited situations by sub-specialists in sexual medicine.

## Treatment options

### *Overview*
In Canada, primary care providers (PCPs) appropriately identify, investigate and initiate first-line treatments in the vast majority of patients with ED. In the contemporary model of ED care patients may be referred to urologists after failure of first-line therapy as second-line therapies may be outside the practice pattern of PCPs[44]. A patient-centred, shared decision-making model is advocated when discussing treatment options with the patient and their

partner. Management of ED typically follows a stepwise progression from conservative measures to first-line phosphodiesterase type-5 inhibitors (PDE5is) through to second- and third-line treatment options, however specific patient factors and expectations may influence treatment decisions and the usual stepwise progression of treatment options (Fig 1).

*Conservative treatment options*

Conservative measures should be offered and continuously addressed with all patients with ED, especially if comorbidities or lifestyle habits are negatively impacting erectile function[45]. These measures include exercise/physical activity[46], smoking cessation[47], reducing alcohol[47] and cannabis consumption[48], and dietary changes. Additionally, the nitric oxide synthase substrates L-arginine and citrulline have been evaluated in limited studies[49-51], but further confirmatory work is required prior to recommending their use in ED at this time.

Clinicians should consider early referral for sexual counselling for patients experiencing ED, especially when there is concern for a psychogenic component[4, 52, 53]. Sexual counselling may be a helpful adjunct to medical management and may improve relationship satisfaction and overall sexual functioning[54].

*Low-intensity shock wave therapy (Li-SWT)*

Low intensity shock wave therapy (Li-SWT) is a treatment option proposed for patients with mild to moderate ED. Li-SWT is administered with a wand-like device delivering low intensity shockwaves to different areas of the penis in multiple sessions. Li-SWT is hypothesized to work by inducing angiogenesis through growth factor activation[55] and inducing nerve regeneration[56], thereby reversing pathophysiological processes to improve erectile function. Although widely offered in numerous centres in Canada, often by non-urologists, Li-SWT is not Health Canada or FDA approved for clinical use for ED. The clinical use of Li-SWT for ED is addressed in the key clinical recommendation section of this guideline.

*Phosphodiesterase type-5 inhibitors (PDE5is)*

Phosphodiesterase type-5 inhibitors (PDE5is) are a class of oral agents that facilitate a penile erection by promoting vascular and cavernosal smooth muscle relaxation in response to sexual stimulation[57]. The PDE5is approved by Health Canada include sildenafil, tadalafil and vardenafil. Each medication has unique pharmacokinetic and pharmacodynamic properties[58] (see Table 1). Patients initiating PDE5is should be counselled regarding potential side effects including headache, flushing, dyspepsia, and nasal stuffiness which are universal in all three drugs with alterations in colour vision (sildenafil and vardenafil) and myalgias (tadalafil) being more drug-specific[58, 59]. Absolute contraindications to PDE5is include intermittent or regular use of nitroglycerin or organic nitrates and hypersensitivity to any component of the

tablet[58]. Patients with an unsatisfactory response to PDE5is should first be counselled regarding proper use of the medication and may require a potential dose adjustment[60].

The panel strongly recommends PDE5is as the first line pharmacological treatment for ED given their impressive clinical efficacy and safety profile in a wide range of patients. A comprehensive systematic review by Yuan and colleagues[61] reports a clinically significant mean improvement in the IIEF-EF score of 6.03 (95% CI: 5.38, 6.68) for sildenafil (12 RCTs, 3404 patients), 8.07 (95% CI: 7.18, 8.96) for tadalafil (8 RCTs, 1877 patients) and 7.05 (95% CI: 5.60, 8.50) for vardenafil (6 RCTs, 1151 patients). These drugs also have a strong safety profile, with the effect estimate for relative risk of serious adverse events being 1.38 (95% CI: 0.67, 2.83) for sildenafil (10 RCTs, 2431 patients), 1.46 (95% CI: 0.63, 3.37) for tadalafil (8 RCTs, 1967 patients) and 1.49 (95% CI: 0.79, 2.83) for vardenafil (10 RCTs, 3628 patients) compared to placebo. Conceptualized another way with considering baseline risks in the included studies, out of 1000 patients taking the drug on average 8 will experience a serious adverse event with sildenafil, 7 with tadalafil and 8 with vardenafil.

