Disorders of Ejaculation: An AUA/SMSNA Guideline

Panel Members

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Executive Summary

Ejaculation and orgasm are distinct but simultaneous events that occur with peak sexual arousal. It is typical for men to have some control over the timing of ejaculation during a sexual encounter. Men who ejaculate before or shortly after penetration, without a sense of control, and who experience distress related to this condition may be diagnosed with Premature Ejaculation (PE). There also exists a population of men who experience difficulty achieving sexual climax, sometimes to the point that they are unable to climax during sexual activity; these men may be diagnosed with Delayed Ejaculation (DE). While up to 30% of men have self-reported PE, few of these men have an ejaculation latency times (the time between penetration and ejaculation) of less than two minutes, making the actual prevalence of clinical PE and DE less than 5%.[1, 2] Regardless, the experience of many clinicians suggest that the problem is not rare and can be a source of considerable embarrassment and dissatisfaction for patients. Data on the prevalence of DE are more limited, but a proportion of epidemiological studies report that men have difficulty achieving orgasm.[3] Disturbances of the timing of ejaculation can pose a substantial impediment to sexual enjoyment for men and their partners. The understanding of the neurobiological phenomena that comprise ejaculation and orgasm is limited. A number of psychological health, behavioral, and pharmacotherapy options exist for both PE and DE; however, none of these pharmacotherapy options have achieved approval from the United States Food and Drug Administration and their use in the treatment of PE is considered off-label. The role of the clinician in managing PE and DE is to conduct appropriate investigation, to provide education, and to offer available treatments that are rational and based on sound scientific data. The Panel recommends shared decision-making as fundamental in the management of disorders of ejaculation; involvement of sexual partner(s) in decision making, when possible, may allow for optimization of outcomes.

The systematic review utilized to inform this guideline was conducted by a methodology team at the Pacific Northwest Evidence–based Practice Center. Scoping of the report and review of the final systematic review to develop guideline statements was conducted in conjunction with the Disorders of Ejaculation Panel. A research librarian conducted searches in Ovid MEDLINE (1946 to March 1, 2019), the Cochrane Central Register of Controlled Trials (through January 2019) and the Cochrane Database of Systematic Reviews (through March 1, 2019). Searches of electronic databases were supplemented by reviewing reference lists of relevant articles. An updated literature search was conducted on September 5, 2019.

Guideline Statements

Premature Ejaculation

1. Lifelong premature ejaculation is defined as poor ejaculatory control, associated bother, and ejaculation within about 2 minutes of initiation of penetrative sex that has been present since sexual debut. (Expert Opinion)
2. Acquired premature ejaculation is defined as consistently poor ejaculatory control, associated bother, and ejaculation latency that is markedly reduced from prior sexual

experience during penetrative sex. (Expert Opinion)

3. Clinicians should assess medical, relationship, and sexual history and perform a focused physical exam to evaluate a patient with premature ejaculation. (Clinical Principle)
4. Clinicians may use validated instruments to assist in the diagnosis of premature ejaculation. (Conditional Recommendation; Evidence Level: Grade C)
5. Clinicians should not use additional testing for the evaluation of a patient with lifelong premature ejaculation. (Conditional Recommendation; Evidence Level: Grade C
6. Clinicians may utilize additional testing, as clinically indicated, for the evaluation of the patient with acquired premature ejaculation. (Conditional Recommendation; Evidence Level: Grade C)
7. Clinicians should advise patients that ejaculatory latency is not affected by circumcision status. (Conditional Recommendation; Evidence Level: Grade C)
8. Clinicians should consider referring men with premature ejaculation to a mental health professional with expertise in sexual health. (Moderate Recommendation, Evidence Level: Grade C)
9. Clinicians should recommend daily SSRIs; on demand clomipramine or dapoxetine (where available); and topical penile anaesthetics as first-line pharmacotherapies in the treatment of premature ejaculation. (Strong Recommendation; Evidence Level: Grade B)
10. Clinicians may consider on-demand dosing of tramadol for the treatment premature ejaculation in men who have failed first-line pharmacotherapy. (Conditional Recommendation; Evidence Level: Grade C)
11. Clinicians may consider treating men with premature ejaculation who have failed first-line therapy with α1-adrenoreceptor antagonists. (Expert Opinion)
12. Clinicians should treat comorbid erectile dysfunction in patients with premature ejaculation according to the AUA Guidelines on Erectile Dysfunction. (Expert Opinion)
13. Clinicians should advise men with premature ejaculation that combining behavioral and pharmacological approaches may be more effective than either modality alone. (Moderate Recommendation; Evidence Level: Grade B)
14. Clinicians should advise patients that there is insufficient evidence to support the use of alternative therapies in the treatment of premature ejaculation. (Expert Opinion)
15. Clinicians should inform patients that surgical management (including injection of bulking agents) for premature ejaculation should be considered experimental and only be used in the context of an ethical board-approved clinical trial. (Expert Opinion)

Delayed Ejaculation

16. Lifelong delayed ejaculation is defined as lifelong, consistent, bothersome inability to achieve ejaculation, or excessive latency of ejaculation, despite adequate sexual stimulation and the desire to ejaculate. (Expert Opinion)
17. Acquired delayed ejaculation is defined as an acquired, consistent, bothersome inability to achieve ejaculation, or an increased latency of ejaculation, despite adequate sexual stimulation and the desire to ejaculate. (Expert Opinion)
18. Clinicians should assess medical, relationship, and sexual history and perform a focused physical exam to evaluate a patient with delayed ejaculation. (Clinical Principle)
19. Clinicians may utilize additional testing as clinically indicated for the evaluation of delayed ejaculation. (Conditional Recommendation; Evidence Level: Grade C)
20. Clinicians should consider referring men diagnosed with lifelong or acquired delayed ejaculation to a mental health professional with expertise in sexual health. (Expert Opinion)

21. Clinicians should advise men with delayed ejaculation that modifying sexual positions or practices to increase arousal may be of benefit. (Expert Opinion)
22. Clinicians should suggest replacement, dose adjustment, or staged cessation of medications that may contribute to delayed ejaculation in men with delayed ejaculation. (Clinical Principle)
23. Clinicians should inform patients that there is insufficient evidence to assess the risk-benefit ratio of oral pharmacotherapy for the management of delayed ejaculation. (Expert Opinion)
24. Clinicians may offer treatment to normalize serum testosterone levels in patients with delayed ejaculation and testosterone deficiency. (Expert Opinion)
25. Clinicians should treat men who have delayed ejaculation and comorbid erectile dysfunction according to the AUA Guidelines on Erectile Dysfunction. (Expert Opinion)
26. Clinicians should counsel patients with delayed ejaculation that no currently available data indicate that invasive non-pharmacological strategies are of benefit. (Expert Opinion)

Introduction

It is typical for men to be able to exert at least partial control of if and when they ejaculate during partnered sexual encounters and masturbation.[4, 5] If a man does not feel that he has control of when ejaculation occurs, and if there is distress on the part of the man or his sexual partner(s), either premature ejaculation (PE) or delayed ejaculation (DE) may be present. The specific diagnosis is determined by whether ejaculation occurs early, late, or not at all.[6]

Disorders of the timing of ejaculation can pose a major impediment to sexual satisfaction for both men and their partners. In the most extreme cases, an ejaculatory disorder may lead to relationship stress or marked trepidation about starting new relationships for men afflicted with the condition.[6, 7]

Both PE and DE are poorly understood and difficult to define. Although the reported prevalence of clinical PE and DE is less than 5%,2, 7 the experience of many clinicians who see patients for sexual problems suggests that these problem are not at all rare. The perception of rarity may stem from the frequency with which other disabling disorders of sexual function (primarily erectile dysfunction [ED]) are present in men with comorbid disruption of ejaculation.[3]

The understanding of the neurophysiology of ejaculation and orgasm remains limited. Biomedical interventions for treatment of conditions that alter ejaculatory latency and control are scant. Although few such treatments have achieved regulatory approval, a number of interventions can be considered for management of distressing disruptions of ejaculation latency time ([ELT], defined as the time between penetration and ejaculation).[2, 6] Education and referral to colleagues with experience in the psychological health evaluation and treatment of sexual problems are essential elements of care for these patients.[8]

Sexual Response Cycle

The sexual response cycle in men is conceptualized as a linear process of increasing sexual excitement, starting with desire and followed by arousal, climax, and resolution. Under normal circumstances, sexual climax in men consists of two distinct physiological events. The first of these is orgasm, a sensation of intense pleasure, relaxation, or intimacy that accompanies peak sexual arousal. The second is ejaculation, antegrade expulsion of semen from the urethra. These events are typically simultaneous and the terms are often used interchangeably in the biomedical literature. However, these are distinct physiological processes[4, 5] that may occur, or not occur, independently.

Ejaculation is triggered by integration of tactile (e.g., sensation from genital or other peripheral nerves) and non-tactile (e.g., sexually arousing audio and visual inputs) stimuli in the brain. At some set point of arousal, a centrally-mediated action potential is triggered leading to ejaculatory and/or orgasmic inevitability.9 Although ejaculation occurs in the pelvis, central nervous system (CNS) involvement plays a critical role. Data from animals, and more recently humans, has indicated the presence of galaninergic neurons arranged in columns within the central spinal cord.[10] Lesion of these structures is strongly associated with ejaculatory failure; it is likely that these neurons are responsible for integrating stimuli from peripheral and cerebral sources and triggering the ejaculatory reflex. Some experts have described this structure as the "spinal ejaculation generator" (SEG).[10]

Ejaculation consists of two distinct phases. The first of these is emission, a centrally-mediated action characterized by closure of the bladder neck and contraction of smooth muscles throughout the seminal tract (mediated by the sympathetic nervous system). The emission phase also includes secretion of seminal fluid into the proximal urethra, a process mediated by the sympathetic nervous system with some possible involvement of the parasympathetic nervous system.[4, 5] The fluid content of semen is derived primarily from the seminal vesicles and prostate, with small contributions from the bulbourethral glands and from spermatozoa transported from the epididymis via the vas deferens.[5] The second phase is ejection, a reflex driven by the somatic nervous system, specifically the pudendal nerve. Ejection is characterized by repeated contractions of the bulbospongiosus and ischiocavernous muscles leading to forceful expulsion of seminal fluid from the urethral meatus.[4, 5] A cluster of motor neurons in spinal segments S2-4 ("Onuf's nucleus") appears to be of particular import for control of the striated muscles of the pelvis.[5]

Normal antegrade ejaculation relies heavily on the normal function of the prostate and bladder neck. Medical and surgical interventions that alter function of the prostate and/or bladder neck often have noticeable and bothersome effects on ejaculation. Specific examples include decreased ejaculate volume and force in men using alpha blockers or 5-alpha reductase inhibitors for management of benign prostatic hyperplasia (BPH).[11] Surgical interventions for BPH tend to cause pronounced and difficult to resolve alterations in ejaculatory function.[12] A number of novel procedural approaches to BPH have been developed due in part to dissatisfaction with ejaculatory outcomes associated with conventional surgical BPH treatments.[13] Surgical removal of the prostate and seminal vesicles for prostate cancer typically results in marked reduction or complete absence of ejaculation as these organs are responsible for the vast majority of seminal volume. Radiation therapy for prostate cancer is also commonly associated with loss of antegrade ejaculation.[14] Disruption of ejaculation is associated with changes in subjective experience of orgasm for some men.

The act of ejaculation has important connotations for many men, aside from its association with orgasmic pleasure and necessity for procreation. Loss or anomaly of ejaculation may lead to a diminished sense of masculinity and disruption of pleasure from orgasm for many men.[15] A significant proportion of men specifically eroticize semen and are likely to be perturbed by disruption of the ejaculatory process.[16, 17] Although published data are scant, female sexual partners of men may endorse that at least some of their sexual enjoyment is derived from their partner's climax,18 however few women specifically prioritize ejaculation itself as an essential element of their sexual satisfaction.[18] Ejaculation may be of greater priority in men who have sex with men (MSM).[17]

Orgasm is a transient neurological state characterized by intense feelings of pleasure, relaxation, and intimacy. There is tremendous variability in the subjective experience of orgasm between persons and within a given person at different times. Orgasm is typically experienced at peak sexual arousal and is followed in men by a refractory period during which arousal and sexual

climax are not possible.[19] The duration of the refractory period tends to become longer with increasing age. The quality and intensity of orgasm may be influenced by a variety of factors that are incompletely understood.

Orgasm is mediated by and experienced in the brain, whereas ejaculatory reflexes are mediated by the putative SEG, making the subjective experience of orgasm an integration of numerous brain centers. The bulk of existing data on the involvement of the CNS in orgasm is derived from rodents studies. Brain regions thought to be intimately involved in central integration of stimuli germane to ejaculatory response include the stria terminalis, the posterodorsal area of the medial amygdala, and the parvicellular part of the supraparafascicular thalamus. Excitatory pathways include projections from the medial pre-optic area to the paraventricular hypothalamic nucleus and lateral hypothalamic neurons, both of which connect to the SEG. The ventral medulla appears to exert an inhibitory effect on the SEG.[5]

In general, dopaminergic and oxytocinergic activation stimulates ejaculation and orgasm whereas serotonergic and gamma-aminobutyric acid (GABA)-ergic activation opposes ejaculation and orgasm. Agonists of opioid receptors, principally mu subtypes, are also associated with impairment of ejaculatory and orgasmic response. Specific receptors may have actions that differ (e.g., stimulation of certain serotonergic receptors in the spinal cord may promote ejaculation and orgasm).[5]

Orgasm is also a neuroendocrine process. Experimental and observational data in animals and humans indicate that androgens are necessary for at least the initial maturation of sexual, including ejaculatory, reflexes.[20-22] Evidence in support of this is derived from studies of female and male cadavers. Male cadavers had a greater density of galaninergic neurons in the L3 and L4 spinal segments as compared to female cadavers, suggesting a sexually dimorphic developmental pathway likely mediated by differential exposure to androgens.[10] These same neurons, elements of the putative SEG, are thought to be essential to the ejaculatory process as evidenced by frequency of failure to ejaculate in response to penile vibratory stimulation in men with L3-5 spinal cord injury.[10]

Serum testosterone (T) levels do not represent peripheral action of T in the tissues, where T acts. Variations in androgen receptor function (e.g., number of CAG repeats), intracellular trafficking of T bound to the androgen receptor, and the balance among modulators of T receptors determine the final action of T within target tissues. T action in the CNS is carried out by nuclear receptors and possibly by non-nuclear G-protein coupled receptors. It is plausible that our gaps in knowledge about modulatory and individualized factors controlling androgens' function impair our ability to link T levels and ejaculatory function convincingly.[23]

A common cause of disruption in ejaculation or orgasm is failure of the earlier elements of sexual response (e.g., lack of sexual desire and/or ED leading to inadequate genital and subjective excitement). In the context of preserved libido and erectile function, ejaculation or orgasm may be specifically impaired by a variety of conditions such as neurological lesions of the sympathetic nervous system (e.g., retroperitoneal lymph node dissection, spinal cord injury), alpha blocker medications, or surgical disruption of the bladder neck with transurethral resection of the prostate or similar procedures. In these particular cases there may be preservation of orgasm. Conversely, it is possible for ejaculatory reflexes to be preserved, presuming an intact reflex arc to the SEG, in the context of psychological, cerebral, or other neurologic lesions that may impair the subjective experience of orgasm. The interplay between the “objective” (i.e., ejaculation) and “subjective” (i.e., orgasmic) elements of male sexual climax are complex and remain incompletely understood.

