Ejaculatory Disorders

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Introduction

The normal male sexual cycle consists of four stages: desire, arousal, orgasm, and resolution. As Masters and Johnson originally reported, each of these stages is associated with distinct physiological changes in the male [1]. Ejaculation, which normally occurs during the orgasm phase, is a highly complex, integrated process essential for the normal delivery of semen into the female reproductive tract during intercourse. Ejaculation disorders can lead to impaired reproductive potential in men and may necessitate the use of a variety of advanced diagnostic and therapeutic maneuvers. The impact of ejaculatory dysfunction is not confined to detrimental effects on men trying to achieve a pregnancy, as a recent study by Rosen et al. showed [2]. In a survey of 12,815 US and European men aged 50 years or older, the authors found that ejaculatory disorders are common, affecting 30.1 % of men between 50 and 59 years of age. A majority (50.2 %) of these affected men reported bother due to their ejaculatory problems. The authors noted that despite the pervasive focus among many clinicians on erectile dysfunction when assessing a patient's sexual health, ejaculatory problems are almost as common and should also be considered. For these reasons, physicians should be capable of identifying and treating the broad spectrum of ejaculatory disorders; this is essential in order to effectively care for the large numbers of affected men.

The Physiology of Ejaculation

Ejaculation in human men occurs simultaneously with orgasm. The concurrent timing of ejaculation with the rewarding sensory experience of orgasm, from an evolutionary perspective, serves to facilitate sexual behavior and human reproduction [3]. Despite the close temporal link between orgasm and ejaculation, these are two distinct and unique physiologic events. Orgasm is largely a central nervous system process that can be generated by cerebral stimulation without any accompanying genital input [4]. Thus, it is possible for men to experience orgasm in the absence of ejaculation. Clinically, this is illustrated in men who have undergone radical retropubic prostatectomy, with surgical extraction of

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their ampullary vas deferens, seminal vesicles, and prostate gland. Despite the absence of these accessory sex glands that play a central role in ejaculation, patients who have undergone radical prostatectomy are typically capable of achieving orgasm postoperatively [5].

Ejaculation consists of two phases: emission and expulsion. Each phase is coordinated by anatomical structures functioning together in a highly integrated fashion and is separately discussed below.

Emission Phase

The anatomical structures involved in emission include the epididymis, vas deferens, seminal vesicles, prostate gland, prostatic portion of the urethra, and bladder neck. These structures have both sympathetic and parasympathetic innervation with nerve fibers that arise predominately from the pelvic plexus. These nerve fibers are located in the retroperitoneum, traveling alongside the rectum and also lying posterolateral to the seminal vesicles [6]. Pelvic plexus nerve fibers come superiorly from the hypogastric and pelvic nerves, and inferiorly from the caudal paravertebral sympathetic chain [7]. Emission is initiated when afferent stimulatory input, primarily arising from sensory fibers within the glans penis, is integrated at the level of the spinal cord [8]. Sympathetic nerves (T10-L2) mediate the release of several neurotransmitters, including norepinephrine, causing epithelial cell secretion and smooth muscle cell contraction throughout the excurrent ductal system [9]. As a result, accessory gland secretions are admixed with spermatozoa and ejected into the posterior urethra.

Expulsion Phase

The anatomical structures involved in seminal expulsion include the bladder neck, urethra, and striated pelvic muscles. Expulsion is a spinal cord reflex triggered once inevitability, or "the point of no return," is reached during sexual activity. During expulsion, the bladder neck smooth muscle fibers, under sympathetic fiber stimulation, forcibly contact to prevent retrograde ejaculation. Next, the striated pelvic floor muscles, in particular the ischiocavernosus and bulbocavernosus muscles, contract in an intermittent, rhythmic fashion, and the external urethral sphincter relaxes. While these muscles are innervated solely by the somatic nervous system (S2–4), the expulsion phase of ejaculation does not appear to have any component of volitional control. In the setting of tight bladder neck contraction, the series of striated pelvic muscular contractions leads to antegrade propulsion of semen through the prostatic, bulbar, and penile urethra and out the urethral meatus. To date, the specific trigger for the expulsion phase has not been clearly elucidated. Early work in a rat model suggested that the presence of semen in the bulbous urethra is the predominant factor that triggers seminal expulsion [10]. Subsequent works describe the presence of a spinal ejaculatory generator that leads to the expulsion of seminal fluid once a critical level of spinal activation has been achieved [11]. The spinal ejaculatory center is believed to integrate stimuli from peripheral and central sites, with efferent output through both parasympathetic and somatic pathways [12]. In 2002, Truitt and Coolen reported that neurons having a role in generating ejaculation are located within lamina X and the medial portion of lamina VII of lumbar segments 3 and 4. These neurons receive descending input from the nucleus paragigantocellularis, the medial preoptic area, and the paraventricular nucleus of the hypothalamus, each providing supraspinal modulatory effects on the spinal ejaculatory generator [13]. While descending cortical input may influence ejaculation, it is not essential for ejaculation to occur. Men with complete spinal cord transection superior to the tenth thoracic segmental level (superior to the location of the spinal ejaculatory generator) exemplify this point; in these men, the ejaculatory reflex is typically still feasible. Penile vibratory stimulation is routinely used in such patients to induce the ejaculatory response for reproductive purposes, in order to collect sperm for assisted reproductive tech-

niques, such as intrauterine insemination or in vitro fertilization. The intact function of the spinal ejaculatory generator neurons is essential for normal ejaculatory function, as their ablation leads to the complete loss of ejaculatory function [12].

Premature Ejaculation

Premature ejaculation (PE) is a highly prevalent condition; based on data from the National Health and Social Life Survey, this condition affects 21 % of men between 18 and 59 years of age in the USA [14]. This disorder is classified into two categories: primary PE, which is present from the time a male first becomes sexually active and secondary PE, which is acquired later in life.

Etiology

The specific cause of PE is not known. A number of etiologies have been proposed, including a variety of psychological and organic causes. Dunn and colleagues performed a cross-sectional population survey in 1999 and found that anxiety was strongly associated with the presence of PE. While the authors acknowledge that the direction of this and other associations from their study need to be clarified, their results suggest that psychological factors such as anxiety could possibly have a causative role in sexual problems such as PE [15]. In contrast to psychosexual causes, organic causes have also been postulated to cause PE. Waldinger et al. proposed that PE is a neurobiological disorder due to serotonergic hypoactivity.

Studies of male rats have shown that serotonin (5-hydroxytryptamine or 5-HT), and various serotonin receptors, play a role in the process of ejaculation [3]. Activation of 5-HT_{1B} and 5-HT_{2c} receptors delays ejaculation, while activation of 5-HT_{1a} receptors facilitates ejaculation. Some authors have related decreased central serotonergic activity (increased 5-HT_{1a} sensitivity or decreased 5-HT_{2c} sensitivity) to PE.

Diagnosis

One of the first definitions for PE was offered by Masters and Johnson, who described it as the inability of the male partner to delay ejaculation long enough for the female partner to achieve orgasm 50 % of the time [16]. Since that time, the definition has evolved. The Diagnostic and Statistical Manual of Mental Disorders (DSM) is the American Psychiatric Association's classification and diagnostic document. While the DSM-5 was published in May 2013, the DSM-IV-revised version 4 (DSM-IV-TR) was the document used as a reference in many of the seminal studies regarding PE. The DSM-IV-TR highlights the individual and interpersonal distress caused by male climax earlier than desired by the male. The key aspects of the DSM-IV-TR definition include:

1. Reduced control over ejaculation.
2. A decrease in the patient's and/or partner's satisfaction with sexual intercourse.
3. Distress or bother in the patient and/or partner regarding the PE.