*Intraurethral alprostadil*

Intraurethral alprostadil, known as MUSE™ (Medicated Urethral System for Erection), is a second line option for men with ED. It is effective for select patients, but has failed to gain a significant market share due suboptimal efficacy and urethral discomfort[62]. Dose titration with an 'in office' trial is advised to improve success[63]. Since it does not require an injection, some patients prefer it over intracavernosal injection (ICI)[64].

*Vacuum erection pump device (VED)*

Vacuum erection pump devices (VED) consist of a cylindrical chamber placed over the penis coupled with a manual or mechanical pump to generate a vacuum. The negative pressure generated promotes blood flow into the penis which is trapped by a constriction ring placed at the base of the penis and can be maintained safely for up to 30 minutes[65]. Given the mechanics involved, VED is considered a more cumbersome and labour-intensive way to achieve an erection. However, 90% of patients will achieve a functional erection with adequate instruction and practice[66]. VED can be associated with penile numbness, pain, bruising, and painful ejaculation. VED has no absolute contraindications making it a reasonable option for those who cannot tolerate or have contraindications to other medical or surgical options.

*Intracavernosal injection (ICI)*

Intracavernosal injection (ICI) was the first pharmacologic treatment available for ED and involves the delivery of vasoactive agents directly into the corpus cavernosum prior to intercourse. Single agent alprostadil has been shown to be highly effective and generally well tolerated, with up to 94% of patients being able to achieve an erection sufficient for

intercourse[67]. Side effects include pain at the injection site, penile bruising, penile pain, penile scarring/curvature and priapism. Although not approved by Health Canada, the addition of papaverine and phentolamine to alprostadil, often referred to as "Trimix", has been shown to be even more efficacious than alprostadil monotherapy while maintaining an acceptable side effect profile and less penile pain[68]. Prior to prescribing ICI, patients or their partners need to have the manual dexterity to prepare and perform the injection and a teaching session is advised to ensure proper injection technique and dose titration[69].

*Penile prosthesis*

While not all nonsurgical options need to be attempted prior to considering placement of a penile prosthesis, all nonsurgical options should at least be discussed with the patient prior to considering surgical intervention. There are two types of prosthesis, malleable and inflatable, and both are surgically implanted into the corporal bodies to allow the patient to regain penile rigidity. The presence of clinically significant penile curvature, which may only be evident during activation of the device, should be discussed preoperatively and surgically corrected at the time of device implantation. Satisfaction rates are high for both implant naïve patients and those undergoing surgical revision of an existing device[70]. Patients considering a penile prosthesis need to be aware that postoperative penile length can be negatively affected by corporal fibrosis or previous prostatectomy and the glans will remain flaccid post implant[71]. Mechanical failure does occur with inflatable devices over time, but almost 50% will still be functional after 20 years of use[72]. Rare but serious late complications include infection or erosion of the device, which in certain cases can lead to refractory and permanent ED.

## Clinical recommendations using GRADE

### *Summary of recommendations*

### 1. Among patients with erectile dysfunction, should daily tadalafil be preferentially prescribed instead of on-demand tadalafil?

Based on the available evidence, the panel ***conditionally recommends against*** preferentially prescribing daily tadalafil instead of on-demand tadalafil for patients presenting with erectile dysfunction. However, certain patient-centered factors may influence what dosing regimen the patient ultimately decides to pursue.

The panel reviewed eight RCTs[73-80] comparing improvement in erectile function between on-demand tadalafil (n=749) and daily tadalafil (n=749) over a follow-up period of 8 to 12 weeks. The meta-analysis demonstrates a mean increase in the IIEF-EF score of 0.8 (95% CI: -0.32, 1.93), favouring daily tadalafil, with a moderate certainty of evidence. This small difference is not clinically significant. Additionally, pooled analyses of 17 on-demand

and 4 daily tadalafil placebo-controlled trials demonstrated both treatment regimens are similarly efficacious across a broad spectrum of clinical subgroups[81]. Based on RCT data, there is virtually no meaningful difference in side effects or discontinuation rates between either dosing regimen.