Definitions

Premature Ejaculation

A variety of terms have been applied to the clinical phenomenon of ejaculation which occurs earlier than a man wishes during a sexual encounter. Ejaculatio Praecox is a historical term; more contemporary terminology includes PE, early ejaculation, rapid ejaculation, rapid climax, early orgasm, and premature climax. The Panel recognizes that all available terms have limitations; the Panel also recognizes that early experience of orgasm, not necessarily ejaculation, and the subsequent refractory period may be the most genuinely troublesome elements of this condition for most men. However, for the sake of familiarity, the most common term of PE is used throughout this document.

PE as a disorder has historically been difficult to define. In the 1960's, Masters and Johnson defined PE as ejaculation that occurs before the female partner has experienced sexual climax during at least 50% of sexual encounters. This definition is problematic not only because it is specific to coitus but also because it does not take into considerations variations in female partner sexual response and context-specific factors that may lead to orgasmic delay in the female partner during coitus. Contemporary definitions have not focused on partner orgasmic response, although partner dissatisfaction or distress remain a consideration in making the diagnosis of PE.

The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-V) defines PE as "a persistent or recurrent pattern of ejaculation occurring during partnered sexual activity within approximately 1 minute following vaginal penetration and before the individual wishes it." The disorder must be present in 75% or more of sexual encounters and persistent over at least the last 6 months. To qualify as a dysfunction, the man must experience personal distress related to the dysfunction and the condition cannot be better explained by a comorbid or concomitant diagnosis. The DSM-V definition permits categorization of PE into lifelong versus acquired and generalized versus situational sub-types. Ejaculation that occurs before penetration or within 15 seconds, between 15-30 seconds after penetration, and from 30-60 seconds after penetration are categorized as severe, moderate, or mild PE, respectively. The empiric basis and clinical relevance of this distinction are not specified.

The World Health Organization's International Classification of Diseases 11th edition (ICD-11) defines male early ejaculation as "ejaculation that occurs prior to or within a very short duration of the initiation of vaginal penetration or other relevant sexual stimulation, with no or little perceived control over ejaculation. The pattern of early ejaculation has occurred episodically or persistently over a period at least several months and is associated with clinically significant distress." This definition has the advantage of being flexible and inclusive but lacks quantitative criteria and is nebulous in terms of the chronicity and frequency of disturbance required for the diagnosis. It mirrors the DSM-IV-TR diagnostic criterion that have been updated in DSM-V.

The International Society of Sexual Medicine (ISSM) defined two specific forms of PE (lifelong and acquired) with chronicity and time of onset as the principle distinguishing features. Per ISSM, PE is defined as ejaculation that always or nearly always occurs prior to or within about 1 minute of vaginal penetration (lifelong PE) or a clinically significant and bothersome reduction in latency time, often to about 3 minutes or less (acquired PE). Additional essential elements include the inability to delay ejaculation on all or nearly all vaginal penetrations and negative interpersonal consequences.[7] This definition is to date the strongest in terms of evidence basis; this robust evidence basis is also a limitation in that the data used in its development were derived from studies of vaginal intercourse and hence it is explicitly specific to coitus.

Waldinger et al. conceptualized two provisional diagnoses that may be applicable in the context of men who have concerns about PE but do not meet specific criteria for either lifelong or acquired PE. Natural variable PE is defined as occasional short ELT that occurs irregularly and inconsistently and over which the man feels diminished sense of control. This condition is typically minimally or non-disruptive of overall sexual satisfaction and does not occur with a frequency that poses serious impediment for the patient. Subjective PE (SPE, also known as PE-

like dysfunction) is defined as subjective concern or preoccupation about short ELT that is within population norms.[24] Data on management of these provisional conditions is limited; for the time being education and/or psychosexual therapy, rather than pharmacotherapy, are favored as the treatments of choice for Natural variable PE and SPE

Delayed Ejaculation

Similar to PE, the phenomenon of delay in ejaculation and/or orgasm has been difficult to define and is known by a variety of terms, including retarded ejaculation, inhibited ejaculation, and delayed orgasm. Recognizing again that ejaculation and orgasm are distinct entities and all available terms are limited, we will utilize the term DE throughout this text.

In 2010, the 3rd International Consultation on Sexual Dysfunction defined DE as the persistent or recurrent difficulty, delay in, or absence of attaining orgasm after sufficient sexual stimulation, which causes personal distress.

The DSM-V defines DE as the condition in which a man experiences “a marked delay in ejaculation” or “marked infrequency or absence of ejaculation.” The disorder must be present in 75% or more of partnered sexual encounters and persistent over at least the last 6 months. To qualify as a dysfunction, the patient must not desire delay of ejaculation and he must experience personal distress. Furthermore, the DE condition cannot be better explained by a comorbid or concomitant diagnosis or situation. The DSM-V definition permit categorization of DE into generalized versus situational sub-types and also includes an ordinal severity scale based on the degree of subjective distress (i.e., mild, moderate, and severe) rather than any quantitative measure. The DSM-V definition of "delay" does not have precise temporal boundaries, as there is no consensus as to what constitutes a reasonable time to reach orgasm or what is unacceptably long for most men and their sexual partners.

The ICD-11 defines “male delayed ejaculation” as “inability to achieve ejaculation or an excessive or increased latency of ejaculation, despite adequate sexual stimulation and the desire to ejaculate. The pattern of delayed ejaculation has occurred episodically or persistently over a period at least several months , and is associated with clinically significant distress.” Similar to the DSM-V definition for PE, this definition is limited by absence of quantitative criteria. The statement that the issue occurs “episodically or persistently” does not make clear the chronicity, frequency, or severity necessary to merit a DE diagnosis.

In 2015, the 4th International Consultation on Sexual Medicine developed new terminology for lifelong and acquired DE. Lifelong, alternatively classified as primary, delayed ejaculation was defined as a lifelong experience or inability to ejaculate in all of almost all (75%-100%) occasions of coital activity, associated with distress. Voluntary cessation of coital activity may subsequently occur after a variable time to avoid frustration, physical exhaustion, or genital irritation of self or partner. Men with lifelong DE might or might not be able to achieve ejaculation by subsequent non-coital activity, including masturbation.[25]

Acquired, alternatively classified as secondary, DE was defined in 2015 by the 4th International Consultation on Sexual Medicine as a distressing lengthening of ejaculatory latency that occurs in most (>50%) coital experiences after a period of normal ejaculatory function or a clinically meaningful change that results in distress. Voluntary cessation of coital activity may subsequently occur after a variable time to avoid frustration, physical exhaustion, or genital irritation of self or partner. Men with lifelong DE might or might not be able to achieve ejaculation by subsequent non-coital activity, including masturbation.[25-28]

The above criteria have been developed primarily from heterosexual samples engaging in penile-vaginal intercourse. There is no strong evidence to counter the assumption that these temporal and subjective criteria also apply to men with other sexual orientations or to other sexual situations and activities, e.g., MSM, anal intercourse, oral sex, and masturbation.

Other Ejaculatory Disorders

Hematospermia is defined as the presence of blood in ejaculated semen. It may present as bright red blood, clots, or disintegrating blood products. Although alarming, hematospermia is almost always benign; it may be found in association with other lower urinary tract conditions.[29] Evaluation should proceed according to standard protocols based on associated symptoms and other risk factors (e.g., age, tobacco history, presence of hematuria, lower urinary tract symptoms [LUTS]).

Retrograde ejaculation is defined by ICD-11 as the condition in which semen is not ejected antegrade but rather flows into the bladder during climax. This is typically due to failure of the bladder neck to close during the emission phase and may be idiopathic or secondary to bladder neck surgery, pharmacological agents, or neurologic lesion. In most cases of retrograde ejaculation, orgasm occurs and feels pleasurable. Some men with retrograde ejaculation may report that their experience of orgasm is qualitatively different.

Anorgasmia may be conceptualized as an extreme variant of DE in which orgasm cannot be achieved. The ICD-11 defines anorgasmia as "the absence or marked infrequency of the orgasm experience or markedly diminished intensity of orgasmic sensations. The pattern of absence, delay, or diminished frequency or intensity of orgasm occurs despite adequate sexual stimulation, including the desire for sexual activity and orgasm, has occurred episodically or persistently over a period at least several months, and is associated with clinically significant distress." The ICD-11 does not distinguish anorgasmia from DE and states that this would be diagnosed as male DE. For the purposes of this document anorgasmia is considered the condition in which sexual climax cannot be reached via any means of stimulation.

Anejaculation refers specifically to the absence of seminal ejaculation with sexual climax. Anejaculation may occur situationally or generally and may also occur with or without orgasmic sensation. Anejaculation most commonly occurs in the context of neurologic injury (e.g., spinal cord injury, neurodegenerative disease, retroperitoneal lymph node dissection).

Anhedonic orgasm is the condition in which ejaculation occurs but is not associated with subjective feelings of pleasure, intimacy, or relaxation. This condition is poorly understood but may relate to medications (particularly antidepressants), neurologic lesions, or psychogenic causes.[30]

Painful ejaculation, also known as dysejaculation, odynorgasmia, post orgasmic pain, dysorgasmia, or orgasmalgia, is a poorly understood condition that may have both psychogenic and organic elements. Pelvic lesion, traumas, or surgery may be contributing factors and painful ejaculation is often comorbid with other types of chronic pelvic pain syndromes.[31] Men with painful ejaculation should be evaluated for lower urinary tract dysfunction and other causes of chronic pelvic pain.

Post Orgasmic Illness Syndrome (POIS)[32-34] is provisional diagnosis which has been applied to cases of somatic symptoms that occur in close association with sexual climax. POIS is distinguished from painful ejaculation by the presence of symptoms outside the pelvis, such as malaise, confusion, myalgias, fatigue, or other somatic concerns. The etiology of POIS is unclear but may be an autoimmune, cytokine-mediated, or allergic reaction to seminal components has been proposed. The condition may be empirically managed with antihistamines, selective serotonin reuptake inhibitors (SSRIs), and benzodiazepines although data to support these modalities is scant.[35]

Epidemiology

There is a wide range of ELT in men. Population data in non-clinical populations from Western countries suggest that the median ELT (measured by stop-watch timing) for men is between 5 and 6 minutes (standard deviation of about 7 minutes) after initiation of vaginal penetration. Latency time ranged between 6 seconds to 52 minutes; there was a slight but statistically significant decline in mean ELT with increasing age.[36, 37] ELT of less than 2 minutes and less than 1 minute occurred in 2.5-6% and 0.5-3% of men, respectively. Time-based criteria have been incorporated as a component of most modern definitions of PE, derived in most cases from these population studies and driven by concerns that an absence of such could lead to a diagnosis of PE even in a man whose ELT is in the highest percentile group.

A number of international studies have demonstrated that up to 30% of men endorse early ejaculation.[38-41] These findings have been used in numerous publications to support a claim that nearly one man in three has clinical PE. However, the majority of these studies included just a single item about early ejaculation without any quantification of chronicity or frequency nor assessment of personal or partner distress. Moreover, if men are asked whether they would like to last longer during sexual activity before they ejaculate, many will answer yes despite an absence of significant bother with their present time to ejaculation.

Although the prevalence of bothersome clinical PE is very unlikely to be 30%. PE is not rare and can be a source of considerable embarrassment and dissatisfaction. A synopsis of the most contemporary literature on early ejaculation occurring in the context of distress and absence of sense of control estimates that less than 5% of men have bothersome clinical PE.[2]

Similar data on the prevalence of DE are more limited; a substantial proportion of men in epidemiological studies report difficulty achieving orgasm, but the degree of associated distress is not reported. Amongst older men, DE is often co-morbid with issues of hypoactive sexual desire or ED and is therefore clinically silent; some patients may report “new onset” inability to achieve climax after institution of successful therapy for ED. Up to 25% of DE patients are reported to have lifelong issues with achieving orgasm during partnered sex.[42] Interestingly, many men who report DE with a partner are able to achieve climax via masturbation.[42] This situation may indicate a psychological or relational component.

Data on disorders of ejaculation outside of the context of coital intercourse are sparse. There is evidence to suggest that, in men with PE, the latency of ejaculation during masturbation tends to be longer than latency time for partnered sex. The difference in latency time between masturbation and coitus is less-pronounced in men not diagnosed with PE.[43, 44] In a single survey study of Finnish men, the latency time between penetration and ejaculation was longer in men who climaxed via oral and anal sex compared to coital intercourse.[45] There are no published stop-watch studies on ELT in MSM; despite the absence of stopwatch data on ELT, single item survey studies in MSM indicate that more than 30% endorse early ejaculation.[46] Using more stringent criteria (e.g., validated scales, DSM-V criteria for the diagnosis) yields prevalence estimates for PE in MSM that are similar to those of strictly heterosexual men.[47, 48]

Methods

The systematic review utilized to inform this guideline was conducted by a methodology team at the Pacific Northwest Evidence-based Practice Center (EPC). In conjunction with the Pacific Northwest EPC, the Disorders of Ejaculation Panel determined the guideline scope and reviewed the results of the systematic review to develop the recommendations and statements in this guideline.

Panel Formation

The Disorders of Ejaculation Panel was created in 2018 by the American Urological Association Education and Research, Inc. (AUA). This guideline was developed in collaboration with the Sexual Medicine Society of North America (SMSNA). The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chair who in turn appointed the additional panel members with expertise in urology and the psychology of sexual dysfunction. The Panel included patient representation. Funding of the Panel was provided by the AUA; panel members received no remuneration for their work.

Searches and Article Selection

A research librarian conducted searches in Ovid MEDLINE (1946 to March 1 2019), the Cochrane Central Register of Controlled Trials (through January 2019) and the Cochrane Database of Systematic Reviews (through March 1, 2019). Searches of electronic databases were supplemented by reviewing reference lists of relevant articles. An update search was conducted on September 5, 2019.

The methodology team developed criteria for inclusion and exclusion of studies based on the Key Questions and the populations, interventions, comparators, outcomes, timing, types of studies and settings of interest. For populations, inclusion focused on men older than 18 years engaging in penetrative intercourse who report distress and/or partner distress related to lifelong or acquired PE or DE, and those diagnosed with PE or DE and receiving treatment for these conditions. Interventions were behavioral therapies, pharmacological therapies, topical anesthetics (for PE) and various experimental therapies. Comparisons were against waitlist, no therapy, placebo, or another active intervention. Outcomes were intravaginal ejaculatory latency time (IELT), measured with a stopwatch or by self-report, ejaculatory control, patient or partner sexual satisfaction, quality of life, mood, composite measures of sexual function, and adverse events (AE). In addition to effectiveness and harms of interventions, Key Questions also addressed medical, psychological, situational, behavioral, and physical examination factors associated with PE or DE; the accuracy of scales or instruments for diagnosing PE; and the prevalence of laboratory abnormalities in persons with PE or DE.

For evaluation of interventions, the systematic review focused on randomized controlled trials (RCTs) and systematic reviews of RCTs. For evaluation of risk factors, scales or instruments, and laboratory abnormalities, the systematic review included studies on prevalence and diagnostic accuracy. Inclusion was restricted to articles published in peer-reviewed journals in or after 1994 (systematic reviews could include studies published prior to 1994). Studies on risk factors had to have sample sizes of at least 100 patients.