This DSM-IV-TR definition has been widely utilized clinically, and the Premature Ejaculation Diagnostic Tool (PEDT) is a five-item questionnaire developed specifically to apply the DSM-IV-TR criteria for PE. In 2006, Waldinger and Schweitzer reported on the limitations of the DSM-IV criteria for PE diagnosis, noting that it resulted in a low, positive predictive value [17]. Symonds et al. subsequently published an article arguing the opposite, stating the PEDT is a reliable and valid PE diagnostic tool [18].

Many investigators favor the use of intravaginal ejaculation latency time (IELT) to diagnose PE. IELT is defined as the time from vaginal intromission to the onset of ejaculation [19]. Advantages include that IELT is, at least in theory, a reproducible, objective measure. However, a 2005 article by Patrick et al. highlighted some of the limitations of IELT [20]. The authors assessed 207 men with PE and 1380 men without PE. At the time of the first study visit, subjects were asked to estimate their own IELT. After this visit, the patient and his

partner were provided with a stopwatch and journal in which to document each episode of sexual intercourse. The IELT was measured and recorded by the female partner. For men with PE, the median measured IELT was 1.8 min, while the mean estimated value was 2.0 min. For men without PE, the median measured IELT was 7.3 min, while the mean estimated IELT was 9.0 min. This study highlights the fact that men with and without PE tend to overestimate their IELT, and it also sheds light on the time of ejaculation in both normal men and men diagnosed with PE [20]. While no firm IELT defining PE has been determined, some authors consider an IELT < 2 min as characteristic of PE.

Normative IELT data have been provided by a recent multinational, community-based, age-ranging study using IELT assessed by stopwatch [21]. The authors found that IELT decreased with age and varied among countries. The distribution of IELT was positively skewed, with a median value of 5.4 min (0.55–44.1 min). Waldinger et al. suggested that men with an IELT < 1 min (0.5 percentile of subjects) have "definite" PE, while men with IELT's 1–1.5 min (0.5–2.5 percentile of subjects) have "probable" PE [22].

The Sexual Assessment Monitor is a new device developed by Dinsmore and colleagues to measure the time from the start of vibration to ejaculation. This device has been shown as safe and effective, and has been validated to collect IELT data in both healthy volunteers and men with PE [23].

In 2003, the Second International Consultation on Sexual Dysfunction (ICSD) met to develop evidence-based guidelines for a variety of disorders of sexual function. At this meeting, PE was defined based on three criteria:

1. Brief ejaculatory latency.
2. Loss of control over ejaculation.
3. Psychological distress to the patient and/or his partner [24].

The specific definition of PE generated at this meeting was, "ejaculation with minimal stimulation and earlier than desired, before or soon after penetration, which causes bother and distress and over which the sufferer has little or no voluntary control [25]." While the ICSD noted that men with IELT < 2 min qualify as having PE, they stipulated that diagnostic criteria required all three components: decreased IELT, inability to delay/control ejaculation, and marked associated distress over their condition. The Fourth International Consultation on Sexual Medicine will be held in June, 2015 in Madrid, Spain and will be hosted by the International Society of Sexual Medicine.

In 2004, the American Urological Association published "AUA Guideline on the Pharmacologic Management of Premature Ejaculation" [26]. This document was reviewed and the validity confirmed by the AUA in 2010. The panel members conducted a literature review and found a lack of standardization in PE studies, with a wide variety of PE definitions, study criteria, and physiological measurements. The panel determined that a meta-analysis was thus inappropriate, particularly in consideration of the variety of PE outcomes measures and populations studied. The panel's recommendations were thus developed based on consensus combined with a review of the limited evidence available.

The guidelines' first recommendation states, "The diagnosis of PE is based on sexual history alone. A detailed sexual history should be obtained from all patients with ejaculatory complaints." The authors highlighted the importance of eliciting a number of clinical factors from the patient, including the frequency and duration of PE, the degree of stimulation resulting in PE, the impact of PE on sexual activity, factors that exacerbate or alleviate PE, and the frequency and nature of sexual activity. The guidelines stipulate that special laboratory or physiological testing is *not* indicated unless the history or physical exam reveals the presence of other complicating medical factors in need of additional investigation.

Treatment

Therapies for PE include psychological, behavioral, and pharmacological approaches. In general, men with lifelong PE likely have lower ejaculatory thresholds compared to unaffected men, and thus may benefit most from medical

therapies [27, 28]. In contrast, men with a history of acquired PE are more likely to be better treated with cognitive or behavioral therapy [29]. Among the psychological approaches, psychotherapy has been reported as a primary therapy, but there is a lack of well-designed clinical trials assessing the efficacy of this intervention.

Behavioral Techniques

Behavioral techniques include the "stop and start technique" and the "squeeze technique." With the "stop and start technique," patients are instructed to manually stimulate themselves in a controlled fashion and involve their partner in the manual stimulation once controlled arousal has been achieved. The couple then proceeds on to intercourse [16]. The "squeeze technique" is very similar to the "stop and start technique," except the penis is manually squeezed during the times when stimulation is stopped [30]. The obvious advantage of behavioral techniques is that they are nonpharmacologic and thus avoid possible side effects associated with medical therapies. While some authors report success with behavioral approaches, these treatment modalities are overall poorly studied and lack long-term efficacy [31].

Pharmacological Therapies

A number of pharmacological therapies have been utilized to lengthen IELT for men with PE. These therapies include both topical and oral agents, and dosing varies from on-demand to daily schedules.

The ICSD recognized three pharmacologic treatment options for PE:

1. Topical anesthetics (lidocaine or prilocaine).
2. Daily treatment with serotonergic antidepressants (paroxetine 20–40 mg, sertraline 50–100 mg, fluoxetine 20–40 mg, or clomipramine 10–50 mg).
3. On-demand treatment with antidepressants.

The ICSD Guidelines stated that none of the above drugs have been approved for the treatment of PE by regulatory agencies, and the majority of studies to assess their efficacy are limited by inadequate design (As discussed elsewhere in this book, dapexetine was subsequently approved for use in Europe.).

Topical Therapies

Topical therapies address the issue of "penile hypersensitivity." Local anesthetic medications are available in topical gel, cream, or spray forms. Busato et al. conducted a double-blind, randomized, placebo-controlled study assessing topical lidocaine–prilocaine; they reported a significant increase in IELT from 1.49 to 8.45 min in the treatment group versus 1.67–1.95 min in the placebo group [32]. In this particular study, no systemic side effects were reported. Possible side effects do include skin irritation or numbness and erectile dysfunction [33]. Additionally, transfer of these topical medications from the treated male to his partner is another possible bothersome side effect potentially limiting the use of this mode of therapy. Hence, the ICSD noted that while topical therapy is moderately effective, penile hypoesthesia is a significant adverse side effect in the male. In the female, transvaginal absorption with possible vaginal numbness and female anorgasmia may limit efficacy for the couple if a condom is not used.

