Management Options for Premature Ejaculation and Delayed Ejaculation in Men

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ABSTRACT

Introduction: Many men experience distressing issues regarding the timing of orgasm and ejaculation, such as premature ejaculation (PE) and delayed ejaculation (DE). Despite being highly prevalent, both PE and DE are poorly understood and present a management challenge for sexual medicine specialists.

Aim: To summarize existing data on the medical management of PE and DE.

Methods: A comprehensive literature review pertaining to the management of PE and DE was conducted using PubMed and clinicaltrials.gov for data published up until May 2019. Our focus was on double-blind, placebo-controlled trials and meta-analyses of such studies.

Main Outcome Measure: Peer-reviewed studies on treatment options for PE and DE were critically analyzed for results and methodological rigor.

Results: The peer-reviewed data on PE management continue to evolve. Psychotherapy, pharmacotherapy, and procedural interventions have all been associated with some degree of efficacy. A strong evidence base supports the off-label use of selective serotonin reuptake inhibitors and local anesthetics in PE given consistent increases in ejaculation latency time. Education and mental health assessments remain important components of PE management despite a dearth of peer-reviewed data on these interventions. Numerous treatment strategies have been evaluated for DE; limited data support psychotherapy, pharmacotherapy, and/or penile vibratory stimulation as management options.

Conclusion: A number of management options for PE or DE exist but none has been formally approved by the US Food and Drug Administration. New and novel treatments would be of great value in managing issues regarding the timing of ejaculation/orgasm. **Martin-Tuite P, Shindel AW. Management Options for Premature Ejaculation and Delayed Ejaculation in Men. Sex Med Rev 2020; 8:473–485.**

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INTRODUCTION

Ejaculation and orgasm in men are often conflated but represent distinct physiological events. Ejaculation refers to the emission and expulsion of semen, whereas orgasm is the transient sensation of pleasure often associated with ejaculation.[1] There are numerous types of ejaculatory dysfunction, including premature ejaculation (PE), delayed ejaculation (DE), painful ejaculation, anejaculation, retrograde ejaculation, and post-orgasmic illness syndrome (POIS). Ejaculatory issues are quite common and a source of marked distress to many men and their partners.[1] Despite the numerous types of impairment that may occur in ejaculation response, our understanding of pathophysiological mechanisms remains limited. Furthermore, there are no US Food and Drug Administration–approved treatment options.[2]

The primary aim of this manuscript is to review the definitions, epidemiology, and pathophysiology of disorders of the timing of ejaculation (ie, PE and DE) and to provide sexual medicine specialists with a critical review of management options for these conditions. We include a brief discussion of other male ejaculatory and orgasmic disorders that may be comorbid or conflated with PE and DE.

METHODS

A literature review was performed on PubMed (www.ncbi.nlm.nih.gov) using the key words "premature ejaculation" and "delayed ejaculation" for papers published through March 2019. Peer-reviewed literature relevant to the topic of therapies was

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identified by the team and assessed for inclusion. We focused our review on double-blind, placebo-controlled trials. Clinicaltrials.gov was consulted on May 28, 2019, for active studies on PE and DE management that may not have been published within the time frame of our PubMed search.

PREMATURE EJACULATION

Definitions

Historically, clinical definitions for PE have been limited by the absence of objective, evidence-based criteria.[3] Concern also existed about a failure to distinguish between lifelong (occurring since first partnered sexual encounter) and acquired (presenting after a period of ejaculation latency that was not a clinical concern for the patient) subtypes.[4] The International Society for Sexual Medicine Ad Hoc Committee for the Definition of Premature Ejaculation addressed these critiques in a series of meetings, leading to evidence-based definitions for clinically relevant PE.[4,5] The most recent iteration of the International Society for Sexual Medicine definition, released in 2014, defined PE as a male sexual dysfunction involving "(i) ejaculation that always or nearly always occurs prior to or within about 1 minute of vaginal penetration from the first sexual experience (lifelong PE, LPE) or a clinically significant and bothersome reduction in latency time, often to about 3 minutes or less (acquired PE, APE); (ii) the inability to delay ejaculation on all or nearly all vaginal penetrations; and (iii) negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy."[3] A similar definition of PE was published in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-V), in 2013, with specification that PE includes ejaculation within 1 minute and over which the man feels a lack of sense of control.[6] The DSM-V also includes criteria for the severity (mild, moderate, severe), duration (lasting longer than 6 months), and lack of an explanatory, nonsexual mental disorder.[6] The International Classification of Disease, Eleventh Revision, for Mortality and Morbidity Statistics, published by the World Health Organization in June 2018, incorporates a PE subtype of "unspecified" which lacks further description.[7]