Using the pre-specified criteria, two investigators independently reviewed titles and abstracts of all citations. The methodology team used a two-phase method for screening full-text articles identified during review of titles and abstracts. In the first phase, investigators reviewed full-text articles to identify systematic reviews for inclusion. In the second phase they reviewed full-text articles to identify primary studies to address key questions and interventions not sufficiently answered by previously published systematic reviews, or studies published subsequent to the systematic reviews. Database searches resulted in 1,851 potentially relevant articles. After dual review of abstracts and titles, 223 systematic reviews and individual studies were selected for full-text dual review, and 8 systematic reviews and 59 individual studies were determined to meet inclusion criteria and were included in the review.

Data Abstraction

For primary studies that met inclusion criteria, information was abstracted on study design, year, setting (inpatient or outpatient), country, sample size, eligibility criteria, dose and duration of the intervention, population characteristics (i.e., age, race, type of ejaculatory disorder where applicable), results, and source of funding. For systematic reviews, characteristics were abstracted on the included studies (i.e., number, design, and sample sizes of included studies, study

settings), population characteristics (i.e., inclusion and exclusion criteria), interventions, methods and ratings for the risk of bias of included studies, synthesis methods, and results. Data abstractions were reviewed by a second investigator for accuracy and discrepancies were resolved through discussion and consensus. All data abstractions were reviewed by a second investigator for accuracy. Discrepancies were resolved through discussion and consensus.

Risk of Bias Assessment

Two investigators independently assessed risk of bias using predefined criteria. Disagreements were resolved by consensus. For RCTs, criteria were adapted for assessing risk of bias from the U.S. Preventive Services Task Force. Criteria included use of appropriate randomization and allocation concealment methods, clear specification of inclusion criteria, baseline comparability of groups, blinding, attrition, and use of intention-to-treat analysis. Methodologists assessed systematic reviews using AMSTAR 2 (Assessing the Methodological Quality of Systematic Reviews) criteria. QUADAS-2 was used to assess the risk of bias of studies on diagnostic accuracy. Criteria included use of appropriate methods to select patients, avoidance of case-control design, use of an appropriate reference standard, blinding assessment of the index test and reference test, and administration of the reference standard in all patients. Studies were rated as "low risk of bias," "medium risk of bias," or "high risk of bias" based on the presence and seriousness of methodological shortcomings.

Studies rated "low risk of bias" are generally considered valid. "Low risk of bias" studies include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of patients to treatment; low dropout rates and clear reporting of dropouts; blinding of patients, care providers, and outcome assessors; and appropriate analysis of outcomes.

Studies rated "medium risk of bias" are susceptible to some bias, though not necessarily enough to invalidate the results. These studies do not meet all the criteria for a rating of low risk of bias, but any flaw present is unlikely to cause major bias. Studies may be missing information, making it difficult to assess limitations and potential problems. The "medium risk of bias" category is broad, and studies with this rating vary in their strengths and weaknesses. Therefore, the results of some medium risk of bias studies are likely to be valid, while others are less likely to be valid.

Studies rated "high risk of bias" have significant flaws that may invalidate the results. They have a serious or "fatal" flaw in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting; or serious problems in the delivery of the intervention. The results of high risk of bias studies could be as likely to reflect flaws in study design and conduct as true difference between compared interventions. Methodologists did not exclude studies rated high risk of bias a priori, but high risk of bias studies were considered to be less reliable than low or medium risk of bias studies. When possible, methodologists performed sensitivity analyses without high risk of bias studies to determine how their inclusion impacted findings. A complete list of the studies are available upon request at **guidelines@auanet.org.**

Data Synthesis and Rating the Body of Evidence

The methodology team constructed evidence tables with study characteristics, results, and risk of bias ratings for all included studies, and summary tables to highlight the main findings, including pooled results from previously conducted meta-analyses in systematic reviews. Investigators did not update meta-analyses reported in systematic reviews with the results of new trials, but examined whether the findings of new trials were consistent with the reviews. There were too few trials of interventions not addressed in prior systematic reviews to conduct new (de novo) meta-analyses.

Determination of Evidence Strength

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 is based on 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. Investigators graded the strength of evidence for key comparisons and outcomes for each Key Question, using the approach described in the Agency for Healthcare Research and Quality Evidence-based Practice Center Methods Guide for Comparative Effectiveness and Effectiveness Reviews. Strength of evidence assessments were based on the following domains:

- Study limitations, based on the overall risk of bias across studies (low, medium, or high)
- Consistency of results across studies (consistent, inconsistent, or unable to determine when only one study was available)
- Directness of the evidence linking the intervention and health outcomes (direct or indirect)
- Precision of the estimate of effect, based on the number and size of studies and confidence intervals for the estimates (precise or imprecise)
- Reporting bias, based on whether the studies defined and reported primary outcomes and whether we identified relevant unpublished studies (suspected or undetected)

The 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.

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 or burdens, and the Panel's judgment regarding the balance between benefits and risks or burdens (Table 2). Strong Recommendations are directive statements that an action should (benefits outweigh risks or burdens) or should not (risks or 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 or burdens) or should not (risks or 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 or burdens 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 patients 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 patients 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 patients 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 evidence strength. When body of evidence strength is Grade A, the statement indicates that benefits and risks or burdens appear balanced,

the best action depends on patient circumstances, and future research is unlikely to change confidence. When body of evidence strength Grade B is used, benefits and risksor burdens appear balanced, the best action also depends on individual patient 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 orburdens, alternative strategies may be equally reasonable, and better evidence is likely to change confidence.

Where gaps in the evidence existed, the Panel provides guidance in the form of Clinical Principles or Expert Opinions with consensus achieved using a modified Delphi technique if differences of opinion emerged. 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.

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 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		

Peer Review and Document Approval

An integral part of the guideline development process at the AUA is external peer review. The AUA conducted a thorough peer review process to ensure that the document was reviewed by experts in the diagnosis and treatment of ejaculation disorders. In addition to reviewers from the AUA PGC, Science and Quality Council, and Board of Directors, the document was reviewed by representatives from SMSNA as well as external content experts. Additionally, a call for reviewers was placed on the AUA website from December 9, 2019 to December 23, 2019 to allow additional interested parties to request a copy of the document for review. The guideline was sent to the Urology Care Foundation to open the document further to the patient perspective. The draft guideline document was distributed to 75 peer reviewers. All peer review comments were blinded and sent to the Panel for review. In total, 33 reviewers provided comments, including three external reviewers. At the end of the peer review process, a total of 433 comments were received. Following comment discussion, the Panel revised the draft as needed. Once finalized, the guideline was submitted for approval to the AUA PGC, Science and Quality Council, and Board of Directors, as well as the governing bodies of SMSNA for final approval.

Premature Ejaculation

Index Patient #1: Adult male who has experienced lifelong poor ejaculatory control, associated bother, and ejaculation within about 2 minutes of initiation of penetrative sex with a partner.

Index Patient #2: Adult male who has developed consistently poor ejaculatory control, associated bother, and ELT that is markedly reduced from prior sexual experience during penetrative sex with a partner.

These index patients are meant to represent common presentations of patients who have concerns about PE; index patient #1 is consistent with lifelong PE whereas index patient #2 is consistent with acquired PE. Individuals patients may vary in their particular concerns and preferences regarding treatment.

The criteria for the definitions of lifelong and acquired PE patients have been developed primarily from heterosexual samples engaging in penile-vaginal intercourse. There is no strong evidence to counter the assumption that these temporal and subjective criteria also apply to men with other sexual orientations and/or to other sexual situations or activities (e.g., MSM, anal sex, oral sex, masturbation).

Guideline Statement 1

Lifelong premature ejaculation is defined as poor ejaculatory control, associated bother, and ejaculation within about 2 minutes of initiation of penetrative sex that has been present since sexual debut. (Expert Opinion)

Discussion

Lifelong PE, sometimes referred to as primary PE, is a bothersome pattern of ejaculation that consistently occurs much earlier than a man desires and that has been present for all or most of a man's sexual life.

The term lifelong is used in the majority of contemporary published literature on this subject. The term lifelong PE also makes clear the temporal nature of the sexual concern. Although lifelong will be the term utilized in this document, certain aspects of lifelong PE may legitimately be construed as "primary," including:

- The condition is not clearly caused by another physical, mental, or psychological health condition.
- Most studies are based on patient recollection and reporting of a lifelong disorder rather than longitudinal prospective documentation.

- One study indicates that half of men with ejaculatory latencies under 1 min (some of whom likely had lifelong PE) show latencies greater than 1 min when re-examined 6 years later in the absence of treatment.[49]

The Panel recognizes the importance of nomenclature, the limits of language, and the controversy regarding this terminology. As additional research becomes available, the terms used in the definition may need to be reconsidered.

Ejaculatiory Control

Men with PE frequently report poor ejaculatory control. Very poor to poor ejaculatory control is characteristic of over 70% of men who have PE.[50] Ejaculatory control is but one expression of the larger concept of self-efficacy, a psychological construct that refers to the perceived ability to be effective at a given task based on previous experiences (Bandura, 1989). An example of lack of self-efficacy in the context of PE is the feeling that one will be unable to postpone or delay ejaculation during intercourse.

Lack of self-efficacy regarding ejaculatory control is a sine qua non for diagnosing PE. This concept is central to both the diagnosis of PE and perceived treatment benefits.[50, 51] Men who have self-efficacy regarding ejaculation control or voluntarily ejaculate with short latency do not by definition have a sexual problem regardless of ELT.

Bother, Distress, or Other Negative Consequences

The systematic review found that men with PE frequently report personal bother. Bother referable to the condition is necessary for a PE diagnosis. Bother stands as a proxy for any number of possible negative consequences, as elaborated in the ISSM definition,[7] and replaces distress which appears in DSM-V diagnostic language. The terms bother and negative consequences should be interpreted broadly and may refer to consequences to the patient himself, the patient's partner, and/or aspects of the relationship. The negative consequences may manifest as psychological states or behaviors. Specific terms that may apply include bothered, dissatisfied, anxious, concerned, depressed, frustrated, or others. Behaviors may include, but are not limited to, verbal catastrophizing about the negative impact of PE, avoidance of physical intimacy, and/or profuse post-coital apologizing.

Personal distress related to short ELT is reported in 45-65% of men with short ejaculatory latency-time.[28, 52] This low percentage may be attributable to the query using the term distress, suggesting a severe condition requiring immediate attention and action.[2] Distress is not a widely used term among men with respect to PE; bother captures a more nuanced perspective of troublesome issues related to PE.[2]

The bother of PE drives treatment-seeking behavior; men or couples not experiencing bother do not require, and typically do not seek, treatment. In these couples, adoption of an alternative sexual repertoire which includes activities in addition to penetrative sex may lead to mutually satisfying encounters and obviate the need for treatment of short ejaculation interval.

Short Ejaculatory Latency

The systematic review found that 80-90% of men seeking treatment for lifelong PE have an ELT of less than one minute. For men who have had short ejaculatory latencies for most or all of their sexual lives, the average estimated ELT during partnered sex should be 2 minutes or less, measured from the time of penetration to ejaculation. This 2-minute criterion differs from ISSM and DSM-V definitions that use a threshold of approximately 60 seconds.

The rationale for using the 2 minutes or less ELT for the current definition of PE is based on the following observations.

- The ISSM definition for lifelong PE states "further qualification of this cutoff to "about 1 minute" affords the clinician sufficient flexibility to also diagnose PE in the 10–20% of PE-treatment-seeking men who ejaculate within 1–2 minutes of penetration without unnecessarily stigmatizing the remaining 80–90% of men who ejaculate within 1–2 minutes of penetration but have no complaints of PE."7 The text of the ISSM definition itself makes it clear that the ELT of 1 minute criterion is not a rigid nor dogmatic requirement for a PE diagnosis.
- Although the majority of men seeking treatment for lifelong PE are characterized by latencies of less than 60 seconds, about 20% of men seeking treatment for PE ejaculate after more than 60 seconds. An extended latency time of 120 seconds would capture most of the remaining 20%. This higher limit increases true positives (decreasing false negatives and Type 2 error), but also increases false positives (Type 1 error). Reliance on control and bother are essential elements for diagnosis.
- The 60-second criterion currently used by ISSM and DSM-V was based on research that did not include non-PE comparison groups, and did not follow the procedure required for validating a measure, which necessitates an independent measure for confirmation of the criterion.[53] Studies that use "ejaculatory control" as the principal criterion for PE report median and mean ELTs longer than 1 minute in men with "poor" ejaculatory control (1.3 minutes and 1.9 minutes, respectively).[28]
- Men who fall within the 60-120 second ELT are more similar to men with latencies less than 60 seconds on dimensions such as frequency and distress or bother than men with latencies greater than 120 seconds.[54]
- The most recent population study of Waldinger et al. indicates that an ELT of about 10 seconds equates with 0.5% of the general male population, and an ELT of 60 seconds equates with 2.5%, assuming normality of ELT distribution in the male population.[37] To our knowledge, these results have not been independently replicated. They present very conservative estimates when used to establish ELT criteria for men with PE. Arbitrary selection of a cut-off based on ELT less than two standard deviations of the mean ELT may be statistically valid but clinically dubious in terms of the highly relevant considerations of bother and control. Most clinicians and researchers in the field estimate PE prevalence of 5-8% from observational studies carried out on community samples.[2, 54]
- A body of existing, high-quality literature on PE management has relied on ELT greater than 1 minute for inclusion. For instance, dapoxetine, an SSRI approved in many countries for on demand treatment of PE, was approved based on studies utilizing DSM-V criteria but allowing for ELT of 2 minutes or less.[55]

Guideline Statement 2

Acquired premature ejaculation is defined as consistently poor ejaculatory control, associated bother, and ejaculation latency that is markedly reduced from prior sexual experience during penetrative sex. (Expert Opinion)

Discussion

Acquired

Within a medical diagnostic context, acquired PE, sometimes known as secondary PE, typically denotes a later life onset. Men with acquired PE experience a period of sufficient ejaculatory control and lack of distress prior to developing the distressing shortened latency.

Acquired PE may result from a newly developed pathophysiological or a psychological or interpersonal condition. The former category might include medical comorbidities, health conditions, pain, surgery or trauma, erectile dysfunction, or medication. The latter condition may include personal and psychological health issues, new environmental pressures, evolving relationship issues and dynamics, and partner-specific issues. In some instances, no clear etiology is delineated (i.e., idiopathic acquired PE).

Ejaculatory Control and Bother

As with lifelong PE, men with acquired PE should meet the criteria of poor ejaculatory control, diminished sexual satisfaction with intercourse, and negative personal or interpersonal consequences.[56, 57]

Shortened Ejaculatory Latency

Given a dearth of evidence-based data, no ELT criterion has been included in the guideline statement for acquired PE. Several reports have confirmed that men with acquired PE have ELTs longer than men with lifelong PE, although no consensus for a particular ELT or range of ELTs exists.[7, 56-58] Specific time cut-offs in existing guidelines are largely based on expert opinion and clinical experience.