Oral Therapies

A number of oral therapies are used to treat PE. This includes the phosphodiesterase type 5 (PDE-5) inhibitors, as well as the selective serotonin reuptake inhibitor (SSRI) agents. Neither of these classes of drug was developed specifically for the treatment of PE, and the use of these medications for patients with PE is thus done in an off-label fashion. However, the AUA Guideline on the Management of Ejaculatory Dysfunction recommends, "In patients with concomitant PE and ED, the ED should be treated first." The rationale for this approach is that PE sometimes improves concomitantly with improvement in the ED. The authors note that in this setting the intense stimulation needed to achieve and maintain an erection, or the anxiety associated with ED, may cause secondary PE.

PDE-5 Inhibitors

The use of PDE-5 inhibitors has been found to provide limited efficacy for the treatment of PE in men without concurrent ED. Nitric oxide (NO), which is augmented by the use of PDE-5 inhibitors, exerts both central and peripheral effects on emission. Hull et al. reported that systemic administration of a nitric oxide synthase inhibitor (*N*-nitro-L-arginine-methyl ester) led to a decrease in latency to the first emission and increased the overall number of emissions [34].

These same authors reported that NO causes a decrease in peripheral smooth muscle activity, likely mediated by a decrease in sympathetic nervous system activity, thus leading to inhibited seminal emission. They concluded, based on their collective findings, that NO may help prevent PE.

The PDE-5 inhibitors have been evaluated clinically in numerous studies for the treatment of PE, both as monotherapy and also in combination with SSRI agents. In 2005, McMahon et al. reported the results of an 8-week, double-blind, placebo-controlled, parallel group study of sildenafil citrate in men aged 18–65 years with PE [35]. The authors reported that while IELT was not significantly improved, subjects on sildenafil did report increased confidence, increased the perception of ejaculatory control, increased overall sexual satisfaction, and decreased refractory time to achieve a second erection. The authors suggested that the lack of a significant increase in IELT suggests a lack of direct central or peripheral effect of sildenafil on ejaculation function. They also noted that the perceived improvement in ejaculatory control and confidence may have been related to the improved erectile functioning and reduced performance anxiety.

McMahon et al. subsequently published a systematic review of the efficacy of PDE-5 inhibitors in the treatment of PE in 2005 [35]. They found that 13 of the 14 published studies did not fulfill evidence-based medicine criteria for ideal PE drug trial design (double-blind, placebo-controlled study, differentiation of lifelong and acquired PE subgroups, exclusion or categorization as a separate subgroup men with concurrent ED or other sexual disorders, and consistent and objective physiological measurements or use of sensitive, validated outcome assessment instruments as study endpoints). The one study that did fulfill these ideal design criteria reported that the treatment with sildenafil failed to increase baseline IELT in men with PE. The authors concluded that there is no convincing evidence to support any role for the use of PDE-5 inhibitors in men with lifelong PE and normal erectile function. They did, however, acknowledge that there is limited evidence for the role of PDE-5 inhibitors either alone or in combination with on-demand or daily SSRI agents for men with PE *and* concurrent ED. They proposed that the mechanisms of action in these men include: the ability to maintain an erection after ejaculation, reduction of the erectile refractory period with reliance on a second, subsequent erection which may be better controlled, reduction in performance anxiety with resultant better erections, and/or a decrease in erectile threshold to a diminished level of arousal, facilitating a relatively greater level of arousal to achieve ejaculation threshold.

Selective Serotonin Reuptake Inhibitor (SSRI) Agents

The SSRI class of medications has been used widely to treat PE. Serotonin is active in the nerve synapse, and low levels are known to cause depression. The tricyclic antidepressant (TCA) and SSRI agents were developed for the treatment of depression. While the TCA agents prevent the reuptake of both serotonin and norepinephrine, the SSRI agents are more specific and work by inhibiting the reuptake of serotonin into the presynaptic nerve terminal. These agents thus prolong or promote serotonin's effects. Therefore, it is not surprising that many patients who were administered SSRI agents, which were developed for the treatment of depression, complained of increased time to reach ejaculation on this therapy.

The ICSD reported that daily paroxetine provides the most robust delay in ejaculation, and delay with daily use of any of these agents is noted by the second week of therapy. Regarding efficacy of on-demand therapy with antidepressants, the ICSD was unable to provide

conclusions due to the limited number of studies, insufficient number of patients, and inadequate study designs.

At the time of the publication of the AUA Guideline on the Pharmacological Management of PE document, as well as at this time, there is no pharmacological agent approved by the US Food and Drug Administration (FDA) for the treatment of PE. As is stated in the AUA Guideline, PE can be treated successfully with several different SSRI agents. The off-label use of the SSRI agents, fluoxetine, paroxetine, sertraline, and the TCA agent clomipramine, were noted in the Guideline to have demonstrated enhanced benefit over placebo in the treatment of PE. Other agents, such as nefazodone, citalopram, and fluvoxamine, were reported to be ineffective in treating PE.

The AUA panel charged with developing the Guideline could not conclude whether daily dosing or on-demand dosing was superior. The authors also noted that medical therapy only provides symptomatic relief, and not cure of PE. Adverse events are a potential concern when using antidepressant pharmacological agents. While adverse event profiles have not been widely studied in the setting of PE therapy, those associated with the use of SSRIs and TCA agents in patients with depression include: dry mouth, drowsiness, nausea, and decreased libido. The most concerning adverse event is called "serotonergic syndrome." In mild cases, patients experience headache, dizziness, sweating, and nausea, while in severe cases patients may experience delirium, hyperthermia, and rigidity. Generally, the dosages of these medications used in treating men with PE are lower than dosages used to treat depression; nonetheless, these potential adverse events remain a concern and should be discussed with patients prior to initiating therapy.

Special mention should be made of dapoxetine hydrochloride, another SSRI agent. Dapoxetine hydrochloride, a short acting SSRI is being studied for the specific indication for PE. In 2006, Pryor et al. published an article in *Lancet* summarizing the efficacy of dapoxetine in two identically designed 12-week, randomized, double-blind, placebo-controlled Phase III clinical trials [36]. Both studies evaluated men with moderate to severe PE who received placebo, dapoxetine 30 mg, or dapoxetine 60 mg as needed 1–3 h prior to intercourse. Both dosages of dapoxetine resulted in prolonged IELT when compared to placebo ($p=0.0001$), and both dosages were associated with only mild side effects [36]. Safarinejad published the results of a double-blind, placebo-controlled, fixed-dose, randomized study of dapoxetine in the treatment of PE in 2007 [37]. He reported that daily dapoxetine has moderately better results in terms of IELT and intercourse satisfaction when compared to placebo. Dapoxetine did not provide men with long-term benefit after withdrawn. In November 2005, the FDA denied the application of dapoxetine in the treatment of PE [38]. However, in January 2012, the European Medicines Agency Committee for Medicinal Products for Human Use authorized the marketing of dapoxetine in the member states of the European Union. An article by Waldinger et al. in the *Journal of Sexual Medicine* questioned what the authors termed the "statistically significant but clinically small ejaculation-delaying effects of dapoxetine" [38]. The authors also questioned several aspects of the methodology of the Phase III clinical trials, including the importance of patient reported outcomes of perceived control over ejaculation and satisfaction with sexual intercourse, over more objective measures such as IELT.

In summary, both the AUA and ICSD guidelines recommend specific antidepressants and topical anesthetics for the pharmacologic management of PE. Only the ICSD, however, highlights the benefits of psychological and behavioral interventions.