*Patient-centred factors influencing daily dosing preference*
Although treatment efficacy and side effect profiles are very similar between on-demand and daily tadalafil, certain patient-centered factors need to be considered when a decision on dosing frequency is made with the patient. Numerous studies have shown that daily tadalafil increases sexual spontaneity, improves sexual self-confidence and there is less of a concern regarding timing of medication and the associated anticipatory anxiety that can be experienced in some patients taking on-demand tadalafil[76, 79, 82]. A study by Conaglen and colleagues found that female partners preferred daily dosing compared to on-demand regimens[83]. In patients experiencing co-morbid lower urinary tract symptoms, daily tadalafil (5 mg) is an approved treatment option and has been shown to decrease symptom scores significantly more than on-demand dosing[78]. Additionally, daily tadalafil may be more cost-effective than on-demand dosing, depending on the frequency of use and whether a low (2.5 mg) or high (5 mg) daily dose regimen is required to achieve an adequate erection.

**2. Among patients with erectile dysfunction, should low-intensity shockwave therapy (Li-SWT) be recommended over no treatment?**

Based on the available evidence, the panel ***conditionally recommends against*** low-intensity shockwave treatment (Li-SWT) as a treatment for patients with ED at this time.

The panel reviewed seven RCTs[84-90] comparing improvement in erectile function between patients treated with Li-SWT (n=293) or a sham treatment (n=202). The studies had different treatment protocols (shockwave machines, energy levels, duration of treatment and schedule of treatments), various sham treatments, inconsistent follow-up timing, short follow-up and varying metrics resulting in significant heterogeneity between the studies. Combining the results of all seven RCTs demonstrates a mean increase in the IIEF-EF score of 4.08 (95% CI: 1.57, 6.58) with a very low certainty of evidence, given that three trials[84, 86, 90] have a high risk of bias. If these three studies are removed, combining the results of the remaining four studies results in a mean increase in the IIEF-EF score of 2.07 (95% CI: 0.19, 3.96) with a moderate certainty of evidence. Given the quality of the evidence, the panel has more confidence in this latter result, indicating that Li-SWT is unlikely to have a noticeable clinical improvement in erectile function.

Fojecki and colleagues[88] collected quality of life data using the Sexual Quality of Life for Men (SQoL-M) tool[91] in their study of 118 patients. Given the cross-over design, the sham group had received five penile Li-SWT treatments compared to ten in the treatment arm at the 18-week mark when the SQoL-M was re-administered after baseline. The Li-SWT arm scored 2.1 points higher (95% CI: -7.9, 12.1) than the sham group with a very low certainty of the evidence, indicating no significant improvement in sexual quality of life between ten versus five Li-SWT treatments.

Li-SWT is believed to be a safe procedure with virtually no short-term adverse effects[92, 93] reported, but more research is required to assess the possibility of longer-term adverse effects.

*Concerns of introducing Li-SWT into the Canadian healthcare setting*

Given the trivial desirable effects on erectile function, the uncertainty regarding the evidence and long-term effects, and concerns regarding cost-effectiveness, equity and feasibility to deliver this treatment in the Canadian health care setting, the panel decided to conditionally recommend against Li-SWT for the treatment of ED at this time. Further adequately powered RCTs focusing on patient safety and more efforts to define the dose, type of machine and patient populations most likely to benefit is required. Additionally, establishing longer-term clinical efficacy using validated and standardized protocols need to be conducted before this modality should be offered for men with ED outside of a clinical trial.

**3. Among patients with erectile dysfunction and hypogonadism, should testosterone replacement be used as monotherapy compared to no treatment?**

Based on the available evidence, the panel ***conditionally recommends against*** using testosterone as monotherapy to improve erectile function in patients with hypogonadism.

Testosterone replacement is the mainstay of therapy for patients with a hypogonadal level of testosterone and symptoms consistent with testosterone deficiency syndrome (TDS), as outlined in other clinical guidelines[94]. Patients initiating testosterone therapy need to be informed of both the potential benefits and risks of treatment, including side effects and serious adverse events. Testosterone therapy improves overall sexual function and sexual quality of life in patients with TDS[95], however the panel wanted to address the specific question of whether testosterone therapy alone improved erectile function in patients with low testosterone levels.