Taking into consideration normative data on ELT, the Panel suggests two temporal criteria regarding ELT for acquired PE. First, for men who have had normative, non-bothersome ELT for much of their sexual lives but who later develop a shorter latency time coupled with lack of control and negative consequences, the average estimated ELT during partnered sex should fall under about 2-3 minutes. Alternatively, ELT should be reduced by about 50% or more from prior estimations. The Panel recognizes that these criteria are limited by lack of evidence; they should be interpreted cautiously and could be improved by additional research. **Clinicians should exercise their own best judgement when making the diagnosis of acquired PE.**

Guideline Statement 3

Clinicians should assess medical, relationship, and sexual history and perform a focused physical exam to make the diagnosis of premature ejaculation. (Clinical Principle)

Discussion

A detailed history is an essential element of good medical practice for any condition. The most consistent characteristics of PE include absence or loss of ejaculatory control; personal or interpersonal bother; and short ejaculatory latency time,[1, 2] and a query on these factors is essential. The systematic review found associations between certain psychological, behavioral, situational, and medical factors and increased likelihood of PE and additional context specific information (e.g., onset, chronicity, frequency, associated factors, comorbid sexual issues, partner-specific issues) and a general medical history are also essential.

Questions in the medical and sexual history which may be relevant to the diagnosis of PE include but are not limited to:

- Does the patient have concerns about his ability to control ejaculation?
- Does the patient ejaculate before he wants to?
- Is the premature ejaculation lifelong or did it begin after having a period of had normal ejaculation?
- Does the patient feel that he has poor or no control of ejaculation?

- Does the patient feel that he cannot postpone or delay ejaculation?
- Does the patient experience negative interpersonal consequences because of PE?
- Does the patient experience anxiety because of PE?
- Does the patient feel depressed because of PE?
- Does the patient try to avoid sexual activity because of PE?
- Does the patient experience distress, bother, concern or other negative consequences due to PE?
- What is the patient's self-estimated ELT?
- For how many years has premature ejaculation been present?
- Does premature ejaculation occur with almost every sexual encounter?
- Are there variations in ELT related to different sexual partners?
- Are there variations in ELT related to different sexual circumstances?
- Does the patient experience PE with masturbation?
- Does the patient have a history of prostatitis or other prostate conditions?
- Does the use of a condom change the ELT?
- Are there non-partner situational factors which alter ELT (e.g., alcohol consumption, stress)?
- Is there a family history of PE?

Questions about the patient's sexual partner which may be relevant to the diagnosis of premature ejaculation include but are not limited to:

- Is the patient's partner upset about PE?
- Does the patient's partner experience distress, bother, concern or other negative consequences due to PE?
- Does the patient's partner request that the patient get treatment for PE?
- Is the patient's partner frustrated because the duration of sexual activity is too short?
- What is the partner's estimate of ELT?
- Is the patient's partner bothered by the patient's focus on intercourse due to fear of his getting too excited by non-coital sexual activity?
- Is the partner interested in sexual activity?
- Does the partner have issues with sexuality?
- Does the partner have difficulty climaxing?
- Can the partner climax from penetration alone?
- Is there strife or stress in the patient and partner relationship?

Assessment should include query on psychological health. This assessment may include, but not be limited to, simple questions about having experienced ongoing or persistent anxiety, mood disorders such as major depression and bipolar affective disorder, or significant psychiatric problems over the past 6-12 months.

Depression occurs in about 20% of men with PE compared to 12% in men without PE ; anxiety occurs in 24% of men with PE compared to 13% in men without.[59] Other studies[60, 61] have reported even higher prevalence rates for anxiety of up to one-third of men with PE. A systematic review of 18,035 men in 8 studies determined that the odds ratio for

depression was 1.63 (95% CI:1.42 - 1.87; I2=0%) in men with PE versus without PE.[62] Assessment by a mental health professional may be of benefit, or even a necessity, depending on severity of mood disorder.[2] Mood disorders may or may not improve with initiation of effective PE therapy.

Physical examination is an essential standard in medical practice; however, physical examination rarely contributes to the evaluation of premature ejaculation. Although it seldom changes management, a focused physical examination is reassuring to patients and may identify issues meriting consideration. A brief genital exam should be considered when feasible. Particular areas of note include penile morphology; testicular size and consistency; and prostate size and consistency. The relevance of any of these factors to management of PE is ambiguous, but evaluation may be informative in other ways and suggest other issues for discussion and management.

Guideline Statement 4

Clinicians may use validated instruments to assist in the diagnosis of PE. (Conditional Recommendation; Evidence Level: Grade C)

Discussion

Five studies[63-67] evaluating the accuracy of validated questionnaires for diagnosing premature ejaculation met the inclusion criteria for this guideline. Scales evaluated were the Premature Ejaculation Diagnostic Tool (PEDT), the Premature Ejaculation Profile (PEP), Index of Premature Ejaculation, the Multiple Indicators of Premature Ejaculation,[68] the Checklist for Early Ejaculation Symptoms, and the Arabic Index for Premature Ejaculation. IELT is another patient reported outcome (PRO) which can be used as a standalone metric or as an adjunct to these other scales. For the purposes of this guideline, unless the Panel is reporting on outcomes from RCTs that specifically used IELT as an outcome measure, the Panel has elected to use the terminology ELT interchangeably with IELT to account for heterosexual as well as other sexual situations and activities (e.g., MSM, anal intercourse, oral sex, and masturbation) since there is no strong evidence to counter the assumption that these temporal and subjective criteria also apply to men with other sexual orientations.

Limitations of patient reported questionnaires include case-control design, possible spectrum bias (e.g., variability in response between clinical milieus), failure to match cases and controls for baseline characteristics, failure to blind the assessment of scales to the reference standard, and use of an inadequate reference standard in some studies. Despite these limitations, these questionnaires have very good sensitivity and specificity scores and high discrimination (the ability to distinguish persons with from those without the condition).

Validated patient-reported questionnaires are useful for research purposes; their value in clinical diagnosis is uncertain. The questionnaires may be useful as an adjunct to diagnosis or as an “ice breaker” to facilitate a conversation about ejaculatory issues. Use of questionnaires such as these is not required to make the diagnosis of PE. The clinical value of these questionnaires as longitudinal measurement tools to assess change over time or in response to treatment has not been studied. In addition, interpreting changes in scores is a challenge, as minimal clinically important differences are unknown.

Guideline Statement 5

Clinicians should not use additional testing for the evaluation of a patient with lifelong premature ejaculation. (Conditional Recommendation; Evidence Level: Grade C)

Discussion

High serum T, hyperthyroidism, elevated serum glucose or HbA1c, and presence of inflammatory cells or infection in the urine or expressed prostatic secretions have been associated with increased likelihood of PE.[69, 70] Evidence supporting these relationships is limited and inconsistent. Existing studies on associations between PE and other disorders have not reliably distinguished between lifelong and acquired PE, limiting the evidence base that can be applied to assessing these distinct conditions. However, with the possible exception of high serum T occurring with onset of sexual maturation, these conditions are generally acquired rather than lifelong, it is not clear that they are applicable to the diagnosis of lifelong PE.

One cross-sectional study (n= 2,437)[71] reported higher T levels in men with PE compared to both men with DE and men with neither PE nor DE. There was also an association between PE and decreased likelihood of T deficiency, defined as a total T <300 ng/dL (<10.4 nmol/L) after adjusting for age and libido. In a study of men with diabetes (n=676) there was no association between T levels and presence of PE.[72]

Waldinger reported that there was no association between thyroid stimulating hormone levels and PE in a cohort of 620 men with lifelong PE.[73] A more recent cross-sectional study (n=102)[74] reported that men with PE had lower levels of thyroid stimulating hormone, luteinizing hormone, and prolactin compared to men without PE as diagnosed by the PEDT. No differences were reported in free T4, total or free T, creatinine, or glucose. After adjustment only luteinizing hormone was predictive of PE.

A number of studies have evaluated the association between genetic polymorphisms and PE. Genotypes associated with shorter ELT include polymorphisms of the neurotransmitter receptors 5-HTTLPR, 5-HT2C, HTR1A, and DAT1 genes.[75-81] There appears to be some variation in polymorphism prevalence based on geographic location. No gene polymorphism assay has been approved for clinical use at his time. The impact of each specific polymorphism on ELT is thought to be minor. There is limited evidence that variations in polymorphism are associated with differential response to SSRI-based therapy for PE.[82, 83] While there may be utility in genetic testing in the future, the clinical utility of genetic testing for PE at the current time is unclear.

Biothesiometry is a means to assess for penile hypersensitivity, which may be a risk factor for PE or DE. Xin et al. reported on 120 patients with primary PE assessed with biothesiometry and compared to 66 healthy controls. Lower penile vibratory sensation thresholds, indicative of greater sensitivity, were noted in men with PE compared to controls.[84] A more recent study in 1,239 men (151 with PE and 45 with DE) did not detect any significant difference in penile sensitivity between men with or without PE or DE.[85] These results suggest a possible etiology for some cases of lifelong PE but do not necessarily indicate that any particular intervention is preferred over another.

Based on MRI, a number of functional and anatomical differences have been reported in the brains of men with lifelong PE compared to controls without ejaculatory dysfunction. Specific differences include, but are not limited to, greater volume of the caudate nucleus;[86] alterations of white matter structure in the right posterior thalamic radiation, posterior corona radiata, bilateral posterior limb of the internal capsule, superior corona radiata, and external capsule;[87] disorders of synergy across dopamine pathways as measured by short-range functional connectivity density;[88] weaker functional connection between the left

interior frontal gyrus and left dentate nucleus and right frontal pole, pathway involved in the central inhibitory network.[89] These findings may have relevance to further study of the mechanisms of PE but the clinical application of these data are at this time unclear.

In summary, a number of adjunctive tests may be informative in making the diagnosis of lifelong PE, but the nature and strength of association is ambiguous or the clinical application of said testing is unclear. The Panel is unaware of any studies indicating that correction of a specific laboratory abnormality is associated with improvement specifically in lifelong PE symptoms. **For these reasons, additional laboratory testing is not routinely necessary for the diagnosis of lifelong PE. Additional laboratory testing may be considered, if clinically indicated for other reasons.**

Guideline Statement 6

Clinicians may utilize additional testing as clinically indicated for the evaluation of the patient with acquired premature ejaculation. (Conditional Recommendation; Evidence Level: Grade C)

Discussion

Acquired PE generally manifests later in life, often in association with one or more comorbid organic diseases. Serefoglu et al.,[90] Zhang et al.,[91] and Gao et al.[58] reported that men with acquired PE have a higher mean body mass index and a greater incidence of comorbid diseases including hypertension, sexual desire disorder, diabetes mellitus, chronic prostatitis, and ED compared to men with lifelong, variable, and SPE.

Many of the conditions listed above are risk factors for ED, making ED an important consideration when diagnosing PE. Acquired PE in this context may be conceptualized as an adaptive practice in a man who lacks confidence in his ability to maintain penile erection; "speeding up" the process may be a means to achieve climax before loss of tumescence. If a man with PE is diagnosed with concomitant ED, evaluation should proceed according to the AUA Guidelines on Erectile Dysfunction.[92]

Corona et al.[69] reported higher T levels in some age bands of men with PE compared to men without PE; given the nature of this study it is unclear whether these high-normal T levels were congenital or acquired; the relationship could conceivable apply to either lifelong or acquired PE. There was also an association between PE and a decreased likelihood of T deficiency.

The association between PE and diabetes and serum glucose has been examined and is similarly ambiguous due to mixed findings and marked heterogeneity in study design. One study of 2658 men[93] found a decreased risk of PE among men with treated diabetes compared to men without diabetes. In an Egyptian study of 199 diabetic men compared to 299 non-diabetic men,[94] the Arabic Index of Premature Ejaculation and stop-watch ELT were measured. Lifelong or acquired PE were found in 79% of diabetic patients compared to 47% of nondiabetic patients. There was no statistically significant difference between patients with and without PE in the duration of diabetes or HbA1c levels. Another study of 151 men[95] reported no difference in the prevalence of PE between men with or without type 1 diabetes; however, significant associations were reported between serum HbA1c levels and PEDT scores and between HbA1c and ELT. An earlier study in 676 men with diabetes also reported that PE is associated with poor metabolic control. In this study, men with HbA1c > 7% were 9.6 times more likely to report PE compared to those with HbA1c < 6.2%.[72]

Acquired PE, along with painful ejaculation and ED, have been documented in men with acute urogenital infection, LUTS, and chronic prostatitis or chronic pelvic pain syndrome.[96-98] PE is the most common sexual complaint in men with chronic pelvic pain syndrome, occurring in 26-77% of cases.[99] Whether these men actually meet criteria for clinical PE as defined in this document is unclear.

Based on evaluation of urine and expressed prostatic secretions in men with PE compared to men without PE, rates of prostatic inflammation, defined as 10 or more WBC per high powered field, have been reported to range between 37% to 64% in PE patients versus 0-9% in controls.[98, 100, 101] In these studies evidence for chronic bacterial prostatitis was identified in 48 to 64% of the PE population compared to 0-9% in the control groups. Additional studies on the relationship of prostatitis to PE were not identified in the extensive literature search performed for this guideline.[98, 100, 101] A non-randomized, open label study of men with PE and positive cultures from either urine or expressed prostatic secretions treated with antibiotics (n=74) or no treatment (n=20) reported that 84% of treated men reported improvement in ELT.[100]

The pathophysiological mechanisms underlying the possible relationship between PE and prostate inflammation are unclear; the limitations and vagaries in the diagnosis of "prostatitis" are an additional challenge. Antibiotic treatment may be considered when symptoms and urinalysis or urine culture is consistent with of chronic bacterial prostatitis (NIH Chronic Pelvic Pain Syndrome Type II). However, given the limited data supporting a potential link between prostatic inflammation and PE, it is not evidence-based to prescribe prolonged courses of antibiotics for empiric management of isolated PE, even in the context of NIH Chronic Pelvic Pain Syndrome Type III.

In summary, evidence regarding additional testing in men with acquired PE is limited and inconsistent. Laboratory tests, particularly tests related to the hypothalamic-pituitary-testicular axis, thyroid function, glucose metabolism, and prostatitis or chronic pelvic pain syndrome should be employed when there is clinical suspicion of these conditions in men with acquired PE. **In general, clinicians may utilize additional laboratory testing as clinically indicated and may treat such abnormalities accordingly. However, such tests are not a required element of evaluation for acquired PE.**

Guideline Statement 7

Clinicians should advise patients that ejaculatory latency is not affected by circumcision status. (Conditional Recommendation; Evidence Level: Grade C)

Discussion

Data on the impact of circumcision status on ELT are fraught with limitations. Regional differences in the prevalence of neonatal or childhood circumcision make comparison of studies from different geographic locations unreliable. Neonatal or childhood circumcision is oftentimes associated with adherence to particular religious or cultural traditions, which may exert a psychosexual influence on ELT in particular and sexual function more generally. It is difficult to predict how the practice of neonatal or childhood circumcision modulates ELT. An adequately powered RCT of circumcision prior to initiation of sexual experience is not feasible for both ethical and logistical reasons. Men who elect circumcision as adults or after sexual debut may already be experiencing some form of physical, sexual, or psychological impairment from presence of foreskin. Circumcision in these cases may yield benefit for the individual man but this cannot be taken as evidence that circumcision itself is necessary to optimal sexual experience for all men.