These efforts to define clinical PE reveal opportunities to grow the current evidence base, produce a more inclusive consensus definition, and expand therapeutic options. Waldinger and Schweitzer proposed 2 additional subtypes of PE: natural variable PE (NVPE) and premature-like ejaculatory dysfunction (PELD).[8,9] NVPE is characterized by irregular, inconsistent episodes of early ejaculation or loss of ejaculatory control, whereas PELD (also known as subjective PE, or SPE) involves the perception of early ejaculation despite an intravaginal ejaculation latency time (IELT) that is within the range of population norms.[9,10] These definitions may be considered when the patient has ejaculation-related distress but does not meet evidence-based diagnostic criteria for clinical PE.[8,9]

Current definitions for PE are exclusively focused on rapid ejaculation in the context of vaginal intercourse. Objective data on rapid ejaculation in other sexual contexts (eg, among men who have sex with men or with oral or anal sex) are scant but existent. Epidemiological studies have suggested bothersome early ejaculation does occur among men who have sex with men.[11–13] Further research is necessary to determine the clinical relevance of rapid ejaculation in non-coital sex.[12,14]

Epidemiology

Despite recognition as a clinical issue, the prevalence of clinical PE is ambiguous. Many authors and experts cite a 30% prevalence of PE; this is based on epidemiological studies in which single-item questions were asked about early ejaculation occurring within the past year.[15] The lack of clarifying questions regarding chronicity and distress makes assignment of a PE diagnosis to 30% of these study populations suspect.[16,17] Althof et al[3] evaluated 33 peer-reviewed studies on PE and concluded that 5% was a reasonable estimate for prevalence of clinically relevant APE and LPE. It is important to note that even a rapid ejaculation time does not necessarily indicate clinical PE. A recent Italian study of the general population reported that 12.4% of respondents had IELT less than 1 minute, but this was not universally associated with distress.[18] It is also conceivable that some men who do not meet criteria for LPE or APE may fit the diagnostic criteria for Waldinger's provisional PE subtypes. In a Turkish general population, the prevalence of NVPE was 8.5% and that of PELD was 5.1%.[19] A similar study in China reported an 11% prevalence of NVPE and a 7% prevalence of PELD.[20]

Pathophysiology

Our current understanding of the pathophysiology of PE centers on the neurotransmitters serotonin and dopamine and their roles in the regulation of the sympathetic and parasympathetic nervous systems. Potential contributors to LPE include decreased neurotransmission of serotonin, 5-hydroxytryptamine $(5\text{-HT})_{2C}$ receptor hyposensitivity, and 5-HT_{1A} receptor hypersensitivity.[21,22] Increased recognition of the role of intact lumbar spinothalamic cells in mediating the excitatory and inhibitory signals that determine ejaculation in rats has also influenced parallel research in humans.[23–25]

The Genetics of Sex and Aggression study in Finland suggested that 28% of phenotypic variance in PE may be related to genetics, but a definitive locus was not identified for any PE subtype.[26,27] Extensive research on serotonin transport mechanisms, particularly studies investigating the association of polymorphisms of the 5-HTT promoter region of the serotonin transport gene, *SLC6A4*, has not yet supported an association between lifelong PE risk and serotonin transport polymorphisms.[28–31] An investigation of serotonin transporter gene promoter genotypes and the treatment response to paroxetine by Salem et al[32] did not show statistical significance with any particular polymorphism, although a larger study may shed light on whether genotypes play a role in treatment response.

A smaller body of research on tandem repeats of the dopamine transporter gene, *DAT1*, using the same Finnish dataset found that the 10R10R genotype was associated with fewer thrusts prior to ejaculation but not a significantly shorter ejaculation latency time.[33] Additional research by Jern et al[34] on the association between dopamine and ejaculation in a separate study population with 149 patients with PE did not discover additional polymorphisms associated with PE.[34] A single study using the Finnish dataset identified a significantly elevated risk for PE with a polymorphism of the oxytocin receptor gene, *OXTR*.[35]

Ejaculation latency may be influenced by genetics, but the effect may be minor and/or present in only a minority of men.[26] Future studies should expand to other racial and ethnic groups; it is important that future study populations fulfill criteria for Hardy-Weinberg equilibrium.[36]

Historical data have suggested that PE is also associated with lower urinary tract symptoms, chronic pelvic pain syndrome, tactile hypersensitivity, erectile dysfunction, and hormonal perturbations such as hyperthyroidism or testosterone disorders. The evidence supporting these associations is not particularly robust, but assessment for these disorders is reasonable as a step in clinical management.[3]

TREATMENT

Contemporary management of PE may be classified into 3 primary categories: (i) sexual and behavioral therapy, (ii) pharmacotherapy, and (iii) procedural interventions.