The panel reviewed six RCTs[96-101] that randomized hypogonadal patients with erectile dysfunction to treatment with testosterone replacement (n=457) or placebo (n=459) and compared improvement in erectile function between these two arms. The follow-up period in these studies ranged from 3 to 12 months. The baseline testosterone level to be enrolled in the

studies differed (range < 8 to < 15 nmol/L) and there was some heterogeneity in the testosterone replacement regimens used, with four studies using testosterone gel at 50 mg/d[97, 98, 100, 101], one study using a testosterone patch at 50 mg/d[96] and one study using intramuscular (IM) testosterone undecanoate 1000 mg/12 weeks[99]. Additionally, these studies did not routinely report what the testosterone levels were at the end of the study. Despite the heterogeneity and methodological considerations, these six RCTs were chosen as they had the least risk of bias amongst other RCTs published on this topic. Our meta-analysis demonstrates a mean increase in IIEF-EF score of 2.65 (95% CI: 0.81, 4.48) with testosterone therapy compared to placebo with a moderate certainty in evidence, indicating testosterone therapy alone unlikely leads to a clinically significant improvement in erectile function in this patient population. These findings are similar to the meta-analysis conducted by Corona and colleagues, which included six studies only including participants with a baseline testosterone level below 8 nmol/L[95]. In this meta-analysis, the mean increase in IIEF-EF score is 2.95 (95% CI: 1.86, 4.03), which remains below the MCID.

*Dual PDE5i and testosterone therapy*

While current evidence does not support the use of testosterone as monotherapy for the treatment of erectile dysfunction in hypogonadal patients, there is some evidence to supports its use as a combination therapy to salvage patients who have failed PDE5is. Numerous non-controlled trials have shown promising results, especially in patients with lower testosterone levels. However, the degree of erectile function improvement is not as profound in controlled trials[102, 103]. Three RCTs[104-106] randomized 326 PDE5 inhibitor non-responders with low to low-normal testosterone levels to combination treatment with either testosterone or placebo over a follow-up period ranging from 4 to 16 weeks. The meta-analysis of these three trials demonstrated a mean increase in the IIEF-EF score of 1.68 (95% CI: 0.30, 3.07) favoring testosterone combination therapy with a low certainty of evidence. Given this uncertainty, sufficiently powered controlled trials with longer follow-up are required in order to definitely address this claim.

## 4. Among patients with erectile dysfunction, does increasing physical activity improve erectile function compared to usual activity?

Based on the available evidence, the panel ***conditionally recommends for*** patients to increase their physical activity to improve their erectile function.

The panel reviewed five RCTs[107-111] comparing improvement of erectile function between patients continuing their regular physical activity level (n=149) or an increased physical activity level (n=217) over a follow-up period ranging from 2 to 24 months. In addition to ED, participants in the RCTs also had obesity[107], ischemic heart disease[108],

hypertension[109] and metabolic syndrome[111]. Two studies treated both the intervention and control arms with PDE5-inhibitors as part of the study design[110, 111]. The exact prescribed physical activity and exercise routines differed amongst the trials, however the goal in each trial was to increase exercise tolerance through aerobic and/or resistance training. The meta-analysis demonstrates a mean increase in the IIEF-EF score of 3.77 (95% CI: 2.04, 5.50), favouring an increased physical activity level, with a low certainty of evidence. Although the improvement in IIEF-EF score is borderline for clinical significance, the safety, relatively low cost, wide accessibility and acceptability of physical activity in the general population influenced the panel to conditionally recommend an increase in physical activity in the ED population. There is a linear relationship between physical activity and overall health status and regular physical activity is a proven primary and secondary prevention strategy in numerous medical conditions, many of which are also associated with ED[112].

**5. Among patients with post-prostatectomy erectile dysfunction, should penile rehabilitation with scheduled PDE5 inhibitor be used over no intervention?**

Based on the available evidence, the panel ***conditionally recommends against*** penile rehabilitation with scheduled PDE5is following RP.

Sexual dysfunction is a significant survivorship concern impacting patients undergoing localized treatment for prostate cancer, with the vast majority of patients having some functional impact after treatment despite advancements in surgical technique. Recovery of erectile function is dependent on both treatment and patient-related factors, and a subset of patients will not experience recovery[19, 113]. Penile rehabilitation is the concept of using interventions to promote the natural recovery of erectile function after an insult to the erectile mechanism which occurs after radical prostatectomy (RP), external beam radiation therapy (EBRT), brachytherapy and other localized prostate cancer treatments. Although there is controversy surrounding the utility and ways to perform penile rehabilitation[114], the majority of studies focus on scheduled PDE5is for variable periods of time leading up to and following RP.