A systematic review of 12 studies on circumcision and premature ejaculation102 found no association between circumcision and increased risk of premature ejaculation (OR: O.90; 95% CI: 0.72-1.13). **In the absence of compelling data to the contrary, the Panel concludes that circumcision status does not exert a significant influence on ejaculation latency.**

Guideline Statement 8

Clinicians should consider referring men diagnosed with premature ejaculation to a mental health professional with expertise in sexual health. (Moderate Recommendation, Evidence Level: Grade C)

Discussion

Psychological and Interpersonal Symptoms Associated with PE

Clinical experience suggests that psychological and interpersonal factors may precipitate PE. These factors may also exacerbate PE and generate additional psychological and interpersonal symptoms for the man, partner, and couple. Psychological and interpersonal factors associated with PE include depression, anxiety, history of sexual abuse, decreased emotional intimacy, and conflict within the relationship.[2] It is important to note that these are associations and that causality is unclear. Compared to men without PE, men with PE have significantly lower self-esteem and self-confidence,[103] more interpersonal conflict, and more anxiety in sexual situations.[104] PE may be a barrier to seeking out and becoming involved in new relationships and hence may pose a particular challenge to men without a partner(s).[61]

PE has a negative impact on female partners. Women in relationships with men who have PE have lower scores for all domains of the Female Sexual Function Index except desire and pain compared to women whose partners do not have PE.[105, 106] One of the most troubling aspects of PE for female partners may be the man's focus on his ejaculatory performance; this may distract him from other salient aspects of a sexual encounter.[107] In support of this finding, a study of infertile couples (n=73 couples) reported that only half of women whose partners reported premature ejaculation agreed with the male partner's assessment. Furthermore, although 30% of men reported that their partners were frustrated by PE, only 43% of these women agreed that that they were in fact frustrated.[108] It may be hypothesized from these findings that female partners may be less bothered by PE than by their partner's reactions to the condition. Discrepancy in perception about ELT between members of the dyad is also readily apparent.

Psychological Treatment

Psychotherapy for men and couples suffering from PE may be useful even when no clear psychological or physiological etiology is apparent. Such therapy has two overlapping goals. First, psychological interventions aim to help men develop sexual skills that enable them to delay ejaculation while broadening their sexual scripts, increasing sexual self-confidence, and diminishing performance anxiety. Second, they help men and their partners resolve psychological and interpersonal issues that may have precipitated, maintained, exacerbated, or resulted from PE.[6]

Most present-day psychological therapies for PE represent the integration of psychodynamic, systematic, behavioral, and cognitive approaches within a short-term psychotherapy model. Treatment may be provided in an individual, couples, group, or on-line format. Single men present unique treatment challenges, as they may be hesitant to

enter new relationships as they blame the failure of past relationships on their sexual dysfunction. Such men may not realize the benefits of therapy until they are willing to seek out sexual relationships.

Behavioral therapy interventions include the stop-start technique, the squeeze technique, and sensate focus exercises.[109] The first two techniques are interventions designed to halt the progressive arousal process that may lead to orgasmic inevitability. Sensate focus trains men to focus on excitatory sensations rather than avoiding them for fear of ejaculating quickly. By mastering these skills, men may learn to increase and control their ejaculatory latency.

Sensate focus in particular helps men and couples broaden their sexual repertoire to include more foreplay by ameliorating fear that prolonged non-coital stimulation will lead to ejaculation. Sensate focus may allow the man to discover the pleasures of foreplay while maintaining ejaculatory control. Combining behavioral techniques with traditional psychotherapy may address the couples' concerns while simultaneously providing behavioral tools to overcome PE.[2]

A systematic review (10 studies; n=521 patients) was recently conducted contrasting psychological and behavioral interventions (i.e., start/stop, squeeze, physical therapy, use of adjunctive sexual enhancement devices) with wait list control (4 studies), pharmacotherapy (3 studies), and combined pharmacotherapy and behavioral therapy (3 studies) for management of PE. Importantly, only 1 of the 10 studies included explicit psychotherapy with the remainder focused on education and advice on behavioral techniques, including sensate focus, to delay ejaculation. This review is hampered by tremendous variability within the source studies in terms of intervention, control group, duration of therapy, outcome measures, and inclusion criteria. However, no studies indicated that psychological or behavioral therapy was inferior and most suggested benefit.[110, 111] An open label study of pharmacotherapy did report superior outcomes (in terms of IELT and response to the PEDT) in men who received adjunctive sexual or behavioral therapy.[112] The durability of psychobehavioral interventions is incompletely understood; three studies have reported that IELT improvements were maintained for 3 – 6 months after treatment cessation.[110, 113, 114] There are no studies of longer duration of effects.

Potential Advantages of Psychological/Behavioral Intervention

Psychological or behavioral interventions offer benefit without the need for pharmacological intervention. Medication, whether daily dose or on-demand, may pose a burden that interferes with sexual enjoyment. All pharmacotherapies also carry risk of AEs. Men may also prefer a psychological or behavioral intervention because it can be integrated into sexual encounters as part of the experience; this may make the treatment feel like an expression of sexual intimacy rather than an external intervention. Changes in PE symptomatology from behavioral or psychological intervention may better establish self-efficacy in comparison to an external pharmacotherapy intervention.

Potential Dysadvantages of Psychological/Behavioral Intervention

It is challenging to study the efficacy of psychological and behavioral interventions in a double-blind, controlled, randomized fashion. Lack of blinding can result in performance bias and bias related to patient expectations and preferences regarding treatment. Sexual behavioral or psychological therapy is a sub-specialty that requires specific training and in some cases certification. Specialists in psychosexual therapy may not be readily available in all geographic regions, although telemedicine or Internet based PE programs may provide an alternative to face-to-face sessions. Behavioral or psychological treatment requires an investment in time, typically at least 5-10 sessions, and may not be covered by insurance carriers.

Pharmacotherapy

Introduction

Numerous pharmacological treatments have been utilized for management of PE. These include SSRI, select tricyclic antidepressants (TCA), topical local anaesthetics, tramadol, phosphodiesterase type 5 inhibitors (PDE5i) and alpha-adrenergic blockers. The use of topical local anaesthetics, such as lidocaine, prilocaine or benzocaine, alone or in association, to diminish the sensitivity of the glans penis is the oldest known pharmacological treatment for PE.[115] The utilization of specific SSRIs (i.e., paroxetine, sertraline, fluoxetine, and citalopram) and the TCA clomipramine has revolutionized the treatment of PE. These drugs block axonal re-uptake of serotonin from the synaptic cleft of central serotonergic neurons by 5-HT transporters, resulting in enhanced 5-HT neurotransmission and stimulation of post-synaptic membrane 5-HT receptors.

Men with Lifelong PE may be well managed with PE pharmacotherapy alone. Existing data are limited by tremendous heterogeneity in terms of outcome measures and treatment modalities. However, based on the Panel's review of existing data, the majority of controlled studies suggest a clinically meaningful patient-reported response from treatment that exceeds placebo response rates by about 40-60%.[112] Integration of patient and/or couple psychosexual therapy may enhance these effects. Men with acquired PE should receive etiology specific treatment if a specific cause can be identified (e.g., psychosexual counselling for men with recent trauma, appropriate pharmacotherapy for men with ED); this may be administered alone or in combination with PE-specific pharmacotherapy. Physicians should recognize the association between PE, comorbid ED, metabolic syndrome, sedentary lifestyle, alcohol consumption, and body mass index. Clinicians should counsel patients on the importance of exercise and other healthy lifestyle choices.[116, 117]

Guideline Statement 9

Clinicians should recommend daily SSRIs; on demand clomipramine or dapoxetine (where available); and topical penile anesthetics as first-line agents of choice in treatment of premature ejaculation. (Strong Recommendation; Evidence Level: Grade B)

Discussion

Off-label selective SSRIs and clomipraine

Daily treatment with off-label paroxetine 10-40 mg, sertraline 50-200 mg, fluoxetine 20-40 mg, citalopram 20-40 mg and clomipramine 12.5-50 mg is effective in delaying ejaculation. A meta-analysis of published data suggests that daily paroxetine exerts the strongest ejaculation delay, increasing ELT a mean of 8.8-fold over baseline.[118] It must be borne in mind that an 8.8-fold increase may still be marginal if baseline ELT is on the order of seconds. The typical range of absolute change in ELT from the systematic review suggested an increase of 1-5 minutes.

On-demand administration of clomipramine, paroxetine, sertraline and fluoxetine 3-6 hours before intercourse is modestly efficacious and well tolerated but is associated with substantially less ejaculatory delay than daily treatment in most studies.[119-123] On-demand treatment may be combined with either an initial trial of daily treatment or concomitant low dose daily treatment.[119]

Noticeable ejaculation delay usually occurs within 5-10 days of starting daily treatment; full therapeutic effect may require 2-3 weeks of treatment and is usually sustained during long-term use.[124] AEs from SSRI treatment of PE have been reported in up 54% of men using these meds although the majority of studies indicate an approximately 1 in 3 chance of AEs.[125] AEs are usually minor, typically start in the first week of treatment and may gradually disappear within 2-3 weeks. They include fatigue, yawning, headache, mild nausea, diarrhea, perspiration, or decreased libido. There are anecdotal reports suggesting that decreased libido and ED are less frequently seen in non-depressed PE men treated by SSRIs compared to depressed men treated with SSRIs.[126] Neurocognitive AEs include significant agitation and hypomania in a small number of patients.

Serotonin Syndrome is a potentially serious complication most often associated with simultaneous use of multiple serotonergic drugs (e.g., SSRI, TCA, and recreational drugs such as amphetamine or cocaine). Common symptoms include clonus (i.e., cyclic relaxation and contraction of muscles), tremor, hyperreflexia, agitation, mental status changes, diaphoresis, fever. Severe cases may associated with seizure and rhabdomyolysis. Treatment includes cessation of serotonergic agents. Benzodiazepines may be used in the short term to manage symptoms.[127-129]

Treatment with SSRIs should be avoided in men with a history of bipolar depression due to risk of mania.[130] The use of off-label SSRIs is favored over the TCA clomipramine because of a better side effect profile.[131]

SSRIs enhance platelet serotonin release and may be associated with increased risk of upper gastro-intestinal bleeding when concurrently used with aspirin and non-steroidal anti-inflammatory drugs.[132] Priapism is a rare AE of SSRIs and requires urgent medical treatment. Long term SSRI use may be associated with weight gain and an increased risk of type-2 diabetes mellitus.[133] Paroxetine has been reported to induce abnormal sperm DNA fragmentation; other SSRI have been associated with declines in semen concentration and normal morphology.[134] The prevalence, magnitude, and implications of these semen changes is unclear and may be of variable concern based on the patient's plans for parenthood or partner factors. Nevertheless, it is prudent to counsel patients about the potential for adverse fertility effects from SSRI treatment.[135]

A systematic review (70 studies; n=18,526 patients) did not identify a significant difference (OR: 1.21; 95% CI: 0.84-1.74) in suicidal ideation in adult men treated with anti-depressants versus placebo;[136] a small increase in the risk of suicidal ideation or suicide attempts was noted in patients under age 18. Elevated risk of suicidal ideation has not been found in trials with SSRIs in non-depressed men with PE. **Nevertheless, caution is suggested in prescribing SSRIs to adolescents with PE and to men with PE and a co-morbid depressive disorder, particularly when associated with suicidal ideation.**[137]

Patients are often reluctant to begin off-label treatment of PE with SSRIs. Salonia et al. reported that 40% of patients either refused to begin or discontinued paroxetine within 12 months of beginning treatment due to concern about taking an antidepressant, treatment effects below expectations, and cost.[138] **Patients should be advised to avoid sudden cessation or rapid dose reduction of daily dosed SSRIs as this may precipitate SSRI withdrawal syndrome.**[139]

Dapoxetine

Dapoxetine is a rapid acting, short half-life SSRI with a pharmacokinetic profile supporting a role as an on-demand treatment for PE.[140] Dapoxetine has not received marketing approval by the United States Food and Drug Administration but has received approval for the treatment of PE in over 50 countries.

In RCTs, dapoxetine 30 mg or 60 mg taken 1-2 hours before intercourse is more effective than placebo from the first dose, resulting in a 2.5 and 3.0-fold increase in IELT, increased ejaculatory control, decreased distress, and increased satisfaction. Dapoxetine was effective in men with both lifelong and acquired PE[56, 141] and was similarly effective and well tolerated in men with PE and co-morbid ED treated with concomitant PDE5i drugs.[142, 143] Treatment related side effects may occur in as many as half of patients taking the drug compared to 27% of patients in the placebo arm but these tend to be very mild and dose dependent.[144] The most common are nausea, diarrhea, headache, and dizziness.[55] AEs were severe enough to lead to discontinuation in just 4% of subjects taking the 30 mg dose and 10% of subjects taking the 60 mg dose.

The incidence of treatment-related AEs appears lower with on-demand dapoxetine compared to daily-dose SSRIs.[131] There was no indication of an increased risk of suicidal ideation or suicide attempts and little indication of withdrawal symptoms with abrupt dapoxetine cessation.[145] No drug-drug interactions associated with dapoxetine, including phosphodiesterase inhibitor drugs, have been reported. Jiann et al. reported that 45% of men were satisfied with their response to dapoxetine (30 mg) and that level of satisfaction was closely related to treatment response.[146] Post-marketing experience does however report that the discontinuation rate for dapoxetine is high (87-90% at 12 months) predominantly due to cost and the lack of spontaneity associated with on-demand administration.[147, 148]

Dialy versus On-Demand Treatment

Initially, the decision to treat PE with either on-demand dosing of dapoxetine (where available) or daily dosing of off-label SSRIs should be based upon the treating physician's assessment of individual patient requirements. Although many men with PE who engage in sexual intercourse infrequently prefer on-demand treatment, many men in established relationships prefer the convenience of daily medication. Well-designed preference trials have not been conducted but are likely to provide additional insight into the role of on-demand dosing. In some countries, off-label prescribing may present difficulties for the physician as the regulatory authorities strongly advise against prescribing for indications in which a medication is not licensed or approved. This may complicate treatment in countries where there is no approved medication and the regulatory authorities advise against off-label prescription.

Topical Anesthetics

The use of topical anesthetics such as lidocaine and prilocaine is well established and is moderately effective in delaying ejaculation.[149, 150] Diminishing glans sensitivity may inhibit the spinal reflex arc responsible for ejaculation.[151] Topical anesthetics may be associated with significant penile hypo-anesthesia and possible transvaginal absorption, resulting in vaginal discomfort and/or numbness.[152] Use of a condom or thorough washing of the penis prior to penetration may help prevent these bothersome effects.

Topical anesthetics may be applied as a gel, ointment, topical wipes, or as a spray. Some spray forms are formulated as mixtures of lidocaine-prilocaine which penetrate the epithelium of the glans penis and not the keratinized skin of the shaft.[153] Dinsmore et al. reported that treatment with a eutectic lidocaine-prilocaine mixture, applied to the penis at least 5 minutes before intercourse, resulted in a 6.3 fold increase in IELT and associated improvements in the PRO measures of control and sexual satisfaction.[154] A second prospective, controlled study in 256 men with PE demonstrated that this spray increased geometric mean IELT from a baseline of 0.56 minute to 2.60 minutes as compared to 0.53 minute to 0.80 minutes in the control arm (4.6- and 1.5-fold change, respectively).[155] There were significantly greater increases in the scores for the Index of Premature Ejaculation domains of ejaculatory control, sexual satisfaction and distress in the anesthetic group

compared to the placebo group. There were minimal reports of penile hypoanaesthesia and transfer to the partner due to the unique formulation of the compound in both studies.