Miscellaneous Approaches

In closing, some investigators have reported efforts to block nerve receptors for penile tactile stimuli via selective dorsal penile nerve division and hyaluronic acid gel injection. Both of these approaches have been reported to prolong IELT, but clearly need further investigation given their very limited evaluation to date [39].

Delayed Ejaculation (Inhibited Ejaculation and Anejaculation)

Delayed ejaculation (DE) is a poorly understood disorder of ejaculation with complex etiologies and multiple treatment options. There is a paucity of randomized, placebo-controlled, blinded research on the topic with only consensus and expert opinions on treatment exist. This section of the chapter discusses etiology, diagnosis, and treatment associated with DE.

Terminology

DE can be defined as personal distress caused by the persistent or recurrent delay, difficulty or absence of orgasm after sufficient sexual stimulation [40]. A similar definition also added the caveat that the DE cannot be attributed to general medical conditions, drugs, medications, or other axis I disorders [41]. There are five axes of psychiatric evaluations that identify different aspects of disorders and disability attributed to a diagnosis in DSM-IV-TR. Axis I—all psychological diagnosis; Axis II—personality disorders and mental retardation; Axis III—general medical conditions and physical disorders; Axis IV—psychosocial and associated environmental factors; Axis V—a global assessment of function. DE thus, is a medical and/or psychological condition that is not associated with other types of psychiatric diagnosis (i.e., paraphilias, psychotic disorders, etc.).

There are no commonly accepted standard times to define delayed ejaculation. Median intravaginal ejaculation latency time (IELT) is 5.4 min in normal subjects from around the world with a range of 4–10 min following intromission [20]. Men who report distress or cease sexual activity due to fatigue or irritation after two standard deviations of the mean IELT (21–23 min) would be considered pathologic [42].

Primary DE is also known as congenital DE, global DE, or lifelong DE which occurs from the first sexual experience through their lives. Anejaculation (absence of the ejaculation reflex) and aspermia (lack of release of an antegrade ejaculate) often accompany primary DE. Secondary DE or, acquired DE is intermittent or situational being restricted to different forms of stimulation resulting in ejaculation, usually outside of partnered sex. An example of secondary DE would be the ability to have an ejaculation with masturbation or oral sex but not with coitus.

Retrograde ejaculation is the expulsion of semen backward into the bladder rather than forward and out through the urethral meatus. Retrograde ejaculation can be caused by an, incompetent bladder neck, a history of prior bladder neck surgery such as TURP or medications such an alpha antagonists. In retrograde ejaculation an orgasm commonly occurs and the intravaginal orgasmic time is not disrupted. Antegrade ejaculation is the normal, forward propulsion of semen. Aspermia is defined as the absence of an antegrade ejaculate, which can cause fertility problems but is not necessarily accompanied by anorgasmia. Likewise, a decrease in ejaculate volume with satisfactory timing of ejaculation is not considered DE and may be reflective of retrograde ejaculation.

Epidemiology

DE is a rare condition. The true incidence and prevalence of DE is likely underreported due to its varied etiologies and incomplete sexual histories obtained by practitioners as well as the disparate non-standardized terms used to describe the entity as demonstrated above. Primary anorgasmia was found in 15 per 10,000 in 1948 [43]. Delayed ejaculation occurred in 2–11 % in the general heterosexual population, and upward of 20–39 % in homosexual and HIV-infected males [44–47]. A 2003 London study found an incidence of 2.5 % of the male general population were unable to have an ejaculation ≥75 % of the time [48]. An American sexual dysfunction national health survey that included 1410 men found that 8 % felt they had been unable to have a climax or ejaculation for a 2 month period over 1 year [14]. Men are living longer and are taking more medications that can potentially affect ejaculation. The recalcitrant nature of DE likely

results in underreporting. This condition also suffers from a lack of understanding and a paucity of quality treatments.

Clinical Impact

The impact of DE on men can be quite detrimental. A cross-sectional study of 331 heterosexual men aged 18–65 found that men with DE had additional medical and sexual problems (hypertension, diabetes, obesity, hyperlipidemia, tobacco use, mood disorders, alcohol abuse, etc.) [49]. Medical conditions predicted scores on both DE and low libido. In addition, performance anxiety was associated with DE. It was not clear whether DE resulted from stress in home/work life or vice versa, but we know that psychological stress has been shown to cause DE [14]. Sexual dissatisfaction, anxiety, depression, performance anxiety, relationship distress, shame, low self-image, intimacy avoidance, and relationship dissatisfaction all can be associated with DE [16, 50–54]. Relationship quality and level of intimacy are key factors in the sexual experience that can bring support, happiness, and satisfaction. DE impacts the patient and the partner necessitating cooperation of both in the treatment for mutually satisfying sexual experiences.

Etiology

DE is a complex medical condition with a multitude of etiologies. Genetically predetermined ejaculatory thresholds in combination with psychosocial, biologic, behavioral, and cultural influences contribute to DE [55–57]. Age, congenital, anatomic, neurogenic, infection/inflammation, endocrine, pharmacologic, and psychological issues all play a causative role in DE development (Table 25.1).

Age

Age causes progressive atrophy of sexual organs, decreased testosterone production, and decreased intensity of orgasm [58]. Neurogenic pathologies that compromise the nervous system and signal transduction may be responsible for this aging effect. The fast conduction within the peripheral nervous system progressively deteriorates in the third decade of life [46]. Difficulty achieving the sensory threshold needed for ejaculation stems from myelin collagen infiltrates, dermal atrophy, and degeneration of Pacinian corpuscles which are sensory units within the dermis [59, 60]. As a result, IELT typically increases in older men [61].

Older patients have more comorbid diseases that contribute to DE. Some commonly seen disease states include depression, peripheral vascular disease, diabetes, and psychiatric pathology. Lifestyle factors such as smoking, obesity, alcohol use, inactivity, and loneliness (such as loss of a partner) can be potent inhibitors of ejaculation and overall sexual function and satisfaction [62, 63].

Congenital

The three most common congenital abnormalities that may affect ejaculation are Wolffian duct abnormalities, Mullerian duct cysts, and prune belly syndrome. Mullerian duct cysts are caused by persistence of embryonic paramesonephric ducts that form a cystic structure within the prostate that can cause obstruction and decreased ejaculate.

Genetic disorders can also cause an absence of structures like the vas deferens or seminal vesicles in carriers of cystic fibrosis (CFTR) gene. Wolffian duct abnormalities can lead to missing or abnormal components of the genital tract, including the bladder neck and ejaculatory ducts. Those born with imperforate anus who have undergone repair were found to have ejaculatory failure which often attributed to nerve damage from surgery [46]. In prune belly syndrome, ejaculation and emission problems occur in part from prostatic hypotrophy and bladder neck disorders. Retrograde ejaculation and climacturia (ejaculation with urine leak with orgasm) have been described [40].