In the post-RP population, the panel reviewed 5 RCTs[80, 115-118] that randomized patients to placebo or no treatment (n=372) or to scheduled PDE5-is (n=385) and compared erectile function restoration rates. The follow-up period in these studies ranged from 24 to 48 weeks. Given methodological issues with these studies leading to a very low certainty of the evidence, the pooled effect estimate suggests that in every 1000 patients who receive penile rehabilitation with scheduled PDE5is, only 28 more patients (95% CI: 50 fewer, 138 more) experienced ED resolution compared to placebo, which is not statistically significant (RR 1.11 (95% CI: 0.80, 1.55)).

Sexual quality of life was assessed using the Expanded Prostate Cancer Index Composite (Sexual Domain) in Montorsi's scheduled tadalafil versus placebo RCT (n=280) and the results suggest little to no difference compared to placebo after the cessation of active therapy[80].

Serious adverse events and treatment discontinuation due to any cause (RR 0.98, 95% CI: 0.72, 1.34) did not significantly differ between scheduled PDE5-inhibitor and placebo in 2 RCTs (n=403) that addressed this[80, 118], albeit the certainty of evidence is very low.

*Penile rehabilitation post-radiotherapy*

There is insufficient evidence for the panel to make any recommendation for penile rehabilitation following treatment with EBRT and brachytherapy for prostate cancer. Radiation damage affects the erectile mechanism differently than surgical injury, with the pathophysiological factors leading to ED being more cumulative and delayed with radiation[119]. Despite this, proponents of penile rehabilitation believe scheduled PDE5is may limit the damage radiation causes in vascular and cavernous tissues. Scheduled PDE5is after EBRT have been shown to be efficacious in the short term after radiation therapy, with 3 RCTs[120-122] demonstrating a cumulative increase in IIEF-EF score of 6.10 (95% CI: 4.69, 7.52) compared to placebo after six weeks of treatment. These studies did not assess longer-term erectile function rates or the protective effect of PDE5is. A small trial of 27 patients compared daily sildenafil treatment taken for six months around the time of prostate brachytherapy (n=14) versus placebo (n=13) and this trial failed to show an improvement in erectile function at one and two years following treatment[123]. A larger RCT by Zelefsky and colleagues[124] had a similar trial design but included men with EBRT and brachytherapy, and although patients previously receiving the six months of scheduled sildenafil demonstrated higher median erectile function scores at 12 months following therapy (26 versus 21.5, p=0.018), the median IIEF-EF of both arms was identical at 25 at the two year mark. Although there is insufficient data to make a recommendation, limited evidence suggests that scheduled PDE5is taken around the time of radiation therapy (EBRT and/or brachytherapy) do not offer any long-term protective effects against future ED.

**Future directions requiring further study**

As technology evolves and a further understanding of the pathophysiological processes contributing to ED develops, we can expect that treatment options to improve erectile function will continue to advance. Regenerative therapies aim to restore the structure and function of the erectile tissue and offer a 'cure' to the disease process as opposed to merely a treating the symptom of ED[125]. Preclinical and early human studies have explored regenerative approaches for treating ED, such as stem cell therapy (SCT), platelet rich plasma

(PRP) and amniotic fluid matrices. However, these options are currently not approved for use outside of clinical trials and remain experimental[125, 126].

***Stem cell therapy (SCT)***

Stem cells function to release growth factors, cytokines, and chemokines in a paracrine fashion to promote wound healing and rebuild damaged tissues[127]. There have been several small phase I-III human trials evaluating SCT for treating ED, but there is significant variability between protocols, inadequate adverse event reporting, and a lack of long-term follow-up[128-131].

***Platelet-rich plasma (PRP)***

Platelet-rich plasma (PRP) is autologous blood plasma that contains supraphysiologic platelet concentrations[132] and numerous growth factors implicated in erection recovery[133]. Penile bruising is common after injection and the protocol for injections and growth factor activation is not well studied or universally accepted. Despite the global use of PRP to treat ED, there are a limited number of peer-reviewed human studies to support this experimental regenerative therapy[134].

***Amniotic fluid matrices***

Dehydrated human amnion/chorion membranes have been applied to cavernous nerves during RP as a source of implantable neurotrophic factors, growth factors, cytokines, proteases, and inhibitors of inflammatory and fibrotic pathways[125, 135]. Limited human studies have applied these grafts during robotic-assisted RP with promising clinical outcomes of expedited recovery in erectile function[136, 137]. The long-term efficacy, side effects and oncologic consequences of these grafts are unknown at this time and require future study.