Guideline Statement 10

Clinicians may consider on-demand dosing or tramadol for treatment of premature ejaculation in men who have failed first-line therapy pharmacotherapy. (Conditional Recommendation; Evidence Level: Grade C)

Discussion

Tramadol is a centrally acting synthetic opioid analgesic and weak inhibitor of re-uptake of GABA, norepinephrine, and serotonin.[156, 157] The efficacy of on-demand tramadol in the treatment of PE has been reported by several authors.[158-163]

Most studies of tramadol for PE are poorly designed open label trials with a wide range of efficacy. The only well-designed double-blind trial demonstrates superiority to placebo but a modest increase in IELT of 2.49-fold, consistent with the weak serotonin re-uptake inhibitor activity of tramadol.[162] In an open-label crossover comparator study of daily paroxetine (20 mg) and on-demand tramadol (50 mg) in 35 subjects with lifelong PE, superior IELT increases and PRO responses were demonstrated with paroxetine (22-fold versus 5-fold for tramadol) after 12 weeks of treatment. A large, international, prospective, randomized, placebo-controlled, double-blind trial of tramadol for the treatment of PE (NCT00983151) was recently stopped prematurely with no reason provided.

There have been four meta-analyses of tramadol published clinical trial data.[164-167] All conclude that tramadol appears effective in the treatment of PE but suggest that these findings should be interpreted with caution given the observed levels of between-trial heterogeneity and the reporting quality of the available evidence. Approximately 20% of patients receiving tramadol experience non-serious AEs including nausea, vomiting, dizziness, somnolence, tiredness, and headache.[168] Serotonin Syndrome has been reported as an AE of tramadol alone or in combination with SSRI drugs.[169-171]

The potential of tramadol for addiction or abuse appears low in most patient populations but has not been assessed in men with PE.[172] Adams et al. reported abuse rates of 0.7% for tramadol compared with 0.5% for non-steroidal anti-inflammatory drugs and 1.2% for hydrocodone, based on application of a dependency algorithm as a measure of persistence of drug use.[173] **These data are reassuring but in light of the ongoing opioid crisis in many nations, caution should be exercised in prescribing an analgesic medication with opioid-like properties for management of PE.**

Table 2: Pharmacotherapies for the treatment PE

Drug	*Daily Dose*	*On-demand dosing*
First Line		
Paroxetine	10-40 mg*	20 mg (+/- 10 mg daily)
Clomimpramine	12.5-50 mg*	25-50 mg
Sertaline	50-200 mg*	50-100 mg
Fluoxetine	20-40 mg*	

Table 2: Pharmacotherapies for the treatment PE		
Citalopram	20-40 mg*	
Second Line		
Tramadol	---	20-100 mg
Terazosin	5 mg	
Alfuzosion	6-10 mg	
Sildosin	4 mg	
Tamsulosin	0.4 mg	
Doxazosin	4 mg	

Guideline Statement 11

Clinicians may consider treating men with premature ejaculation who have failed first-line therapy with α1-adrenoreceptor antagonists (Expert Opinion)

Discussion

α1-Adrenoceptor antagonists are widely used in the treatment of LUTS associated with or without BPH. These drugs may induce ejaculatory dysfunction such as retrograde ejaculation and/or failure of emission.[174, 175 176 177, 178] Several published studies have investigated α1-adrenoceptor antagonists for the treatment of PE.[179-183] **Existing studies of α1-adrenoceptor antagonists are limited by flaws in sample size, inclusion criteria, PE definitions, and outcome measures.**

In a double-blind placebo-controlled cross-over study of 91 men, Cavallini et al. reported that both alfuzosin (6 mg/day) and terazosin (5 mg/day) were "effective" in delaying ejaculation in approximately 50% of the cases.[179] Similarly, a study of 90 men with concomitant PE and LUTS reported that after one month of treatment with terazosin (5 mg/day) led to "improvement" in 68% of men compared to 30% treated with placebo.[180] Both studies were limited by the use of subjective study endpoints of patient impression of change and sexual satisfaction. Change in IELT was not reported in either study.

Sato et al. evaluated the feasibility of off-label silodosin (4 mg) in eighty patients with PE.[181] In patients on treatment IELT was significantly prolonged from a baseline 3.4 minutes to 10.1 minutes (P=0.003). At study end, all PROs in the PEP significantly improved and all subjects rated their PE as at least "better" on the clinical global impression of change question.[184] Akin et al. compared silodosin (4 mg), tamsulosin hydrochloride (0.4 mg), alfuzosin (10 mg), terazosin (5 mg), and doxazosin mesylate (4 mg) in 108 men with PE and reported that IELT, PEP and quality of life responses were statistically improved for all drugs; silodosin appeared most effective (P<0.05).[183] No control group was reported in either of these studies so the potential for placebo effect is high.

Bhat et al. recently reported that silodosin 4 mg was more effective than placebo (as determined by PEP and global impression of change) as a salvage treatment for 64 men with PE (83% of whom had lifelong PE) who were either unresponsive or intolerant of dapoxetine. Mean pre-treatment mean IELT was approximately 0.55 minutes in both groups but differed significantly post-treatment (4.5 minutes in the treatment group versus

2 minutes in the placebo group; actual values not provided in the paper but derived from review of a figure). ELT values were obtained "prior to the initiation of the treatment and the very next day of the treatment with drug."[185] The implication from the paper is that ELT data represent a single time point immediately after initiation of treatment so the durability of this response is ambiguous.

α1-Adrenoceptor antagonists are widely available and generally safe. **Existing efficacy data remains very limited. Additional controlled studies are required to determine the true role of α1-blockers for management of PE.**

Guideline Statement 12

Clinicians should treat comorbid erectile dysfunction in patients with premature ejaculation according to the AUA Guidelines on Erectile Dysfunction. (Expert Opinion)

Discussion

Epidemiological data on the coincidence of clinical PE and ED are scant. Based on published data and clinical experience, it is the Panel's opinion that in some cases acquired PE may be secondary to ED (i.e., intensifying stimulation to induce ejaculation before loss of erection) whereas some men with lifelong PE may develop ED related to performance anxiety. **Clinicians should thoroughly evaluate patients with both ED and PE to gauge temporal relationships between the conditions and determine which disorder is more troublesome.**

To our knowledge there are no peer-reviewed studies on appropriate initial therapy for the man presenting with both PE and ED. Prior guidance from the AUA stated that treatment of ED should precede management of PE.[186] The rationale for this ordering of treatment was the consideration that acquired PE may be an adaptation to ED. This Panel recognizes and agrees that management of ED should be primary in such cases. However, a more nuanced and clinically appropriate strategy is to determine primacy of incidence and bother for both ED and PE and to treat according to which condition is most sexually disabling and/or primary. In the ideal circumstance, management of the primary sexual concern will mitigate bother from the secondary concern. Providers should strive to limit the number of pharmaceutical interventions required to optimize sexual function. Some patients may ultimately require specific therapy for both ED and PE.

The management of co-morbid ED in the PE patient should be focused on minimally invasive strategies (e.g., education, behavioural change, sex therapy, oral pharmacotherapy). Invasive therapies (e.g., intracavernous injection, prosthesis placement) are appropriate for properly-counselled patients with ED not responsive to other therapies but should not be considered standard of care in patients whose principle concern is PE and in patients with PE and ED who are satisfied with non-invasive ED treatments.

ED pharmacotherapy alone or in combination with PE pharmacotherapy may be considered for the treatment of lifelong and acquired PE in men with co-morbid ED. Clinical trials of dapoxetine have included men with PE and mild ED per international index of erectile function (IIEF) criteria. The efficacy of dapoxetine for PE was less robust in men with mild ED compared to men with no ED.[56]

Several authors have reported experience PDE5is alone or in combination with SSRIs as a treatment for PE.[187-204] PDE5i modulate activity of the NO/cGMP pathway, which is in turn a central and genital mediator of nitrergic neurotransmission that may influence ejaculatory

responses.[205] It is also conceivable that use of PDE5i improves sexual confidence and erection durability, enabling men with PE to focus on behavioural changes that help prolong ELT.[206, 207]

In a study of 42 men with lifelong PE and no ED who were randomized to vardenafil vs placebo, Aversa et al. reported a 7.5-fold increase in geometric mean IELT following treatment with vardenafil (4.5±1.1 versus 0.6±0.3 minutes with placebo; P<0.01). Significant improvements were also noted in the IPE domains of ejaculatory control, confidence, overall sexual satisfaction, and distress.[202] A recent meta-analysis of RCTs of PDE5i for management of PE indicated that PDE5i are effective compared with placebo and that a PDE5i combined with a SSRI is more effective in PE management than an SSRI alone.[208]

Guideline Statement 13

Clinicians should advise men with premature ejaculation that combining behavioral and pharmacological approaches may be more effective than either modality alone. (Moderate Recommendation; Evidence Level: Grade B)

Discussion

Behavioral strategies, including start-stop, squeeze, and sensate focus, have been studied in combination with pharmacological approaches to increase ELT and sexual satisfaction beyond that resulting from pharmacological treatment alone. Several studies have shown that inclusion of behavioral therapies increases ejaculatory latencies by about 1 min over pharmacological therapy alone (Li et al., 2006; Shao et al., 2008; Yuan et al., 2008). PROs such as sexual satisfaction, anxiety, and partner satisfaction also improve. Other studies have suggested that incorporation of psychobehavioral intervention increases ELT an additional 1-3 minutes compared to pharmacotherapy (in this case dapoxetine) alone.[112] Combination therapy is also associated with greater improvement in scores on validated instruments for assessment of PE such as the PEDT.[112, 209, 210] In these studies, combination treatments lasted from 1.5 to 6 months and the frequency of therapy ranged from several hours to sixteen 2-hour sessions.

Although trials of combination therapies have focused on behavioral strategies as a means of lengthening ELT, incorporation of cognitive-behavioral therapy may also improve sexual satisfaction by expanding the couple's sexual behavioral repertoire, improving communication, and addressing relationship dynamics. Psycho-behavioral therapies impart no significant AEs, but typically require a specialist in psychosexual therapy and may not be covered by insurance.

Several resources are available to patients and healthcare professionals interested in sexual/behavioral health intervention. Online resources include the Society for Sex Therapy and Research web referral site **https://sstarnet.org**, the AASECT web referral site **https://www.aasect.org/referral-directory**, and the Psychology Today referral site **https://www.psychologytoday.com/us/therapists/sex-therapy**. Patients and clinicians may also consult the SMSNA website **www.smsna.org** or **https://www.wikihow.com/Find-a-Sex-Therapist** to identify qualified therapists.

Guideline Statement 14

Clinicians should advise patients that there is insufficient evidence to support the use of alternative therapies in the treatment of premature ejaculation. (Expert Opinion)

Discussion

Intracavernous self-injection treatment of PE has been reported but is currently without any evidence-based support for efficacy or safety. In one study which included eight patients with PE, a solution of papaverine hydrochloride (30mg/mL) and phentolamine mesylate (1.0mg/mL) was injected.[211] Subjects were diagnosed as "potent" based only on self-report and all had failed to respond to prior treatment of PE with behavioral therapies. All patients responded with supraphysiological erections which persisted beyond ejaculation and reported satisfaction with the results of this treatment. Ejaculation delay was not objectively measured. This study is limited by the small sample size, the lack of an active comparison or placebo group, minimal follow up, and incomplete characterization of erectile function. In addition, intracavernous injection does not truly address issues of PE but rather medically induces erection that is not reversed by ejaculation. Legitimate concerns exists about the risk of priapism in men without ED who utilize injectable agents to induce erections.

Cooper et al. performed a systematic review of trials of the serotonin noradrenaline reuptake inhibitors (SNRIs) duloxetine (40 mg/day) and venlafaxine (75 mg/day) for PE.[212] There was no statistically significant difference in stopwatch IELT between venlafaxine versus placebo and a modest difference between duloxetine and placebo.[212] Given the modest benefit and availability of SSRI, duloexetine is not a recommended treatment option for PE. While duloexetine should not be first-line therapy for the treatment of PE, it can be considered if first-line treatments fail.

An RCT comparing the effectiveness of twice a week acupuncture therapy with paroxetine (20 mg/day) and placebo (sham-acupuncture) in the treatment of PE demonstrated that acupuncture had a significantly stronger ejaculation delaying effect than placebo (65.7 versus 33.1 seconds), although it was less effective than daily paroxetine (82.7 seconds; p=0.001).[213] Similar results were reported by Sahin et al. who reported that higher IELTs occurred with dapoxetine compared to acupuncture and with acupuncture compared to sham acupuncture.[214] Acupuncture is generally low risk but efficacy appears inferior to pharmacotherapy. Acupuncture is not a first-line therapy, however, it may be considered for patients who fail other treatments.

There are insufficient high-quality studies demonstrating benefit of any specific herbal therapy for the treatment of PE. Cooper et al. evaluated ten randomized controlled trials of complementary and alternative medicine interventions for the management of premature ejaculation in a systematic review.[215] The authors concluded that there was preliminary evidence for the effectiveness of Chinese herbal medicine, Ayurvedic herbal medicine, and topical severance secret cream in improving IELT and other outcomes. However, results were based on clinically heterogeneous studies of flawed methodology and unclear quality with little data on AEs or potential for drug interactions. Further well-conducted randomized controlled trials are required before any herbal therapy should be considered evidence-based.

Botulinum toxin,[216-218] modafanil,[219] and oxytocin antagonists[220-223] have limited evidence base as pharmacological management options for clinical PE. These medical agents are discussed in more detail in the Future Directions section as they may have utility for medical practitioners caring for PE patients pending further clinical study.

Guideline Statement 15

Clinicians should inform patients that surgical management (including injection of bulking agents) of premature ejaculation should be considered experimental and only be used in the context of an ethical board approved clinical trial. (Expert Opinion)

Discussion

Several authors have reported the use of surgically induced penile hypo-anesthesia via selective dorsal nerve neurotomy, pulsed radiofrequency ablation of dorsal penile nerves, or hyaluronic acid gel glans penis augmentation in the treatment of lifelong PE refractory to behavioral and/or pharmacological treatment.[224-226 227, 228] Surgery may be associated with permanent loss of penile sensation; as such, **the Panel recommends that surgical intervention for PE only be considered in the context of an ethical board-approved trial for patients who have failed or cannot tolerate alternative management strategies for PE.**[229]

Alahwany et al. have published a study on the use of hyaluronic acid (HA) in the treatment of PE. This randomized (single-blinded) controlled crossover study aimed to assess the efficacy and safety of glans penis injection with HA in treating PE.[230] ELT increased by a median of 2.6-fold in the HA group compared to 1.1-fold in the saline injection group. AEs were minimal. These results are limited by the small group of patients studied in a single center. This treatment for PE cannot be recommended until multiple centers report clinically significant benefit from the treatment technique.