Sexual and Behavioral Therapy for PE

Sex therapy (individual, couple, or group) is an established management option for PE.[37–39] Psychotherapy may be useful as monotherapy or in conjunction with biomedical treatment for PE.[37] The primary aim of most psychotherapy for PE is management of psychological barriers or interpersonal factors that precipitate, prolong, or result from PE.[37] Another common aim of this therapy involves building and enhancing sexual skills related to slowing or halting progressive arousal; an early example of this is the squeeze technique, an exercise first introduced by Masters and Johnson centered on compressing the penis to halt rapidly progressive arousal.[40]

Psychotherapeutic interventions for PE with exercises have shown an 8-fold increase in IELT as well as satisfaction with therapy in comparison to control groups.[41] However, the current evidence base for psychotherapy and appropriate exercises is inconclusive due to wide variation in definition and study methodology.[42–44] Sexual therapy may also be inaccessible for many men due to cost or logistical issues; online therapy options may be useful in the future, given the preliminary success of similar platforms for treatment of erectile dysfunction (ED).[45]

Physical therapy (PT), another approach for PE, requires time-intensive training with specialized professionals.[46] Although the therapeutic protocols differ among studies on PT, approaches generally reinforce awareness and selective contraction of pelvic floor muscles (eg, ischiocavernosus, bulbospongiosus) involved in erection and ejaculation. The intention is to help men recognize and control the ejaculatory reflex through repeated PT sessions.[47–49]

Results of PT for PE are variable across studies. La Pera et al[48] reported resolution of symptoms in 43 of 78 patients with LPE (55%) following extended PT, and Pastore et al[47] reported an increase in mean IELT from 39.8 seconds to 146.2 seconds after PT in 40 men with LPE. As summarized in a new meta-analysis of pelvic floor rehabilitation for PE and ED by Myers and Smith,[46] these published studies for PE have low to moderate methodological quality given the lack of available detail regarding study design or a lack of comparator. More recently, Rodriguez et al[50] published results of a small randomized control trial of 35 men with an analogous therapy focused on the external urethral sphincter. A significant increase in self-reported IELT (from 70.13 seconds to 166.63 seconds) occurred only in the 18 patients who completed treatment with the aid of a masturbation device. To date, only weak evidence suggests that physical therapy interventions for PE are successful, but risks appear low. Accessibility and cost are the primary barriers to this form of therapy for PE.

Acupuncture, a form of traditional Chinese medicine thought to act by neuromodulation through tissue stimulation, has been studied for PE. A randomized controlled study of 120 patients comparing acupuncture, sham acupuncture, and dapoxetine showed an increase in IELT (44.3–87.2 seconds) in the 29 patients receiving acupuncture. Acupuncture was not superior to dapoxetine but had a favorable side effect profile, with no adverse effects reported.[51]

Pharmacotherapy for PE

Selective Serotonin Reuptake Inhibitors

The off-label use of selective serotonin reuptake inhibitors (SSRIs), particularly paroxetine 10–40 mg, sertraline 50–200 mg, fluoxetine 20–40 mg, and citalopram 20–40 mg, is a first-line management strategy for lifelong and acquired PE.[3,52] This well-studied class of drugs enhances serotonergic activity and is associated with delay in ejaculation and orgasm, an adverse event in initial studies of these drugs for management of depression that has been capitalized on for management of PE.[53]

Prior reviews have established daily-dose paroxetine as a superior SSRI for PE management; across studies there was a mean 1,492% increase in IELT in men taking paroxetine.[54] Other SSRIs with demonstrated efficacy included sertraline (mean 790% IELT increase) and fluoxetine (mean 295% IELT increase).[54] A 2019 systematic review and meta-analysis of 19 randomized controlled trials investigating paroxetine for PE confirmed that this agent is more efficacious than at least 2 other SSRIs (fluoxetine and escitalopram) in the treatment of PE.[55] Four randomized controlled trials (RCTs) comparing paroxetine and fluoxetine gave a between-group difference of 0.54

(95% CI, 0.07−1.02; $P = .02$) favoring paroxetine, suggesting that paroxetine more strongly extended IELT compared to fluoxetine.[55] This analysis cites a single RCT of 100 men in Egypt that meets criteria for comparing paroxetine with escitalopram; however, the original RCT showed no significant difference between the SSRIs for any relevant parameter, including IELT.[56] A more recent systematic review and meta-analysis by Zhang et al[55] reported that there was no statistically significant difference in IELT for paroxetine in comparison to sertraline (4 pooled RCTs), tramadol (3 RCTs), dapoxetine (1 RCT), phosphodiesterase-5 inhibitors (PDE5is; 3 pooled RCTs), lidocaine gel (1 RCT), or behavior therapy (1 RCT). Across the 4 pooled RCTs comparing paroxetine and sertraline, paroxetine was shown to be more effective, yet the difference in IELT was not significant.[55]

We can conclude from these data that numerous SSRIs (taken daily or on-demand after a 1-month loading dose) are viable options for management of PE. Because paroxetine is superior or non-inferior to other available SSRIs, it should be considered as an agent of choice barring contraindications to its use.[3] Common adverse effects of SSRIs include fatigue, yawning, nausea, and diarrhea, with resolution within 2 to 3 weeks.[57]

Dapoxetine is an SSRI with a short half-life of 19 hours that has been approved in many countries for on-demand treatment of PE. Dapoxetine is taken at doses of 30 mg and 60 mg 1 to 3 hours prior to sexual intercourse.[57,58] An integrated analysis of 5 phase III trials involving 6,081 men showed a 2.5- to 3-fold increase in IELT with both dosages of dapoxetine.[58] Adverse effects reported in these phase III trials include nausea (17.3%), diarrhea (9.4%), headache (7.9%), somnolence (3.9%), fatigue (3.9%), and insomnia (3.8%).[58] McMahon et al[58] found rare severe effects related to sexual function (eg, erectile dysfunction in 2.6% of participants using dapoxetine 60 mg prn) and no notable changes in mood.