**Limitations and unanswered questions**

This guideline primarily focused on patients with ED as a single presenting symptom. However, patients presenting with ED often have other concurrent elements of sexual dysfunction (low libido, orgasmic dysfunction, ejaculatory dysfunction), Peyronie's disease, testosterone deficiency, lower urinary tract symptoms/BPH, prostatitis/pelvic pain, psychological or psychiatric conditions, and other medical problems (neurologic, gastrointestinal) that influence both their erectile function directly, and more broadly quality of life as it relates to sexual function. Due to the complexity of the interactions between these factors and the lack of comprehensive studies assessing all of these factors together, the panel was not able to provide recommendations that address the impact that these factors have, individually or collectively, on ED therapy. Therefore, the recommendations in this guideline need to be contextualized based on the patient's history and presenting symptoms and conditions that may be influencing sexual function in its entirety.

Given the methodology of ED therapeutic trial design, the vast majority of studies referenced in this guideline compare an intervention to placebo and don't assess combination therapy. Synergistic effects of multiple treatments are not specifically addressed in this guideline, however may appropriate depending on the clinical scenario.

It is well known that the MCID in erectile function score depends on initial ED severity, with greater improvements in IIEF-EF score necessary for satisfactory results in patients with more severe ED[35]. Moreover, the underlying cause of ED may impact treatment response depending on its mechanism of action. Given the methodological challenges in data reporting, including the lack of power and routine reporting of underlying ED etiology, the vast majority of studies do not perform subgroup analyses based on either severity of ED or on the primary cause of ED.[17] This limitation significantly impacts the panel's ability to make recommendations for specific subgroups of patients with ED based on the current literature.

The panel identified several deficits in the body of literature focussing on ED assessment and treatment, including a lack of quality of life metrics, patient reported outcomes other than erectile function, assessment of partner satisfaction, and a lack of harms data (particularly for some treatments). This made it challenging for the panel to comment on some of the a priori outcomes that were felt to be important when a patient has to make an ED treatment decision. Hopefully future ED studies include these important measures in their design.

## Conclusions

These guidelines were developed using transparent and rigorous methods in order to provide the healthcare community with the most current data and recommendations regarding ED patient assessment and treatment through the Canadian lens. Special attention was taken to provide clarity on the most controversial aspects of ED treatment in Canada today.

Evaluating a patient with ED requires a sufficiently detailed yet focussed history and physical exam to establish an etiologic working diagnosis. Reversible factors contributing to ED should be identified and corrected, including positive lifestyle changes that optimize overall health. In patients requesting treatment, it is reasonable to begin with conservative and less invasive therapies and introduce additional therapeutic measures when necessary, through a shared decision-making process with the patient and their partner.

***Competing interests:*** *Dr. Flannigan has been an advisory board member for Acerus; has received honoraria for speaking and educating from Boston Scientific and Paladin Labs; and participated in a clinical trial on the injection of novel lidocaine polymer for chronic scrotal pain supported by Sustained Therapeutics. Dr. Patel has been an advisory board member for Aytu Biosciences; a consultant for Nestle Health and Boston Scientific; and gave a talk on men's health for Boston Scientific and Paladin. Dr. Krakowsky has been an advisory board member for Acerus, Felix, Paladin, Pfizer, Sprout, and Verity. No other author reports any competing personal or financial interests related to this work.*