A recent study[227] of 96 Chinese men with lifelong PE found that selective dorsal penile neurectomy plus circumcision was associated with longer post-surgical IELT than circumcision alone (4.29 versus 0.82 minutes; p=0.02). AEs included abnormal glans sensation in 4.5% and delayed ejaculation in 6.8% of patients. This single center study has not been reproduced in other centers.

Clinicians should counsel men considering surgical treatment for PE that there is a paucity of data concerning circumcision with or without dorsal penile neurectomy or HA injection; the risks and benefits of dorsal penile neurectomy and HA injection are not known; and there may be as yet undefined chronic disabilities resulting from dorsal penile neurectomy or HA injection.

Delayed Ejaculation

Index Patient #3: Adult male patient who has consistent and bothersome difficulty achieving orgasm during penetrative sex with a partner.

Guideline Statement 16

Lifelong delayed ejaculation is defined as lifelong, consistent, bothersome inability to achieve ejaculation, or excessive latency of ejaculation, despite adequate sexual stimulation and the desire to ejaculate. (Expert Opinion)

Guideline Statement 17

Acquired delayed ejaculation is defined as an acquired, consistent, bothersome inability to achieve ejaculation, or an increased latency of ejaculation, despite adequate sexual stimulation and the desire to ejaculate. (Expert Opinion)

Discussion

DE is arguably the least studied, least reported and least understood male sexual dysfunction. DE is of particular concern when procreation is desired. Regardless of the desire for procreation, the impact of failure to achieve orgasm is significant in that it typically results in a lack of sexual fulfilment for both the man and his partner.

Herein, the preferred terminology DE is meant to describe any and all of the ejaculatory disorders resulting in a delay or absence of ejaculation and concomitant impairment of orgasm. Alternative terms include retarded ejaculation, inadequate ejaculation, inhibited ejaculation, idiopathic anejaculation, primary impotentia ejaculations, psychogenic anejaculation, and delayed orgasm. Subtle differences do exist in the meanings of these terms, as articulated in the introduction section of this guideline.

In the study of DE, latency of ejaculation, sexual satisfaction, motives for cessation of intercourse and negative personal and interpersonal consequences (e.g., distress) represent constructs that require operationalization. A construct is a non-observable, latent variable that is presumed to exist, is an attribute of people, and is used to help explain or predict variation in responses or behavior.[26] Operationalization is the process of defining a construct or variable by the development of a measure, procedure, or process for identification of that construct or variable. Operationalization and the careful determination of cut-offs for each variable will minimize but never completely eliminate inclusion (false positive) or exclusion errors (false negative) of DE classification of those who have DE versus those who do not.

The constructs of DE are difficult to define and have not been sufficiently operationalized. The median ELT in Western countries is between 5-6 minutes following intromission.[28] Twenty-one to twenty-three minutes represents about two standard deviations above the mean of normal ejaculatory latency. A clinician might assume that men with latencies beyond 25 or 30 minutes who report distress, or men who simply cease sexual activity due to their partners request, fatigue or a sense of ejaculatory futility qualify for this diagnosis. Such symptoms, together with the fact that a man and/or his partner decide to seek help for the problem, are usually sufficient for a DE diagnosis.

Guideline Statement 18

Clinicians should assess medical, relationship, and sexual history and perform a focused physical exam to evaluate a patient with delayed ejaculation. (Clinical Principle)

Discussion

A detailed history is the cornerstone of medical practice; in many cases this practice alone is sufficient to make a diagnosis. Evaluation of men presenting with DE or anejaculation should include a full medical and sexual history, a focused physical examination, determination of serum T levels, and any additional investigations suggested by these findings.

In the context of DE, essential elements include determination of whether DE is lifelong or acquired, global or situational, and the assessment of time of onset, chronicity, frequency, and associated factors, such as alleviating and exacerbating. Evaluation includes establishment of whether a man can ejaculate during intercourse and the time elapsed between penetration and ejaculation. If ejaculation fails to occur, the duration of thrusting before suspension of intercourse, the reasons for suspension of intercourse (e.g., fatigue, loss of erection, a sense of ejaculatory futility, or partner request), and whether ejaculation can occur during post-penetrative self- or partner-assisted masturbation must be

determined. The presence of premonitory ejaculatory sensation during intercourse or masturbation suggests achievement of sufficient arousal to almost attain the ejaculation threshold. Variables that improve or worsen performance; the man's ability to relax, sustain, and heighten arousal and the degree to which he can concentrate on sensations; and any current medications should be noted and documented.

A general medical history should be obtained, including assessment for history of conditions associated with neuropathy (e.g., myelopathy, radiculopathy, diabetes, HIV, side effects of medications, neurologic lesions), metabolic derangements, and traumas (e.g., iatrogenic trauma from surgical procedures) to the nervous system or pelvis. A sexual history should be obtained, assessing factors such as relationship status, relationship quality, partner feelings on the acute issue, and on sexuality in general.

The patient should be queried on whether the problem of DE is situational (related only to a specific partner or specific sexual context) or generalized (occurring in all situations). Attention should be directed towards obtaining information on historical and current masturbation habits; some authorities have associated idiosyncratic or traumatic masturbation habits with difficulty achieving climax during partnered sexual activity.[42, 231] The presence and extent of patient, partner or interpersonal related negative psychological consequences such as bother, distress, frustration or the avoidance of sexual contact should be established. The frequency of intercourse and the identity of the initiator of sexual contacts are useful surrogate measures for these negative psychological consequences. The quality of the nonsexual relationship should also be explored.

There are no physical exam findings that have been clearly linked to DE; however, a focused physical exam is often reassuring to patients and may yield clues to conditions that may be comorbid or even related to DE. The general physical exam should include assessment for signs of metabolic disorders (e.g., obesity), decreased serum T (e.g., minimal body hair, muscle atrophy, habitus consistent with Klinefelter or other endocrinopathies), or prior injury (e.g., midline scars, traumas involving the CNS). A focused genital examination should include assessment of penile morphology, the condition of genital skin, turgor and size of the testicles, sensation of the scrotum, and based on the clinician’s judgment, a digital rectal examination of the prostate. Basic neural testing may include assessment of anal sphincter tone and bulbocavernosal reflex. The relevance of any of these factors to management of DE is ambiguous but evaluation may be informative in other ways and/or suggest other issues for discussion and management.

Guideline Statement 19

Clinicians may utilize additional testing as clinically indicated for the evaluation of delayed ejaculation. (Conditional Recommendation; Evidence Level: Grade C)

Discussion

The utility of additional testing in the management of DE is unclear, in large part because the etiology of the disorder is incompletely understood and predisposing factors can generally be elicited with a careful history. The prevalence of symptoms consistent with DE increase at progressively lower serum T levels.[232] Given the relationship between many domains of male sexual function and serum T concentration, the Panel supports morning T testing as recommended by the AUA Guideline on the Management of Testosterone Deficiency.[233]

There are few data to support additional adjunctive laboratory studies. Basic serum studies including electrolytes, lipids, glycosylated hemoglobin, and possibly others may be informative of medical conditions that could predispose to neuropathy (e.g., diabetes, HIV infection in at risk patients) or vascular disease (e.g., hypertension, hyperlipidemia). These conditions may contribute to sexual dysfunction, including DE.

Biothesiometry may be informative as a means to diagnose sensory neuropathy of the penis.[234] In the context of DE this testing is applied to the penis, particularly the glans. Assessment may include but is not limited to characterization of sensitivity to temperature, pain, pressure, and vibration in the penis versus other body regions. However, a recent study in 1,239 men (n=45) with DE did not detect any significant difference in penile sensitivity between men with or without DE.[85] While useful for diagnostic purposes it is unclear how biothesiometry might change clinical management.

A recent small study utilized functional MRI to evaluate brain activity in three men with lifelong DE compared to six controls without ejaculatory dysfunction. During audiovisual sexual stimulation men with DE had significantly increased activation in the right fusiform gyrus of the occipital lobe and the right hippocampus. The authors conclude that a number of neurotransmitters known to be active in these brain regions may be targets for future pharmacotherapy in DE; at this time however the clinical utility of MRI in evaluation of DE is unclear.[235]

The occurrence of orgasm in the absence of antegrade ejaculation suggests retrograde ejaculation and can be confirmed by the presence of spermatozoa in post-masturbation voided urine. Ultrasound scan of the testicles, epididymides, and or prostate may help elucidate any local disease that could contribute to disruption of ejaculation.

Patients with unilateral or bilateral ejaculatory duct obstruction or congenital absence of vasa usually present with thin or watery low volume semen, azoospermia, and infertility. Semen analysis demonstrates azoospermia or oligospermia with low concentration of fructose and a low pH. In the patient with unilateral absence of the vas deferens ultrasound scanning of the entire urinary system is indicated as coexisting renal anomalies may be present. Bilateral absence or malformation of the vasa may be associated with the cystic fibrosis gene.[236]

A variety of genetic tests have been utilized in studies of ELT. None of these tests have been approved for use in the clinical context of DE. Furthermore, the degree of influence of any single genetic variant, such as polymorphisms of dopamine transporters, is likely to be marginal.

Guideline Statement 20

Clinicians should consider referring men diagnosed with lifelong or acquired delayed ejaculation to a mental health professional with expertise in sexual health. (Expert Opinion)

Discussion

Ejaculatory thresholds differ across men and, within men, across situations and age. While biomedical options for increasing the ejaculatory threshold are available (e.g., SSRIs), no clear options are available for lowering the threshold and thus decreasing ejaculation time. Psycho-behavioral strategies are unlikely to directly alter the ejaculatory threshold but may enhance psychosexual arousal and/or remove barriers and inhibitions that interfere with psychosexual excitement.[6, 237]

There are no large scale, randomized, placebo controlled studies with sufficient follow-up in the psychological treatment of men with DE. Existing data are generally small trials of psychological interventions based on the theoretical assumption underlying the etiology of DE.

One of the most significant factors in DE is age, which likely combines psychological and physiological processes. Age-related increases in latency may be managed with psychological and behavioral approaches (e.g., increasing the repertoire of behaviors) aimed at increasing physical and psychological arousal. These approaches avoid the risks of pharmacotherapies for DE that also have a very limited evidence basis and carry some risk of treatment-related AEs.

There are four major psychological approaches to managing DE, based on different theories about pathogenesis. No one approach accounts for all the varied presentations of DE and no approach by itself has strong empirical support. Three of the four approaches share the common condition of insufficient arousal, which itself has different developmental courses.

The first approach is applicable to men in whom there is insufficient penile or psychological stimulation. These men may report having an insensate penis, or diminished ability to experience penile sensations. A psychogenic etiology is strongly suggested when men report having normal penile sensation while masturbating, yet have diminished sensation when being stimulated by a partner. Psychological intervention aims to increase penile and psychological stimulation by using a vibrator, enhancing psychological arousal, or recommending vigorous pelvic thrusting while addressing the psychological factors that may inhibit ejaculation.

The second approach is applicable to men in whom there is a discrepancy between masturbatory patterns and fantasy life and the experience of partnered sex. Specifically, some men with DE report high-frequency masturbation, an idiosyncratic (i.e., referring to speed, pressure, and intensity that do not mimic sensations during intercourse) masturbation style, or a discrepancy between the reality of sex with a partner and sexual fantasy. In this context the therapist recommends adaptation of the man's masturbatory style to be more reflective of what is experienced during partnered sex and assists the man with reconciling fantasy and reality (Perelman, 2005).

The third approach is applicable in the context of DE as a response to preference for masturbation over partnered sex. Some men may prefer self-stimulation to stimulation by a partner. Psychological intervention aims to diminish the man's focus on himself and enhance his ability to accept pleasure from his partner (Apfelbaum, 1989).

The last approach is applicable when there is psychological conflict regarding ejaculation and orgasm. This conflict may reduce arousal and inhibit orgasm. Possible sources of conflict include fear that semen loss will lead to health problems; fear of harm from female genitals; fear that ejaculation may hurt the partner; fear of impregnating a female partner; fear of defiling the partner with semen; hostility toward partner; unwillingness to give oneself; and guilt about sexuality in general, in many cases due to conservative religious upbringing. Psychological intervention focuses on resolving the psychological conflict, which may help normalize ejaculatory patterns.[6]

Guideline Statement 21

Clinicians should advise men with delayed ejaculation that modifying sexual positions or practices to increase arousal may be of benefit. (Expert Opinion)

Discussion

Behavioral interventions are a low risk option that may help some men with DE enhance arousal and trigger orgasmic response. This may include incorporation of alternative sexual practices and scripts (e.g., oral or manual stimulation of the penis, use of alternative sexual positions, stimulation of other erogenous zones, incorporation of fantasy or roleplay), and incorporation of sexual enhancement devices (e.g., vibrators). The specific nature of changes to sexual practice are dictated by what the couple is currently doing sexually, what each partner considers arousing, and what is physically and psychologically acceptable to both partners in terms of novel sexual practices. At a minimum, recommending a discussion about sexual needs and desires may help open lines of communication between partners and help facilitate treatment.

A limited evidence basis exists for application of penile vibratory stimulation for management of acquired DE.[238] The Panel is unaware of any other robust evidence basis for this recommendation. Given the remarkably diversity of human sexual preference and ethical and logistical concerns, it is unlikely that any trial of standardized alteration of sexual practices for DE could be designed with adequate scientific rigor. In the absence of rigorous scientific evidence, it is nevertheless sensible to conclude that granting permission for sexual exploration, within the bounds of what is mutually acceptable to the patient and his partner(s), may yield benefit for some patients with DE.

Guideline Statement 22

Clinicians should suggest replacement, dose adjustment, or staged cessation or of medications that may contribute to delayed ejaculation (Clinical Principle)

Discussion

A variety of medications have been clearly linked to disruption of orgasmic function in both men and women. Examples include SSRI, SNRI, TCA, opioids, CNS-acting agents, and various others.[239, 240] Table Three (adapted from Sadowski et al.) highlights agents known to be associated with DE.[240]

Table 3: Agents known to be associated with Delayed Ejaculation

Alcohol	Clomipramine	Mebanizine	Phenelzine Sulfate
Alprazolam	Demethylimpiramine	Mesoridazine	Prazosin
Amiocaproic Acid	Fluoxetine	Methadone	Protriptyline
Amitriptyline	Fluvoxamine	Methyldopa	Reserpine
Amoxapine	Guanadrel	Naproxen	Sertraline
Baclofen	Guanethidine	Nortriptyline	Thiazides
Bethanidine	Haloperidol	Pargyline	Thioridazine
Butaperazine	Hexamethonium	Paroxetine	Trazodone
Chlordiazepoxide	Imipramine	Perphenazine	Trifluperazine

Table 3: Agents known to be associated with Delayed Ejaculation			
Chlorimipramine	Iproniazid	Phenotiazine	
Chloropromazine	Isocarboxazid	Phenoxybenzamine	
Chlorprothixene	Lorazepam	Phentolamine	

Cessation of these medications should be considered patients who present with troublesome DE, particularly if the onset of DE coincides with initiation of the medication. When cessation is not possible, dose adjustment or substitution may yield benefit.