Anatomic/Trauma

Surgical procedures are performed on many men to treat certain disease states in the pelvis that can affect the genital tract. Treatments such as transurethral resection of the prostate and transurethral incision of the bladder neck/

Table 25.1 Etiologies of anorgasmia, anejaculation, and delayed ejaculation

Aging male psychogenic	Degeneration of penile afferent nerves inhibited ejaculation
Congenital	Genetic abnormalities Mullerian duct cyst Wolffian duct abnormalities Prune Belly syndrome Imperforate anus
Anatomic causes	Bladder neck reconstructive surgery Transurethral resection of prostate Bladder neck incision
Neurogenic causes	Diabetic autonomic neuropathy Multiple sclerosis Spinal cord injury Radical prostatectomy Proctocolectomy Bilateral sympathectomy Abdominal aortic aneurysmectomy Para-aortic lymphadenectomy
Infective/inflammation	Urethritis Orchitis Prostatitis Genitourinary tuberculosis Schistosomiasis
Endocrine	Prolactin disorders Hypogonadism Hypothyroidism Hyperthyroidism
Medication	See additional table
Psychological	Acute psychological distress Relationship distress Psychosexual skill deficit Disconnect between arousal and sexual situations Masturbation style

Data from refs. [40, 46, 50, 52, 123]

prostrate can cause retrograde ejaculation and DE. A post-ejaculatory urinalysis is needed to distinguish between the two conditions. Radical prostatectomy for cancer results in removal of the prostate gland and seminal vesicles, and as a result no antegrade ejaculation will occur. Other deep pelvic surgeries such as cystectomies and perineal resections can affect sexual functions through disruption of pelvic ganglia. Retroperitoneal lymph node dissection can result in problems in emission from disruption of the sympathetic chain.

Neurogenic

Neurogenic causes of DE can be divided into medical disease states and trauma. Diabetes and multiple sclerosis are strongly associated with DE [50, 64, 65]. DE and problems with emission and ejaculation occur in up to 33 % of diabetic men [52]. A survey of male patients with multiple sclerosis demonstrated up to 45 % being affected by DE [66].

Ninety-five percent of men with complete upper motor neuron lesions are not able to ejaculate [67]. The ability to ejaculate increases progressively with descending spinal injuries. Ejaculatory dysfunction can occur with damage to the sympathetic ganglia resulting from para-aortic lymphadenectomy. Sperm banking should be discussed with young men who will undergo this procedure as seminal emission can be completely disrupted rendering post ejaculatory urine processing impossible [40]. Prostate surgery, pelvic surgeries and even radiation to these areas can affect the nervous system responsible for ejaculation as well as erections.

Men who have primary DE may also have a degree of hyposensitivity to the glans penis and overall decreased excitability perhaps secondary to decreased nerve density and/or deposition in sexual organs. Men with primary DE often have greater success ejaculating with masturbation than with partnered sex [68]. This is different than men with PE who typically have greater success (increased IELT) with partnered sex [40].

Infective/Inflammation

Orchitis, epididymitis, and severe prostatitis can all lead to DE when pain leads to subsequent fear of pain with ejaculation. Urethritis, epididymitis, tuberculosis of the genitourinary tract, and schistosomiasis can all cause obstruction and cicatrization or scarring of the ejaculatory ducts. This can present as hematospermia, which usually is benign. However, 8 % of men under 30 years old with hematopsermia were found to have other serious conditions present in an international study [69]. When investigating ejaculatory pain with transrectal ultrasound, calcifications from

tuberculosis or other etiologies including idiopathic causes can be identified. Often prostatic, seminal vesicle, and ejaculatory duct stones can be cited as sources of pain and or evidence of possible infection. Treatment of the underlying cause can restore normative function. Please see the section on Painful Ejaculation later in this chapter for a more through explanation of diagnosis and treatment of this condition.

Endocrine

The hormonal milieu is important for normal ejaculation. Hypogonadism was comorbid with DE at a rate of 26 % in a group of over 2400 men with sexual dysfunction [70]. Androgen receptors are present throughout the whole body including the areas of the brain associated with orgasm and arousal. Pelvic musculature may be dependent on testosterone mediated pathways [50]. Testosterone levels are related to ejaculatory disturbances where higher levels can be found in those with premature ejaculation and lower levels in delayed ejaculation [71]. Several studies have examined the role of testosterone levels in various ejaculatory disorders and have found that levels vary widely. This hormonal mismatch can be associated with DE resulting in decreased quality of life [72, 73]. However, a recent multicenter, randomized, double blind, placebo control trial revealed T normalization in hypogonadal men showed no significant improvement in ejaculation dysfunction including anejaculation, delayed ejaculation, reduced ejaculate volume, or ejaculation satisfaction [74]. The authors state that androgen deficiency is not the sole contributor to ejaculatory dysfunction. They also speculate that perhaps testosterone levels were not titrated high enough to see an overall benefit in the trial.

DE might also be associated with thyroid hormone levels. Thyroid hormones are believed to have a possible role in controlling contractions of the seminal vesicles and ejaculatory musculature. Hyperthyroidism is associated with premature ejaculation and hypothyroidism is associated with DE [75].

Prolactin may be a surrogate marker of serotonergic activity, hence elevated prolactin levels limit not only be linked to low testosterone levels, but also to ejaculatory dysfunction [50, 76]. Prolactin and dopamine are inversely related. As dopamine rises (as what happens with climax and orgasm) prolactin is suppressed. After orgasm, prolactin spikes while dopamine is suppressed. Prolactin is thought to be partly responsible for the refractory period in men after orgasm [77, 78]. Routine hormonal testing investigating perturbations of testosterone, prolactin and thyroid levels should be considered in patients with ejaculatory dysfunction and corresponding disease symptomatology (See Appendices 25.1 and 25.2 for suggested treatment algorithms.).

Pharmacology

DE can occur as a side effect of pharmacological therapy, thus it is imperative to routinely investigate patient medications as a part of the workup for DE. A well known and common side effect of the selective serotonin receptor inhibitors (SSRIs) is a sevenfold increased risk of DE. Hence, SSRIs are commonly used in an off-label fashion for the treatment for premature ejaculation as described earlier in the chapter [79, 80]. IELT is delayed with these drugs due to the serotonergic tone and receptor activation on the central nervous system [50]. There are also many other medications that can result in DE (Table 25.2).

Anti-psychotic medications such as risperidone, olanzapine, clozapine, and quetiapine can all cause sexual dysfunction in the form of decreased libido, arousal, and anorgasmia. These medications can result in decreased dopaminergic tone in the hypothalamus and hyperprolactinemia from excess prolactin secretion [81]. Quetiapine is thought to have less prolactin stimulating effect. Amantadine, bromocriptine, and cabergoline are medications that help control for hyperprolactin states. Regulation of prolactin may help correct testosterone levels which may help restore normal sexual function and ejaculation.

Psychological

Dissatisfaction, performance anxiety, and relationship distress can be both causes and effects of DE [54, 56, 82]. Although some may enjoy longer coital practices, delay in ejaculation may not

Table 25.2 Medications known to affect male ejaculation

Alcohol	Clomipramine	Lorazepam	Phentolamine
Alprazolam	Desmethylimipramine	Mirtazapine	Phenelzine sulfate
Aminocaproic acid	Fluoxetine[a]	Mesoridazine	Prazosin
Amitriptyline	Fluvoxamine	Methadone	Protriptyline
Amoxapine	Guanadrel	Methyldopa	Reserpine
Baclofen	Guanethidine	Naproxen	Sertraline[a]
Bethanidine	Haloperidol	Nortriptyline	Thiazide diuretics
Butaperazine	Hexamethonium	Pargyline	Thioridazine
Chlordiazepoxide	Imipramine	Paroxetine[a]	Trazodone
Chlorimipramine	Iproniazid	Perphenazine	Trifluoperazine
Chlorpromazine	Isocarboxazid	Phenothiazine	
Chlorprothixene	Labetalol	Phenoxybenzamine	

[a]All selective serotonin reuptake inhibitors (SSRIs)
Data from refs. [40, 46, 50, 52, 123]

only cause potential discomfort for the patient in terms of penile pain and abrasions; but also for the partner who may feel that the patient does not love them or find them attractive. It is not uncommon for men to "fake" orgasm to help their partner feel accepted and secure when in fact, the male is actually experiencing DE. Distress increases when infertility results from lack of ejaculation within a relationship [56].