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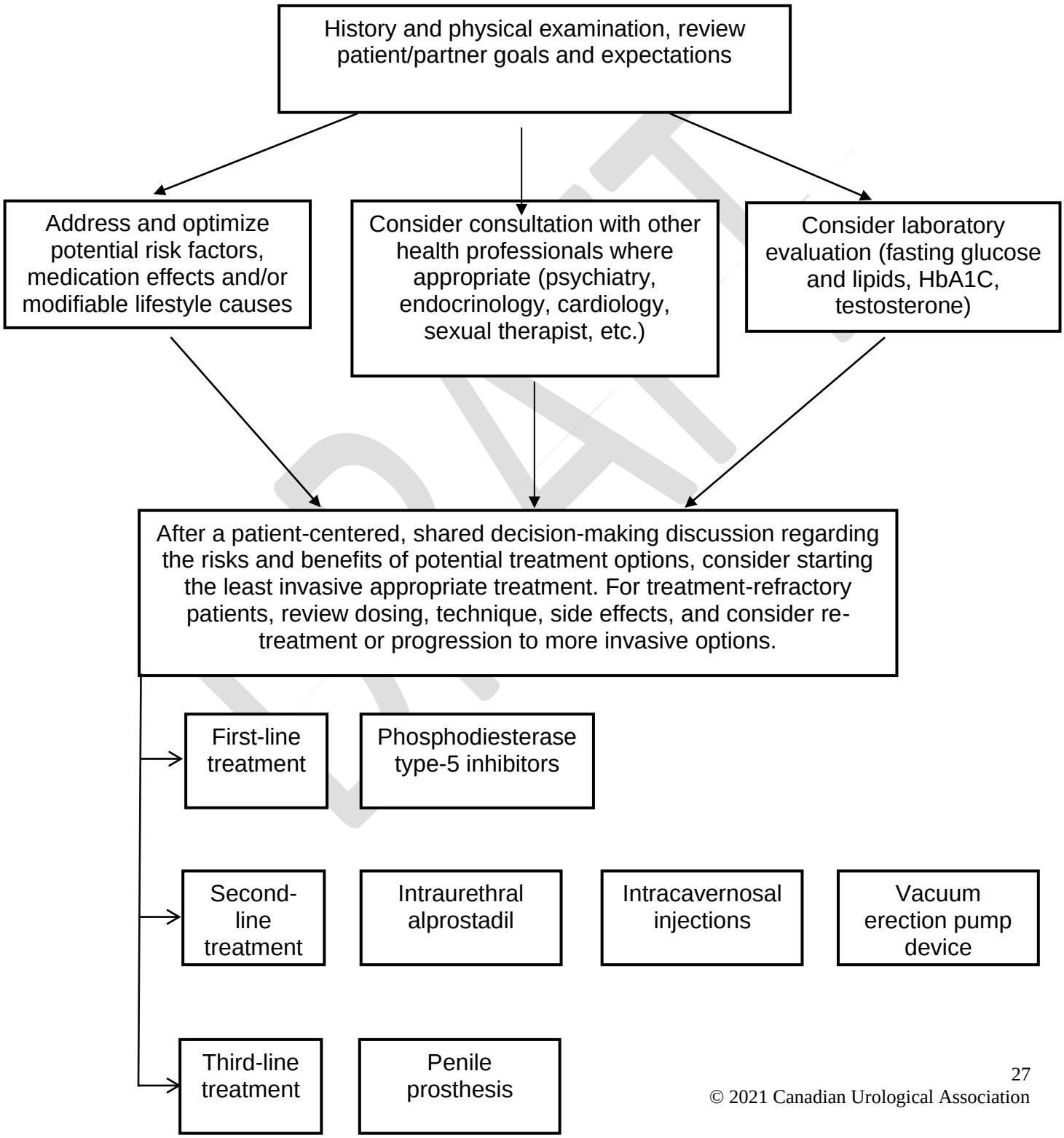
**Figures and Tables**

***Fig 1.*** Management summary of erectile dysfunction.



| Table 1. Questions that may help to differentiate psychogenic from organic erectile dysfunction | | |
|---|---|---|
| **Question** | **Psychogenic ED** | **Organic ED** |
| Presence of nocturnal erections? | Often present | Reduced |
| Presence of erection during masturbation or with alternate partners? | Often present | Reduced |
| Significant recent psychosocial stress? | Strong impact | Minimal impact |
| Feelings of performanc anxiety around sexual activity? | Strong impact | Minimal impact |
| Situational variability c erectile dysfunction (improved while on vacation)? | Potential for wide variability | Minimal variability |

| Table 2. Erectile dysfunction validated assessment tools | |
|---|---|
| **Tool** | **Summary** |
| Erection Hardness Scale (EHS) | Self-reported assessment of penile hardness on a scale of 0 (no engorgement) to 4 (complete rigidity) |
| Sexual Health Inventory of Men (SHIM) | Five questions that provide a score out of 25 for the subjective patient-reported assessment of erectile dysfunction |
| International Inventory of Erectile Function (IIEF) | Fifteen questions exploring five domains (desire, erectile function, intercourse satisfaction, orgasmic function and overall sexual satisfaction) of sexual function |