Additional evidence published since these trials has supported the safety and tolerability of dapoxetine. In a 3-period crossover study of 23 healthy subjects, Kim et al[59] found no interaction and no adverse events between dapoxetine 60 mg and the PDE5i udenafil 200 mg. A larger observational study of 10,028 men with PE, which enrolled 6,712 men with dapoxetine 30 mg or 60 mg, found a lower overall incidence of adverse events (12.0%) compared to the earlier phase III trials, with nausea (3.1%) and headache (2.6%) being the most common adverse events among dapoxetine users.[60] DA-8031, a novel SSRI developed in order to produce a more tolerable and efficacious SSRI for PE, failed in human trials.[61,62]

Tricyclic Antidepressants

Clomipramine, a mixed serotonin-norepinephrine reuptake inhibitor, has been shown to be efficacious (4- to 6-fold increase in IELT) and safe in off-label daily or on-demand use.[54,63] At dosages of 12.5 to 50 mg, clomipramine enhances both serotonergic and noradrenergic transmission through the inhibition of transmitter reuptake into presynaptic neurons.[63] Consistent with prior research, a recent multicenter, randomized, double-blind study on clomipramine 15 mg in 159 men in Korea found a significant fold change in IELT in comparison to placebo (4.40 vs 2.68; $P < .05$). Nausea (15.7%) and dizziness (4.9%) were the most common adverse effects.[64]

Topical Anesthetics

Local anesthetics with evidence of efficacy in treatment of PE include lidocaine, prilocaine, and benzocaine. These medications are available in gel, cream, or spray forms for application to the glans penis 5 to 10 minutes prior to sexual intercourse. Anesthetics reduce the sensitivity of the glans penis with the aim to partially inhibit the reflex arc involved in ejaculation.[3] Previous evidence on mixed lidocaine-prilocaine sprays from a randomized sample of 300 men across Europe suggested a 6.3-fold IELT increase.[65] In comparison to placebo, the anesthetic spray was associated with significant improvements in ejaculation control (7-point difference) and satisfaction (6-point difference) as assessed by the Index of Premature Ejaculation.[65] Studies on lidocaine-prilocaine spray for PE are ongoing.[66]

A 2016 systematic review and meta-analysis of anesthetics highlighted 2 RCTs (N = 49) showing a pooled mean difference of 6.44 for IELT when comparing lidocaine-prilocaine cream to placebo.[67] One RCT of 144 men found lidocaine gel to be more effective than paroxetine (between-group difference of 0.83 minutes) and sildenafil (between-group difference of 1.53 minutes), but not compared to tramadol (between group-difference of 1.21 minutes).[68] Common effects of anesthetics in studies include mild loss of sensitivity with numbness and increased genital irritation in partners.[65,68,69] Carson and Wyllie[69] reported ED (5.4%), penile hypoesthesia (5.4%), and vulvovaginal burning in partners (7.8%) as side-effects of this therapy. It is recommended that men wipe away anesthetic prior to sexual activity to minimize the potential for severe numbness and/or partner irritation; condom use may also be considered to minimize partner transfer.

Phosphodiesterase-5 Inhibitors

PDE5is are primarily used for the management of ED but have also been used off-label for PE as monotherapy or as an adjunct to SSRIs.[3,52] PDE5is selectively inhibit cyclic guanosine monophosphate−specific phosphodiesterase type 5. In the context of PE, these drugs may play a role in reducing performance anxiety and enabling men to focus on modulating arousal with less fear of losing their erection.[57,70,71] A recent meta-analysis of 15 RCTs showed variable results, highlighting the lack of evidence and significant between-trial heterogeneity for 6 RCTs in which PDE5is were combined with SSRIs.[72] Supportive findings in a comparative study of 150 men with LPE found a 145% increase in IELT for tadalafil and paroxetine in combination vs 94% increase for paroxetine alone.[73] Despite

mixed results in improving IELT, PDE5is have shown improvement compared to placebo in ejaculatory confidence (2.2 vs 1.9), ejaculatory control (1.8 vs 1.5), and sexual satisfaction (3.1 vs 2.8) on the Index of Premature Ejaculation questionnaire.[74] Adverse effects of PDE5is in PE management include headache (15%), flushing (15%), and dyspepsia (5%).[74]

