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Disorders of Ejaculation: An AUA/SMSNA Guideline (2020)

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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

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

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

GUIDELINE STATEMENT 4

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

DISCUSSION

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

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

GUIDELINE STATEMENT 7

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

DISCUSSION

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

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

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

GUIDELINE STATEMENT 11

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

DISCUSSION

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

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

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

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

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

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

GUIDELINE STATEMENT 19

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

DISCUSSION

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

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

GUIDELINE STATEMENT 22

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

DISCUSSION

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

GUIDELINE STATEMENT 24

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

DISCUSSION

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

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

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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