| Table 3. Physical exam for erectile dysfunction | |
|---|---|
| **Area** | **Factors to be assessed** |
| Overall | Blood pressure, body habitus, virilization, mood, gynecomastia |
| Penis and Groins | Penile length and girth, presence of penile plaques, phimosis, frenular tether, meatal stenosis, quality of femoral pulses |
| Testicles | Volume and consistency |

| Table 4. Comparison of the properties of PDE5-inhibitors | | | |
|---|---|---|---|
| **Property** | **Sildenafil** | **Tadalafil** | **Vardenafil** |
| >$T_{MAX}$ | 30–120 minutes (median 60 minutes) | 30–360 minutes (median 120 minutes) | 30–120 minutes (median 60 minutes) |
| $T_{½}$ | 4 hours | 17.5 hours | 4 hours |
| Absorption | Fatty meals cause a mean delay in TMAX of 60 minutes | Not affected by food | Fatty meals cause a reduction in CMAX |
| Available doses | 25 mg, 50 mg, 100 mg PRN | 2.5 mg, 5 mg daily<br>5 mg, 10 mg, 20 mg PRN | 10 mg oral dissolvable tablet<br>2.5 mg, 5 mg, 10 mg, 20 mg PRN |
| Maximum dose | 100 mg daily | 20 mg daily | 20 mg daily |
| Efficacy | Each of the PDE5 inhibitors offers similar efficacy | | |
| Dose adjustments may be needed for | – Patients >65 years<br>– Hepatic impairment<br>– Renal impairment (CrCl <30 | – Patients >65 years<br>– Hepatic impairment<br>– Renal impairment (CrCl <30 | – Patients >65 years<br>– Hepatic impairment<br>– Renal impairment (CrCl<30 ml/min) |

| | | | |
|---|---|---|---|
| | ml/min)<br>– Concomitant use of potent cytochrome P450 3A4 inhibitors, such as ritonavir and erythromycin<br>– Concomitant use of cimetidine | ml/min)<br>– Concomitant use of potent cytochrome P450 3A4 inhibitors, such as ritonavir and erythromycin | – Concomitant use of potent cytochrome P450 3A4 inhibitors, such as ritonavir and erythromycin |
| Contraindications | Any patient using organic nitrates either regularly or intermittently<br>Known hypersensitivity to any component of the tablet | | |
| Side effects (five most common in order of frequency when compared to placebo) | Headache, flushing, dyspepsia, nasal congestion, alteration in color vision | Headache, dyspepsia, back pain, myalgia, nasal congestion | Headache, flushing, rhinitis, dyspepsia, sinusitis |

Please consult the individual product monographs for additional information. Adapted from references 44 and 58.

| **Table 5. CUA erectile dysfunction guideline: Summary of recommendations** | |
|---|---|
| **1. Among patients with erectile dysfunction, should daily tadalafil be preferentially prescribed instead of on-demand tadalafil?** | |
| We suggest against the preferential use of daily tadalafil rather than on-demand tadalafil for patients with erectile dysfunction | Conditional recommendation, low levels of certainty in evidence |
| **2. Among patients with erectile dysfunction, should low-intensity shockwave therapy (Li-SWT) b recommended over no treatment?** | |
| We suggest against the use of low-intensity shockwave therapy for patients with erectile dysfunction | Conditional recommendation, low levels of certainty in evidence |
| **3. Among patients with erectile dysfunction and hypogonadism, should testosterone** | |

| | |
|---|---|
| **replacement be used as monotherapy compared to no treatment?** | |
| We suggest against the use of testosterone as monotherapy for patients with erectile dysfunction and hypogonadism | Conditional recommendation, low levels of certainty in evidence |
| **4. Among patients with erectile dysfunction, does increasing physical activity improve erectile function compared to usual activity?** | |
| We suggest increasing physical activity, rather than usual activity, among patients with erectile dysfunction | Conditional recommendation, low levels of certainty in evidence |
| **5. Among patients with post-prostatectomy erectile dysfunction, should penile rehabilitation with scheduled PDE5 inhibitor be used over no intervention?** | |
| We suggest against the use of scheduled PDE5 inhibitor for penile rehabilitation among patients with post-prostatectomy erectile dysfunction | Conditional recommendation, low levels of certainty in evidence |