Multiple proposed psychological underpinnings of DE include fear of pregnancy, fear of "defiling" a partner through ejaculation, suppressed anger, and unwillingness to accept pleasure [55, 56]. Four diverse psychological theories based on empirical support explaining DE involve: (1) insufficient stimulation (mental and physical), (2) masturbation (too frequent, idiosyncratic style, and incongruence between fantasy and reality), (3) psychic conflict (fear, anxiety, guilt from religious upbringing, loss of self with ejaculation, etc.) and (4) subtle desire disorder concealed as ejaculatory dysfunction (autosexual orientation, partner's touch is inhibiting, compulsion to satisfy partner, etc.) [83] (See Appendix 25.2 for sexual therapies.).

Physical and mental/emotional stimulation are important components of the normal male sexual cycle. DE can result if sufficient stimulation is not achieved in both of these areas. In one study of males with a malleable penile prosthesis there was a 10 % prevalence of DE [84]. This study demonstrates that although penile erections could be simulated, orgasm and ejaculation were still impaired. Despite the overly simplistic misconception that male sexual arousal is defined solely by erectile quality, a pathologic "disconnect" between the quality of mechanically induced erections (from VED, penile implants, etc.) and cognitive arousal often exists.

In a recent United States epidemiological study by the Global Online Sexuality Survey, it was found that 76.1 % of the 1133 English speaking men with mean age of 52 years with Facebook accounts admitted to masturbation [85]. Other studies indicate that 92 % of all men masturbate [43, 86]. Although masturbation has not been linked to any significant problems for the general population, the frequency, intensity, style, and fantasy associated with the practice has been attributed to ejaculatory problems. Idiosyncratic masturbation style refers to an individual's technique that involves the combination of pressure, speed, duration, and intensity needed to achieve an ejaculation and orgasm which is not reproducible with a partner using hands, mouth, and/or vagina [83, 87]. Men who practice this type of masturbation have a higher rate of sexual dysfunction [86, 88]. Some in the popular media has proposed that masturbation with pornography use and addiction can subsequently lead to sexual dissatisfaction and delayed ejaculation [89]. Recent studies have demonstrated that

pornography-related masturbation in coupled men is associated with decreased sexual desire [90]. This could potentially lead to DE based on lack of mental/emotional stimulation.

Psychic conflict is a cluster of issues that causes psychological opposition to ejaculation, mostly from fear. Fear of becoming a father, fear that the female genitals may harm them, shame from religious beliefs, fear of hurting, or anger towards their partner can all manifest in DE and sexual dysfunction [83]. Anxiety disorders and loss of sexual confidence can also occur in these individuals.

Subtle desire disorder is a group of disorders that mimic other diagnoses, making the treatment more difficult. An example of this condition would be a man with DE who enjoys self-sex more than partnered sex (autosexual orientation). Affected individuals are commonly inhibited by partners' touch and/or may feel the need to please their partners due to the diminutive effect of partnered sex compared to autoarousal and ejaculation. In the absence of mental/emotional arousal, these men may experience natural erections that have decreased penile sensation leading to DE [83].

Assessment

When evaluating for DE, patients should all have full medical and sexual histories performed along with detailed physical exams. Urologists may feel uncomfortable with the level of sexual detail that is warranted in obtaining a full sexual history. Understanding the cultural context and history of the disorder; the quality of the sexual response cycle (desire, arousal, ejaculation, orgasm, and refractory period); details of the ejaculatory response, sensation, frequency, and sexual activity/techniques; the partners' assessment of the disorder and if the partner suffers from any sexual dysfunction her/himself; and the overall satisfaction of the sexual relationship are all important to garner during history taking [91]. Investigation by a sexual therapist is often required to help get a complete psychological evaluation. It is incumbent for the urologist to diagnosis medical pathologies that cause or contribute to DE such as assessing the hormonal milieu, anatomy, and overall medical conditions. Good communication between sexual therapist and medical practitioner is paramount to successful diagnosis and treatment of DE.

Appendix 25.1 provides an algorithm which helps to differentiate between retrograde ejaculation, delayed ejaculation, and ejaculatory duct obstruction, with subsequent treatment recommendations in Appendix 25.2.

Treatment

The workup and treatments for DE vary based on its definition and etiology. Knowing that a patient has secondary DE would trigger an investigation into his medications, quality of his sexual relationship and partners' health. Partner's health is an important factor as DE may be caused by fear of hurting her or decrease in sexual attractiveness if she had a mastectomy, hysterectomy or other types of disfigurements. Patients with anatomical abnormalities (unilateral or bilateral absences of vas for example) may need additional imaging looking for corresponding renal abnormalities or transrectal ultrasound to evaluate for ejaculatory structure defects. Signs of infection (prostatitis, hematospermia, lower urinary tract symptoms) should be evaluated with treatment of underlying medical conditions. Similarly, neurologic conditions such as spinal cord injury or multiple sclerosis should be addressed [42]. If a man is able to ejaculate with masturbation only it would be important to assess for an idiosyncratic masturbatory style [56].

A recent study by Mulhall et al. shows the importance and relative success with goal directed medical therapy targeted towards etiologies of DE. These authors found that 34 % of men had DE pathology due to SSRI therapy, among which 82 % of those who had SSRI cessation improved and 34 % of those who had medication adjustment improved. These authors also found that 35 % of men with DE had abnormal penile sensation, of which 60 % got better with penile vibratory stimulation (Please see Penile Vibratory Stimulation later in this chapter for details.).

Fifteen percent of men with DE were hypogonadal, and 24 % of them improved with hormonal treatment. Psychogenic issues were the root cause in 16 % of men with DE [92]. Of note, when a psychogenic cause is found, sexual therapy traditionally has had a much higher success rate than treatment of non-psychogenic causes [55, 56].

Treatments for DE can be broken down into medications, penile vibratory stimulation, psychological (sexual therapy, masturbation retraining, etc.), and the "sexual tipping point" model that incorporates the balancing of the biologic, psychological, social, and behavioral aspects that contribute to the disorder.

Pharmocology

Pharmacologic agents have been used to treat DE with varied success. Unfortunately, there is no FDA approved medication to treat DE as the majority of cited research is based on case and cohort studies that have been non-randomized, non-blinded, and non-placebo controlled. Many drugs have been used as both treatment and/or antidotes to other medications causing DE. The majority of the drugs that are used for DE are classified as anti-serotonergic, alpha-2 adrenergic antagonist or central dopaminergic medications. A recent survey of sexual health providers demonstrated an overall treatment success of 40 % with most providers commonly using cabergoline, bupropion, and oxytocin for treatments [93]. However, this survey measured anecdotal results of practitioners and there was no proven efficacy or superiority of any drug due to a lack of placebo controlled, randomized, blinded, comparative trials. All medications that have been suggested for therapeutic intervention can be found in Table 25.3 along with suggested DE dosing, the overall indication of the agent and the side effects of these medications (black box warning, serious side effects, and most common side effects) [40, 42, 46, 50, 52, 91, 94–96].