Tramadol

The opiate analgesic tramadol has been extensively studied for PE treatment, as its dual activation of opioid receptors and inhibition of serotonergic and noradrenergic reuptake suggests strong potential efficacy as a PE treatment.[75,76] A meta-analysis of RCTs (N = 721) found a pooled mean difference in IELT of 1.24 minutes when comparing tramadol to placebo. Tramadol was not conclusively superior to paroxetine, sildenafil, or topical anesthetics.[75] Tramadol appears to be an efficacious treatment, but given its opiate-like properties some experts have expressed concern about its potential for abuse or addiction.[75,76] Other significant adverse effects of opiates in humans include ED, constipation, nausea, headache, somnolence, and serotonin syndrome.[75]

Other Pharmacotherapy

A study of on-demand oral caffeine consumption (100 mg 2 hours before intercourse) by mouth in 40 men demonstrated significant post-treatment difference in IELT (314 vs 144 seconds) and sexual satisfaction (97 vs 77 on the index of sexual satisfaction) despite an unclear mechanism of action.[77] The eugeroic drug d-modafinil has been explored for on-demand use in the context of LPE given its propensity to decrease dopaminergic and increase serotoninergic activity.[78,79] A recent case report of modafinil with one individual saw an increase in IELT from 40 seconds to 15 minutes, a 2-point improvement in ejaculatory control on the Premature Ejaculation Profile questionnaire, as well as few adverse effects beyond initial dyspepsia and insomnia. Large-scale studies are required to establish whether this drug may be a viable option for PE management.[79]

Investigational Pharmacotherapies for PE

A novel class of treatments under investigation for PE are oxytocin antagonists, particularly those that selectively impact central oxytocin receptors.[3,80] Double-blind, placebo investigations of epelsiban, an oxytocin antagonist, at 50 mg and 150 mg have found favorable safety profiles but only minor increases in IELT (0.59−0.69 minutes for 150 mg).[81] The most common adverse effect was headache.[81] A randomized placebo-controlled trial of cligosiban, another oxytocin receptor antagonist, indicated that 44% of treated patients reported improvement compared to 11% of placebo-treated patients. Mean IELT increased 3.6-fold in treated men (95% CI, 2.2−5.0) compared to 1.8-fold in men given placebo. As of this writing, these data were reported on clinicaltrials.gov but have not been subjected to external peer review.[82]

Resiniferatoxin, a naturally occurring chemical that serves as a chemical analog to capsaicin, has been studied as a possibility for PE treatment, given its ability to reduce the sensitivity and excitability of peripheral sensory nerves through the secretion of the polypeptide substance P.[83] An initial placebo-controlled study in 41 patients showed significant increases in mean IELT (1.29−4.55 minutes) only in participants with concomitant redundant prepuce (n = 11).[83] Adverse effects of discomfort and dysuria were reported but not quantified.[83]

Injection of botulinum-A toxin (0.5 or 1 unit) into the bulbospongiosus muscle of 22 rats significantly increased latency to ejaculation when compared to a saline vehicle.[84] A phase II multicenter study of this agent in humans was discontinued as of October 2018.[85] Intracavernosal injection therapy with vasodilators such as phentolamine and/or papaverine (common therapies for ED) has not shown efficacy for PE, although such treatment does facilitate maintenance of erections even after ejaculation.[86]

Procedures for PE

A study of hyaluronic acid injection into the glans penis was performed in 30 men with PE with initial IELT improvement (34−120 seconds) that decreased over time.[87] Selective dorsal neurectomy, a form of penile nerve ablation to reduce glans hypersensitivity recently investigated by Liu et al,[88] produced a significant increase in IELT of 218.7 seconds from baseline in a subgroup of 48 men with LPE with few postoperative complications. This study population is notable for all participants initially presenting for circumcision due to redundant foreskin, which may limit the generalizability of this study.[88] Surgical procedures for PE should be considered with caution due to their potentially irreversible nature; these are likely best performed in a clinical trial setting.

DELAYED EJACULATION

Delayed ejaculation is poorly understood and ambiguously defined. Typically, the term DE is used to describe delay of both ejaculation and orgasm. Current definitions highlight personal distress from inability to ejaculate despite sufficient stimulation and desire.[89,90] The DSM-V criteria for DE include delayed ejaculation/orgasm for approximately 75−100% of sexual activity with a partner for at least 6 months.[6] Similar to PE, there are distinctions among lifelong, acquired, and situational DE.[6] In these suggested guidelines, there is no strong evidence base for a specific time demarcation for DE. An empiric time-based definition of IELT of 25 minutes or more, corresponding to 2 standard deviations above the mean derived from population-based studies, has been proposed for DE.[53] A prevalence of about 1% for lifelong DE and around 4% for acquired DE has been estimated, but the evidence basis is limited.[89]