The use of adjunctive therapies may be of benefit in some cases of drug-induced DE. Substitution of the offending psychiatric drug (most often an SSRI or TCA) with an alternative agent (e.g., bupropion, buspirone)241-243 may be the most medically feasible way to adjust therapy. Use of drugs as adjunct therapies (e.g., bethanecol, cyproheptadine)[244, 245] have also been reported. While effective, this practice may contribute to polypharmacy and should be given careful consideration prior to starting. Table Four highlights pharmacotherapy options applicable to men with likely SSRI-induced DE.

The majority of drugs associated with DE are not commonly utilized in urological practice; the practicing urologist is unlikely to be fully familiar with indications and particular considerations regarding dose adjustment and cessation. The prescribing physician(s) and possibly a pharmacist should be advised of the potential issue with the prescribed medication; the decision on cessation and dose adjustment must be made using shared decision-making involving all parties after careful consideration of risks and benefits.

Table 4: Pharmacotherapies with potential efficacy in the setting of SSRI-induced DE		
Drug	**PRN Dosage**	**Daily Dosage**
Cyproheptadine	4-12 mg (3-4 hours prior to sex)	--
Bethanechol	20 mg (1-2 hours prior to sex)	--
Amantadine	100-400 mg (for 2 days prior to sex)	75-100 mg BID/TID
Bupropion	--	75 mg BID/TID
Buspirone	--	5-15 mg BID
BID: twince a day; mg: milligrams; TID: three times a day		

Guideline Statement 23

Clinicians should inform patients that there is insufficient evidence to assess the risk-benefit ratio of oral pharmacotherapy for the management of delayed ejaculation. (Expert Opinion)

Discussion

There are no FDA approved pharmacotherapies for DE, nor is the Panel aware of any pharmacotherapies that have received regulatory approval from other national regulatory agencies. The body of literature on DE pharmacotherapy is scant, with the bulk of published studies consisting of case reports and non-randomized, non-placebo-controlled

case series. Pharmacotherapies that have been evaluated for management of DE include bupropion (oral),[241, 242] oxytocin (typical administered as a nasal spray or lozenge)[246, 247], cabergoline (oral),[248] buspirone (oral),[243] sympathomimetics (e.g. pseudoephedrine or midodrine,[249-251] particularly in the case of disruption of ejaculation), imipramine (oral),[250, 251] Yohimbine (oral),[252] amantadine (oral),[253] and cyproheptadine (oral).[245] A list of these agents and reported dosing is included in Table Five.

A single randomized controlled trial of bupropion for orgasmic dysfunction enrolled 10 men with DE.[241] Subjects were randomized to placebo, bupropion 150 mg/day, or bupropion 300 mg/day, with those in the bupropion groups having improvement in orgasmic delay compared to placebo. A randomized cross-over trial of bethanecol enrolled 12 patients with DE related to clomipramine and reported significantly better subjective experience of orgasm with treatment.[244] A non-randomized, non-controlled case series of 131 men with DE reported on cabergoline with favorable results in 66% of patients; absence of a control group and ambiguity regarding outcome measures hampers interpretation of these data.[248]

The Panel does not believe that existing evidence is robust enough to render an opinion on the actual risk/benefit ratio of DE pharmacotherapy. Well-designed, appropriately powered studies are needed to better define efficacy and safety of pharmacotherapies for DE.

While the Panel does not feel that an evidence-based recommendation can be made regarding of various DE therapies, we recognize the current needs of DE patients and their partners for therapeutic options which may include pharmacotherapy. The Panel is supportive of clinicians offering appropriately selected and counseled patient's pharmacotherapies that have a physiologic rationale for benefit in DE treatment. Patients should be counseled on the weak evidence base and the potential for both known and unknown side effects. The benefit of enhanced orgasmic function must be weighed by the patient against the potential risks; an individualized decision can then be made based on the patient's own personal values.

The majority of these drugs are not commonly utilized in urological practice; the urologist who is not comfortable prescribing these medications should consider referral of the patient for discussion of these management options.

Table 5: Pharmacotherapies with potential efficacy for the treatment of DE

Drug	PRN Dosage	Daily Dosage
Oxytocin	24 IU intranasal/SL during sex	--
Pseudoephedrine	60-120 mg (120-150 minutes prior to sex)	--
Ephedrine	15-60 mg (1 hour prior to sex)	--
Midodrine	5-40 mg daily (30-120 minutes prior to sex)	--
Bethanecol	20 mg daily	--
Yohimbine	--	5.4 mg TID
Cabergoline	--	0.25-2 mg BIW
Imipramine	--	25-75 mg Daily

BIW: twice a week; IU: international units; mg: milligrams; SL: sublingual; TID: three times a day

Guideline Statement 24

Clinicians may offer treatment to normalize serum testosterone levels in patients with delayed ejaculation and testosterone deficiency. (Expert Opinion)

Discussion

Ejaculatory dysfunction is increasingly common with age, which is itself associated with declining serum T levels. It is logical to hypothesize that the androgenic milieu has an influence on ejaculation and orgasm. However, not all men with biochemically low T levels suffer from DE, and not all men with the DE have low T levels.

A randomized clinical trial (n=66) of T 2% solution versus placebo to treat men with ejaculatory and/or orgasmic dysfunction showed no statistically significant difference in ejaculatory function between men receiving T or placebo.[263] However, the published results of this trial did not consider the fact that few men in the treatment group achieved normal T levels.

This study and understanding of the relevance of T to ejaculation and orgasm supports checking T level in men with delayed orgasm and ejaculation. In men with biochemically low T and symptoms, clinicians may consider T replacement therapy as per the 2018 AUA Guideline on the Management of Testosterone Deficiency.[235] There is no RCT to guide desirable T levels in T deficient men with DE. Most experts recommend a target T level at or above the 50th percentile (>500-550 ng/dl) during treatment unless positive response is achieved with lower levels. T therapy is not indicated in men with DE and normal T levels. Benefit from T treatment of T deficient men should be evident within 90 days of the patient becoming eugonadal. If the patient does not report satisfactory improvement within that time-frame, the treatment should be discontinued unless there are other indications to support continuing the treatment. Periodic follow up of men successfully managed with T for DE is indicated to gauge need for continuing treatment.

T therapy is intended to ameliorate symptoms and minimize risks; the clinician should assess both patient-perceived and objective measures of T treatment effectiveness and potential side effects during routine visits. The AUA guidelines provide reference points for clinical and laboratory evaluation and follow up of men with low T.[235] The choice of T therapy should be patient-specific as available T preparations in USA differ pharmacokinetics, costs, and side-effects profile.

Guideline Statement 25

Clinicians should treat men who have delayed ejaculation and comorbid erectile dysfunction according to the AUA Guidelines on Erectile Dysfunction. (Expert Opinion)

Discussion

ED and DE are oftentimes comorbid. The two entities share a number of common risk factors, including medications (e.g. SSRI, SNRI), endocrine conditions (e.g., T deficiency, hyperprolactinemia), penile sensation loss, and psychological factors (e.g., anxiety, depression, relationship stress). The critical step in evaluating patients with concomitant ED and DE is to define the chronology of their relationship. ED can predate or postdate the onset of DE. When DE precedes the onset of ED the focus should be on defining the etiologies of DE and trying to determine if they have played a role in the development of ED

and address any etiological factors appropriately. When ED precedes the onset of DE, common etiological factors should be sought and addressed. When no overt etiological factors (e.g., penile sensation loss, low serum T, SSRI use) are present for DE, careful attention should be focused on the secondary psychological sequela of the presence of ED. Decreased sexual self-confidence, self-esteem, or sexual avoidance related to ED may trigger or exacerbate DE. While evidence is lacking, empiric clinical experience suggests that effective treatment of antecedent ED may improve DE. Reducing patient anxiety related to erectile problems and decreasing the likelihood of self-observation during sexual activity may alleviate the distraction associated with impaired erectile self-confidence and permit greater ease of achieving orgasm.

Guideline Statement 26

Clinicians should counsel patients with delayed ejaculation that no currently available data indicates that invasive non-pharmacological strategies are of benefit. (Expert Opinion)

Discussion

Given the paucity of effective treatments for DE, some clinicians have explored non-pharmacological strategies such as pudendal nerve release, intracavernosal injections, platelet rich plasma, and surgical interventions. No published, peer-reviewed data exists supporting any of these approaches. Given the risks and potential expense the panel does not recommend use of any invasive procedure for DE outside the context of an ethical board-approved clinical trial in which participants give informed consent for participation in research and are charged no or minimal costs.

Men with penile sensory neuropathy and sensation loss due to surgical trauma, diabetes, chemotherapy, pudendal nerve entrapment may experience DE. Penile vibratory stimulation has been suggested as a potential management strategy in men with DE, particularly in men with a penile sensory deficit. A single cohort study reported on 36 men who had an acquired inability to achieve an orgasm during sexual relations in the previous 3 months in the absence of any penile sensation loss.[242] They were instructed in the use of penile vibratory stimulation. Outcome was assessed by self-report of ease and consistency of orgasm achievement and using the orgasm and satisfaction domains of the IIEF. Assessment was conducted at 3 and 6 months after initiation of therapy. Twenty-six (n=26; 72% of patients) reported "restoration," not otherwise defined, in orgasmic function. These responders reported that orgasm during sexual relations occurred 62% of the time. A statistically and clinically significant increase occurred in the orgasm and satisfaction domains of the IIEF between the baseline visit and the 3-month follow-up visit. (2.3 to 6.75 points and 10.4 to 17.2, respectively). These gains were sustained at 6 months. Given the relative safety of this approach it may be a consideration for select men with DE as part of a comprehensive treatment plan.

Future Directions

Work continues on better means to elucidate the etiology for PE. Assessment of vibrational thresholds, nerve conduction times, somatosensory latency testing, and others are currently useful for research purposes but may in the future have clinical relevance. Improvements in our understanding of the relationship between androgens and ejaculation and orgasm may also permit more nuanced guidance on androgen therapy for ejaculation concerns. Novel molecules, including melatonin, carbon monoxide, and nitric oxide may also have relevance to ejaculation and orgasm that is not completely understood.

Botulinum toxin is a protein and neurotoxin produced by the bacterium *Clostridium Botulinum*. It is a selective blocker of acetylcholine release from nerve endings which blocks neural transmission when injected into muscle.[218] This drug has been widely used as a cosmetic anti-ageing treatment, and as a medical treatment for a diverse range of conditions including neurogenic detrusor overactivity.[264]

Serefoglu and Silay theorized that the repeated contractions of bulbospongiosus and ischiocavernosus muscles during the ejection phase of ejaculation may be inhibited by the injection of botulinum-A toxin.[219] They subsequently demonstrated that percutaneous injection of botulinum-A toxin into the bulbospongiosus muscle bilaterally increased ejaculatory latency in male rats in a dose-dependent manner compared to pre-treatment latency.[220] However, the difference between the post-treatment geometric mean ejaculatory latency of botulinum-A toxin and saline failed to reach statistical significance possibly due to the small sample size and/or the high variability in ELT.

Botulinum-A toxin may be a safe and effective means to prolong ejaculatory latency without affecting other aspects of sexual behaviour. However, dose-ranging Phase II clinical trials of botulinum-A toxin as a treatment for PE in humans were discontinued due to lack of efficacy in interim analysis. Until data become available botulinum-A toxin should not be considered as standard of care in PE.

Modafinil is a wake-promoting agent used for the treatment of narcolepsy with a complex and poorly understood mechanism of action upon dopamine, serotonin, g-Aminobutyric acid (GABA)/glutamate and orexin-containing neurons.[265,266] Several pre-clinical studies support modafinil as a potential treatment for PE.[267-271] An uncontrolled pilot study of on-demand modafinil in treatment-naïve men with lifelong PE reported a modest but significant two-fold change in self-reported IELT and positive PROs.[221] The short-acting modafinil d-isomer is undergoing pre-clinical trials as an investigational drug for the "on demand" treatment of PE.

Oxytocin is a peptide hormone of nine amino acids which facilitates sexual reproduction in mammals.[222] An increasing number of studies report the involvement of central and peripheral oxytocinergic neurotransmission in the ejaculatory process.[223-225] In human males, plasma oxytocin levels are elevated during penile erection and at the time of orgasm.[272,273] Systematic administration of oxytocin decreases the number of intromissions required for ejaculation in young adult rats,[274] and reduces ejaculation latencies and post-ejaculation intervals in older sexually sluggish rats.[275,276] Several pre-clinical studies suggest a potential role for highly selective oxytocin receptor antagonists in the treatment of PE.[277-279]

In a placebo controlled RCT of epelsiban in men with PE, Shinghai et al., demonstrated that 50 mg and 150 mg were well tolerated but did not result in a clinically nor statistically significant change in ELT in men with PE, compared with placebo.[280] The failure of this study to demonstrate efficacy is likely due to the inability of epelsiban to penetrate the blood brain barrier and enter the CNS. The molecular weight of epelsiban is 518.6 Da and exceeds the 400 Da threshold for blood brain lipid membrane permeation.[281]

Cligosoban is a small molecule oxytocin receptor antagonist (MW 419.65 Da) with adequate CNS penetration in pre-clinical studies.[282] A phase IIA double-blind placebo controlled RCT trial in men with lifelong PE demonstrated clinically and statistically significant treatment-related effects for geometric ELT (3.6 fold versus 1.8 for placebo) and the PROs of ejaculation control and ejaculation-related distress.[283] Although a post-hoc exploratory analyses demonstrated a direct dose-response relationship and suggested a potential for increased efficacy when larger doses are administered, a second fixed dose study using higher doses failed to demonstrate statistically significant treatment outcomes.[284]

Oxytocin antagonists are an appealing target for PE therapy given their mode of action and relevance to ejaculation reflexes. Further study and potentially development of agents with different distribution is required to determine if these therapies will have a role in PE management in the future.

With regards to DE, there is a pressing need for additional epidemiological data and development of evidence-based definitions. Novel imaging modalities may play a role in providing clinically usable data in the future.[237] Appropriately designed studies to establish the prevalence and characteristics of DE will enable better designed clinical trials which will provide a more robust evidence basis for management.

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< script type = "text/javascript" > zE(function() { $zopim(function() { $zopim.livechat.departments.filter(''); }); }); // Must set timer in order for chat to load first setTimeout(function() { // Check all departments var depts = $zopim.livechat.departments.getAllDepartments(); var deptsStatus = []; // Create list of dept status for array testing depts.forEach((item, index) => { deptsStatus.push([item.status, item.name]); }) // If no departments are online, keep the widget hidden, otherwise show deptsStatus.forEach((item, index) => { var status = item[0]; var thisDepartment = item[1]; var thisSite = window.location.host; if (status == "online") { // Set department according to routing switch (thisSite) { // Support case "auanet.org": case "www.auanet.org": if (thisDepartment == "Support" && status == "online") { console.log("Show Support Chat Dept"); $zopim.livechat.departments.setVisitorDepartment("Support"); zE.show(); } break; // Help Desk case "thehub.auanet.org": // Double check this dept is available if (thisDepartment == "Helpdesk" && status == "online") { console.log("Show Help Desk Chat Dept"); $zopim.livechat.departments.setVisitorDepartment("Helpdesk"); zE.show(); } break; case "auau.auanet.org": case "www.auau.auanet.org": if (thisDepartment == "Education" && status == "online") { console.log("Show Education Chat Dept"); $zopim.livechat.departments.setVisitorDepartment("Education"); zE.show(); } break; default: } } }); }, 2500);