Cyproheptadine

This is a serotonin (5-HT) antagonist and antihistamine used to treat allergic rhinitis and anorexia nervosa. It has demonstrated shorter refractory periods and increased sexual activity in male rats [97]. Cyproheptadine was successfully used as an antidote at doses of 2–16 mg as needed or chronically to help counter the effects of SSRIs in humans [98]. In non-controlled case studies, cyproheptadine may reverse the sexual side effects of DE or anorgasmia of citalopram, nortriptyline, fluoxetine, fluvoxamine, imipramine, and clomipramine [99–102]. This drug's most frequent side effects include somnolence and poor tolerability. In addition, it may reverse the effects of the antidepressant or anti-obsessive properties of SSRIs [103].

Alpha-1-Adrenergic Agonists

Medications that act as agonists to the alpha-1-adrenergic receptors have typically been used for nasal congestion, hypotension, and acute bronchospasm. Pseudoephedrine, ephedrine, and midodrine have been shown to aid in the emission process and result in antegrade ejaculation [96]. Their mechanism is thought to be from stimulation of the sympathetic tone and closure of the bladder neck. Midodrine was shown to have nearly 60 % efficacy in treating and/or reversing anejaculation [104]. Patients with multiple sclerosis had the greatest response; those with bilateral sympathectomies had the least response.

Amantadine

This central dopaminergic agonist is used to treat the flu, Parkinsonism, and extra pyramidal symptoms. In rats, chronic amantadine administration induced shorter refractory periods and increased sexual frequency with no change in arousal [105]. Taking this drug 5–6 h before sex in humans has been suggested to help treat DE caused by SSRIs at a dose of 100 mg [42, 106].

Cabergoline

Cabergoline is a dopamine 2 agonist that inhibits prolactin secretion and is used for the purpose of treating hyperprolactinemia. In Parkinson's disease it was shown to enhance erections and orgasms with a decrease in refractory period [107]. In a single-blinded, placebo-controlled, crossover study between protirelin (prolactin stimulant) and cabergoline, cabergoline decreased the refractory period and lowered prolactin levels [108].

Table 25.3 Drug therapy for delayed/inhibited ejaculation[a]

Drug generic/(trade)	Delayed ejaculation dosage (not FDA approved indication)		Indication (FDA approved)	Side effects (at therapeutic FDA indication dose)
	As needed	Daily		
Cyproheptadine[b] (Periactin)	4–12 mg (3–4 h prior to sex)	–	• Allergic rhinitis • Urticarial • Anorexia nervosa	**Nausea**, **dizziness, urinary retention, photosensitivity, rash, abdominal pain, fatigue**, agranulocytosis, thrombocytopenia, heat stroke
Oxytocin[c] (Pitocin)	24 IU intranasal during sex or SL prior to sex	–	• Labor induction • Abortion adjunct • Postpartum hemorrhage	**Nausea, vomiting**, hypertension, afibrinogenemia, SAIDH Not for elective labor induction[d]
Pseudoephedrine[e] (Sudafed)	60–120 mg (120–150 min prior to sex)	–	• Nasal congestion	**Insomnia, anxiety, nausea, insomnia, tremor, urinary retention, headache, palpitations,** arrhythmias, hypertension
Ephedrine[e]	15–60 mg (1 h prior to sex)	–	• Acute bronchospasm • Hypotension	**Nausea, headache, dizziness, insomnia, hypertension, tremor, urinary retention, anxiety, palpitations,** arrhythmias, stroke, seizures, MI, nephrotoxicity, hepatotoxicity
Midodrine[e] (Orvaten, ProAmatine)	5–40 mg daily (30–120 min. prior to sex)	–	• Orthostatic hypotension	**Dysuria, paresthesia, rigors, pruritis, piloerection, rash,** bradycardia, erythema multiforme, visual field defect Supine elevated blood pressure[d]
Apomorphine (Apokyn)	0.5–1.5 mg intranasal (20 min before sex)	–	• Parkinson Ds	**Yawning, dyskinesia, rhinorrhea, hallucinations, anxiety, UTI, chest pain, diaphoresis,** hypotension, syncope, MI, priapism, abuse potential, hallucinations
Bethanechol[b] (Urecholine)	20 mg po (1–2 h prior to sex)	–	• Urinary retention • Neurogenic bladder • GERD • TCA adjunct treatment • Phenothiazine adjunct Tx	**Abdominal pain, nausea, diarrhea, headache, urinary urgency, malaise, flushing, miosis,** bronchospasm, hypotension, tachycardia, seizures
Amantadine[b] (Symmetrel)	100–400 mg (for 2 days prior to sex)	75–100 mg BID or TID	• Influenza A Tx and prophylaxis • Extrapyramidal sx • Parkinsonism	**Nausea, dizziness, depression, anorexia, hallucinations, compulsivity, hypotension, abnormal dreams, headache, constipation/diarrhea,** arrhythmias, psychosis, coma, impaired vision, pulmonary edema, neutropenia, seizure, heat stroke
Bupropion[b] (Wellbutrin, Zyban, Budeprion, Forfivo)	–	75 mg BID or TID	• Major depressive disorder • Seasonal affective disorder • Smoking cessation • Attention deficit-hyperactivity disorder (ADHD)	**Palpitations, urinary frequency, blurred vision, chest pain**, agitation, psychosis, hallucinations, seizures, hepatotoxicity, HTN, arrhythmias Suicidality, neuropsychiatric symptoms[d]

(continued)

Table 25.3 (continued)

Drug generic/(trade)	Delayed ejaculation dosage (not FDA approved indication)		Indication (FDA approved)	Side effects (at therapeutic FDA indication dose)
	As needed	Daily		
Buspirone[b] (BuSpar)	–	5–15 mg BID	• Anxiety	**Dizziness, nausea, headache, fatigue, blurred vision, numbness, weakness, abdominal pain, insomnia,** serotonin syndrome, tardive dyskinesia, sytonia, hostility, depression
Yohimbine (Yocon)	–	5.4 mg TID	• Impotence	**Urinary retention, hyperglycemia, tachycardia, irritability, tremor, nausea, dizziness, headache, flushing, diaphoresis, hypertension,** respiratory depression
Cabergoline[c] (Dostinex)	–	0.25–2 mg twice a week	• Hyperprolactinemia	**Nausea, dizziness, fatigue, abdominal pain, somnolence, anxiety, vertigo hot flashes, flatulence, breast pain, compulsivity,** orthostatic hypotension, pleural effusion, retroperitoneal fibrosis, depression, psychosis, pulmonary and pericardial fibrosis
Loratadine[b] (Claritin, Alavert)	–	10 mg daily	• Allergic rhinitis • Chronic idiopathic urticaria	**Drowsiness, fatigue, headache, dry mucous membranes, pharyngitis,** bronchospasm, hepatotoxicity, syncope, seizures, thrombocytopenia
Roboxetine (not available in USA)	–	4–8 mg	• Major depressive disorder • Panic disorder • Attention deficit-hyperactivity disorder (ADHD)	**Insomnia, nausea, excessive sweating, constipation, urinary tract infection, dysuria, urinary retention, ejaculatory pain,** tachycardia, blood pressure changes
Imipramine[e] (Tofranil)	–	25–75 mg daily	• Depression • Chronic pain	**Drowsiness, dizziness, blurred vision, palpitations, increase appetite, weakness, confusion, anxiety, impotence, galactorrhea, gynecomastia, photosensitivity, change in libido**, hypotension, syncope, QT prolongation, AV block, MI, stroke, seizures, ataxia, leukopenia, hallucinations, depression, hepatitis, angioedema, heat stroke, psychosis, withdrawal symptoms Suicidality[d]

Bold terms represent more common reactions and unbolded terms represent serious reactions
Data from refs. [42, 95, 96, 121, 123]
[a]None of these drugs are FDA approved for delayed ejaculation
[b]Works in part as a possible antidote for SSRI and SSNRI for sexual side effect of DE
[c]May help when abnormalities of Prolactin or other hormonal issues considered
[d]Black box warning
[e]Known to help with retrograde ejaculation

This study also showed evidence of improvement in both ejaculation and libido. Other authors have found similar outcomes with anorgasmic men [96]. Some providers have described anecdotal success with cabergoline [93]. It is hypothesized that when prolactin levels are elevated or high normal at baseline, cabergoline can be a good first choice. Low or normal prolactin levels prompt some providers to then use oxytocin as their first line agent.