The etiology of DE includes both biological and psychological factors. Biological factors may include nerve lesions, congenital urogenital duct abnormalities, hypothyroidism, and systemic disorders such as diabetes mellitus, spinal cord injury, or multiple

sclerosis, which may lead to neuropathy.[57,91] Age and associated declines in testosterone, tactile sensitivity, and tissue atrophy may also play a role.[90] Medications, particularly antidepressants (SSRIs), antipsychotics, and opioids may contribute. Psychological causes of DE involve conflicting feelings, fear, and/or anxiety manifesting during sexual activity due to histories of repression, trauma, abuse, or previous performance difficulties.[90] Perelman and Rowland[92] proposed that idiosyncratic masturbation (masturbation techniques that produce stimulus intensity that is difficult to replicate in a sexual encounter with a partner) or desire for stimuli that are not provided by the current partner (eg, paraphilic interests) may also be a risk factor for DE.[92]

Management of DE focuses on understanding current medications, conditions, and exposures; modifying lifestyle and sexual habits that may affect ejaculation; and encouraging exploration of interpersonal and psychological issues that affect sexual relationships. Contemporary treatment for DE relies on evidence from 3 domains: (i) psychological and sexual therapy, (ii) pharmacotherapy, and (iii) other approaches. Treatment specific to anejaculation is noted within these domains.

Psychological and Sexual Therapy for DE

Psychotherapy as a primary approach to DE management focuses on personalized assessment of individual and relationship issues influencing ejaculation. Despite a limited evidence base, common approaches to psychotherapy for DE aim to destigmatize the condition, promote communication with partners, provide appropriate sex education, and reduce overall anxiety related to sexual activities. The intention of these interventions is to help the patient successfully reach ejaculation and orgasm, but adaptation and acceptance are also acceptable goals.[89,92,93] Efforts can be encouraged between willing patients and partners to engage in role playing activities and/or incorporating alternative sexual practices.[57] Part of this therapeutic approach to DE can involve individual work through masturbatory retraining, an activity designed to condition men to respond sexually to stimuli they are likely to encounter with partnered sex. Men with DE can adjust personal techniques, amount of friction, and overall pace of masturbation in a lower demand setting as a form of preparation for sexual activities with partners.[90] Some men may require advice on limiting frequency of masturbation and concomitant use of erotic materials.[90] The success of psychotherapy for DE remains difficult to quantify given the lack of standardization of terminology and endpoints and absence of large-scale studies.

Pharmacotherapy for DE

Cabergoline

Cabergoline is a dopamine-2 receptor agonist and 5-HT_{2B} receptor agonist used in the setting of hyperprolactinemia to suppress prolactin levels via dopamine receptors.[93] Given the role of dopamine in ejaculation, cabergoline has been studied as a treatment for DE. In an early study with 10 healthy men, administration of cabergoline 0.5 mg decreased serum prolactin levels and improved sexual drive (as measured by the acute sexual experience scale designed by the study researchers), and increased prolactin levels induced by protirelin (a synthetic analog to thyroid-stimulating hormone) led to extended ejaculation latency (without specification by how much).[94] A retrospective pilot analysis of 131 men with DE and anorgasmia given cabergoline 0.5 mg twice weekly showed subjective improvement in orgasm in two-thirds (66.4%) of participants; ejaculation latency time was not explicitly quantified.[95] Adverse effects of cabergoline were not reported in these studies, but at therapeutic levels this medication has been associated with nausea, headache, and gastrointestinal upset.[95] Cabergoline also carries a risk of cardiac valve regurgitation (incidence rate ratios of 4.58—4.90 when compared to other anti-Parkinsonism drugs) noted from 13 collected studies examining extended use of cabergoline in patients with Parkinson's disease.[96] Further research, ideally with placebo control, is needed with to determine the efficacy and safety in DE patients.

Alpha$_1$-Adrenergic Agonists

Agents with α_1-adrenergic activity, such as pseudoephedrine, midodrine, imipramine, and ephedrine, have been investigated for treatment of abnormalities of ejaculation given the presence of α_1 receptors across the urogenital system.[93] Alpha$_1$-adrenergic agents lead to smooth muscle contraction of the vas deferens and prostate, promoting ejaculation.[93] Studies of α agonists for DE or anejaculation due to spinal cord injury (SCI) have been completed with midodrine (7.5—30 mg) in combination with penile vibratory stimulation for enhanced autonomic stimulation, with 102 of 158 participants (64.5%) experiencing ejaculation.[97] A smaller study of patients with SCI and anejaculation (N = 20) did not replicate earlier findings, as only one patient using midodrine experienced ejaculation.[98] Although Soler et al[97] did not discuss adverse effects of these agents, Leduc et al[98] noted a mean elevation of 16.2 mm Hg in systolic blood pressure in the 10 participants using midodrine but no adverse effects of elevated blood pressure.[97,98] As the majority of studies to date have focused on ejaculation (not necessarily orgasm) and men with SCI, the role of these drugs in non-SCI men with generalized DE remains ambiguous.

Bupropion

Buproprion is an atypical antidepressant that inhibits dopamine and norepinephrine reuptake. Rat studies show that high doses of buproprion enhance epididymal tract contractions and facilitation of ejaculation, likely due to inhibition of norepinephrine reuptake.[99] A 2011 study of 150 mg bupropion-SR in 19 men with lifelong DE showed a significant decrease in mean IELT from 30.6 to 22.8 minutes, as well as improved control over ejaculation reported by 4 patients.[100] Adverse effects of buproprion reported in this small study include dry mouth (21.1%), headache (15.8%), and nausea (15.8%).[100]

Buspirone

Buspirone is a dopamine-2 receptor agonist and 5-HT_{1A} receptor antagonist that is thought to reduce the threshold required for ejaculation primarily through decreased serotonergic activity.[101−103] Early retrospective research with 39 men living with depression showed limited improvement in sexual dysfunction in 11 of 16 men with likely SSRI-induced sexual dysfunction (incorporating complaints of reduced libido and delayed orgasm), but the nature of improvement was not disclosed.[104] In a study population of 117 men and women taking SSRIs for depression in which 40% of participants reported one component of sexual dysfunction (reduced libido, ejaculatory dysfunction, or orgasmic function), Landen et al[105] found improvement of orgasmic function for 58% of participants with buspirone 20−60 mg, although the effect was more pronounced in women. Given the limited population of 12 men with orgasmic dysfunction in this study, with only few men reporting improvement in orgasmic function with buspirone, these data must be interpreted with caution. Adverse effects of buspirone include drowsiness and dizziness.[105]

Oxytocin

Oxytocin is a naturally occurring neuropeptide known to mediate physiologic ejaculation.[93] Two studies limited to healthy men (without sexual dysfunction) administered oxytocin prior to masturbation have been performed. Walch et al[106] exposed 49 healthy men to 16 IU of oxytocin intranasally prior to masturbation but did not find a statistically significant difference in time to ejaculation in comparison to 49 control participants. A smaller crossover study of 10 healthy men exposed to 24 IU of oxytocin vs placebo and prompted to masturbate reported that ejaculation latency was 1 minute shorter in the oxytocin-treated patients (5.3 vs 6.3 minutes).[107] Given that these studies were performed in healthy men, their applicability to men with DE is unclear.[106,107] Adverse effects of intranasal oxytocin include flushing, headaches, and report of a strange taste.[106,107]

Testosterone

Testosterone replacement has been studied for DE in the setting of androgen deficiency. An association has been established between hypogonadism and DE, and androgen receptors are present on urogenital smooth muscle.[108−110] One double-blind, multicenter randomized study designed to study the role of testosterone in modulating multiple forms of ejaculatory dysfunction did evaluate for improvement in delayed ejaculation as a secondary objective.[111] Testosterone (60 mg of 2% solution) administered to 66 androgen-deficient men with DE did not result in a significant improvement compared to placebo in patient surveys.[111] Adverse effects of testosterone in this study included 3 of 66 patients experiencing increases in hematocrit above 54%.[111]

Bethanechol

Bethanechol has muscarinic receptor agonist activity as well as mixed adrenergic effects.[112] Bethanechol 20 mg was investigated in a double-blinded study with 12 psychiatric patients living with DE induced by clomipramine. Bethanechol administration was associated with improvements in orgasmic function (as assessed by a visual analog sexual function scale) in 9 out of 10 participants who completed the study; no data were provided on ejaculation latency time.[112] No adverse effects were reported in this small study, although a later review of DE mentions diarrhea, cramps, and diaphoresis as potential adverse events associated with this medication.[93,112]

Yohimbine

Yohimbine is a naturally occurring alkaloid that may facilitate ejaculation through a α_2-adrenergic receptor effect (facilitating norepinephrine release) and a 5-HT_{1A} agonist effect, which is associated with reduced ejaculation latency.[113−115] A study of yohimbine 20 mg in 29 men with known orgasmic dysfunction led to successful orgasm through masturbation or sexual intercourse in 55.2% of participants; no data were provided on ejaculation latency time.[116] Adverse effects of yohimbine include agitation, elevated blood pressure, heart palpitations, and nausea.[116]

Amantidine

Amantadine hydrochloride inhibits the *N*-methyl-D-aspartate receptor and reduces glutamate-mediated excitation.[117] Amantadine also enhances dopaminergic activity, with preliminary research in rats demonstrating increased sexual response and decreased ejaculation latency.[118−121] However, these effects have not been reproduced in human research, even in populations with antidepressant-induced orgasm dysfunction.[93]

Cyproheptadine

Cyproheptadine is a first-generation antihistamine with antiserotonergic and anticholinergic properties.[122] Animal research suggests a prosexual effect of cyproheptadine through stimulation of the vas deferens or its antiserotonergic effects.[123−125] Limited research on cyproheptadine includes a retrospective case review of 596 patients with SSRI-induced sexual dysfunction that noted improvement by 48% of 25 patients receiving cyproheptadine to reverse medication-induced sexual dysfunction.[126] Adverse effects include sedation and weight gain.[126]

Other Agents

Apomorphine, quinelorane, anandamide, and reboxetine have received less attention in the setting of DE management. Apomorphine has non-selective dopamine receptor agonist activity as demonstrated in rats, but has not been convincingly

studied for use in delayed orgasm.[127–130] Quinelorane has similar dopamine agonist activity, with research pointing toward a pro-ejaculatory effect in rats with the side effect of reduced erections.[131] Anandamide, a cannabinoid receptor agonist, demonstrates increased acceleration to ejaculation in animal research, suggesting a further role of the endocannabinoid system in sexual behavior.[132–134] Reboxetine, a selective noradrenaline reuptake inhibitor, was found to bring about spontaneous ejaculation in a 39-year-old man with depression and has been proposed as a tool to reverse SSRI-induced DE.[135]

Other Approaches to DE

Penile vibratory stimulation (PVS), used for sperm retrieval for men with SCI who are unable to ejaculate through masturbation or coitus, has been explored as an adjunct treatment for DE or anejaculation. Application of PVS to the ventral penis and frenulum stimulates afferent nerves involved in the ejaculatory reflex.[136] In a study of 36 men with self-reported anorgasmia for at least 3 months, PVS helped 62% of participants reach orgasm in the setting of sexual intercourse based on responses to the International Index of Erectile Function.[136] As mentioned previously, a study combining midodrine with PVS to increase autonomic stimulation in 158 men with SCI led to ejaculation in 64.5% of patients.[97]

OTHER EJACULATORY AND ORGASMIC DISORDERS

Retrograde ejaculation is the reflux of some or all semen into the bladder due to the inability of the bladder neck to sufficiently close during ejaculation. This failure of the bladder neck can result from congenital anatomic abnormalities, traumatic or surgical injuries, pharmacologic side-effects, or neurovascular disruption from diabetes.[137] Surgical management of retrograde ejaculation has included collagen injection into the bladder neck, which in a small study of 24 diabetic patients led to an average increase of 0.7 mL in semen volume.[138] Medical management of retrograde ejaculation includes use of sympathomimetic and anticholinergic agents to enhance bladder neck tone, similar to the use of α_1-adrenergic agents to promote ejaculation in DE. Early research efforts involving diabetic patients with retrograde ejaculation that tested both imipramine 25 mg twice a day and pseudoephedrine 120 mg twice a day, individually and in combination, showed successful antegrade ejaculation in 16 of 33 patients (61.5%) when using both agents.[139] Recent research following 20 men with retrograde ejaculation showed that pseudoephedrine 60 mg, given every 6 hours the day prior to sperm analysis and twice the day of sperm analysis, led to some improvement in 14 (70%) patients when monitoring ejaculate volume and total sperm count in antegrade ejaculate.[140]

Unpleasant or unsatisfactory sensation with ejaculation summarizes another category of disorders, including both painful ejaculation (dysejaculation) and ejaculatory anhedonia. The prevalence of these disorders is unclear. Painful ejaculation (pain in the genitals during or immediately following ejaculation) is rare but significantly more common in patients with chronic pelvic pain.[141,142] Ejaculatory pain is associated with a range of other disorders, including sexually transmitted infections, prostate cancer, and psychological issues. When an underlying entity may be culpable, treatment should focus on the underlying cause.[141,142] Ejaculatory anhedonia is a rare condition where ejaculation proceeds without pleasure or enhanced sensation. Ejaculatory anhedonia appears most common in the setting of a hormonal or metabolic imbalance, psychological abnormality, or disruption from medications such as SSRIs.[141]

POIS is a rare condition with fewer than 50 cases identified since 2002. POIS is associated with distressing somatic symptoms (eg, flu-like symptoms, fatigue, headache) occurring at or shortly after ejaculation. An autoimmune/allergic mechanism has been proposed as one potential etiology for POIS. Hormonal issues and/or psychosomatic problems are also potentially involved. There are no established treatment options for POIS, but antihistamines or other allergy-based treatments may have utility.[143]

CONCLUSION

Disorders such as PE and DE remain a burden on an unknown but significant number of individuals. No unifying factor has yet been able to fully explain the etiology of either ejaculatory dysfunction, and no management strategy has been universally agreed upon as the standard of care for either disorder. Although high-quality evidence for PE pharmacotherapy has emerged, particularly regarding SSRIs and topical anesthetics, further rigorous research is necessary for any formal approval in the United States. Current evidence for pharmacologic, psychological, or alternative treatments of both PE and DE otherwise remains medium or low quality, often due to limited sample sizes or underwhelming efficacy, and the availability, uptake, and adherence of off-label treatment remains limited by significant costs and known adverse effects.

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