Oxytocin

Oxytocin is a non-peptide hormone that has been shown to have effect in many areas in men. In women it has been used to induce uterine contraction and lactation during nursing. In men it has been shown to increase ejaculation, paternal nurturing, long-term romantic bonds and attachments, stimulation of sexual desire and conditioning of the sexual experience in preparation of ejaculation and orgasm [109]. Oxytocin surges during male ejaculation, orgasm, and detumescence, returning to baseline by 10 min after surge [71].

Bupropion

This is a dopamine and norepinephrine reuptake inhibitor that is used to treat depression, smoking addiction, and attention-deficient-hyperactivity disorder. It can be used as an antidote to the side effects of sexual dysfunction and DE associated with SSRIs and has been shown effective in humans [103, 110]. Daily or as needed bupropion resulted in a complete reversal or improvement of negative sexual side effects in 66–69 % of patients on SSRIs [111].

Buspirone

The anxiolytic buspirone binds to serotonin and dopamine 2 receptors. It has been used to treat the side effects of sexual dysfunction associated with SSRIs [112]. Buspirone was shown to be effective in patients with generalized anxiety and sexual dysfunction in ranges of 16–60 mg daily [94].

Yohimbine and Herbal Supplements

Yohimbine is a plant derivative herbal supplement used for decreased libido and ejaculatory dysfunction. Rat models of ejaculatory exhaustion demonstrated nullification of refractory periods and reinitiation of the ejaculation motor reflex after intravenous yohimbine administration [113]. In another study, men treated with Fluoxetine for 2 years were given yohimbine. This countered the effect of the SSRI on orgasm and ejaculation [114]. Multiple studies in humans have found yohimbine to help treat ejaculatory and orgasmic dysfunction along with other sexual dysfunction; however, these studies have not been performed in large blinded, randomized, or placebo-controlled fashion [42, 50, 96, 98, 115].

Yohimbine, horny goat weed, MACA root, tribulus terrestris, and saffron are all ancient herbal medicines that have been used for thousands of years in Chinese, Indian, ancient Egyptian, Roman, and Greek cultures to help treat all forms of ejaculatory dysfunction. The use of these particular medications has been tested in animal models and in human research, and these studies have shown some evidence towards decreased ejaculatory latency periods [116].

Bethanechol

Bethanechol is an FDA approved drug used for urinary retention, gastroesophageal reflux disease, and as an adjuvant for tricyclic antidepressants and phenothiazines. Bethanachol is a cholinergic agonist that increases detrusor and gastrointestinal motility and has been shown to help reverse the DE effects of protriptyline, amoxapine, and imipramine [46, 117, 118].

Apomorphine

Apomorphine is a central and a peripheral stimulator of postsynaptic dopamine 2 receptors used for hypomobility in Parkinson disease. Rat studies showed increased activity of the sympathetic branches of the hypogastric nerve innervating the vas deferens resulting in neuronal activity that occurs during sexual climax [119]. This has been shown to excite the nerve patterns in the lumbosacral plexus associated with ejaculation. Although the drug is commonly administered subcutaneously, it seems to have equal efficacy on sexual function intranasally in experiments [120]. Episodic doses in humans have been successful in patients who were using it for sexual dysfunction including erectile dysfunction [121].

Others

The intermittent use of other drugs has shown to help reverse the DE effect of SSRIs, which include amphetamines [122] and loratadine (10 mg daily) [95]. In addition, alpha-1 adrenergic receptor agonists like imipramine and pseudoephedrine may be of limited utility for retrograde ejaculation [123]. Reboxetine is a selective noradrenaline reuptake inhibitor that can be used as an alternative to SSRI for depression and is thought to have less sexual side effects. However, there are reports of spontaneous ejaculation with the use of this drug [124–126]. Alterations of SSRI regimens in addition to antidotes can be effective in treatment of DE [127, 128]. Additional drugs that may help DE are ropinirole, pramipexole, and flibanserin [50].

Penile Vibratory Stimulation (PVS)

Electro-ejaculation techniques have been used for many years to treat ejaculatory problems in neurogenic patients who present for infertility. Ejaculation can be obtained via stimulation to the pudendal nerves which helps to initiate the ejaculatory reflex [129]. In DE patients, PVS has been used on the frenulum for certain time periods to help increase the sensation to the penis allowing for the ejaculatory reflex to be triggered. It has been shown to work with secondary DE at a rate of 62 % [130]. For men with multiple sclerosis, PVS has also been shown to be helpful [131]. Combining PVS with medical therapy increases the efficacy of DE treatment. However, to date there have been no studies that are either placebo-controlled or randomized [50].

Psychological

Psychological treatments include but are not limited to: sexual education; retraining masturbatory practices; increased genital specific stimulation; role-playing on his own and in front of his partner; anxiety reduction on ejaculation and performance; and recalibrating the mismatch of sexual fantasies with arousal (such as with pornography use and fantasy stimulation compared to reality) [91]. Men and women can realistically evaluate their sexual practice and manage expectations by having a basic understanding of the sexual cycle for their respective partners. Masturbation can be considered practice for the real performance for greater psychosexual arousal to orgasm for both parties [55]. Although fantasy can be harmful when not associated with appropriate sexual arousal, fantasy can be quite helpful if it allows blockage of critical thoughts that may be preventing orgasm and ejaculation. The reduction of anxiety as a component of DE is very important as performance anxiety often interrupts the natural ejaculatory and orgasmic progression [132]. A well-trained sexual therapist can be invaluable for these treatments to work. Other addressable psychopathologies that may be masquerading or comorbid with DE can be uncovered via sex therapy. Female sexual dysfunction can contribute to DE in men so evaluation of this is a critical part of treatment. Referral to a properly qualified therapist, psychiatrist or psychologist is appropriate and often times warranted (See Appendices 25.1 and 25.2).

Sexual Tipping Point Model

Dr. Michael A. Perelman has written extensively on the multifactorial etiology of DE and "The Ejaculatory Tipping Point" which is a dynamic process. Dr. Perelman theorizes that every man has a multidimensional predetermined ejaculatory threshold that will result in tipping the "scale" of balancing factors towards ejaculation and orgasm. In his model he has a scale balancing the excitatory and inhibitory factors between the physiologic and organic issues and the psychosocial and behavior issues. Deciphering between the biogenic and psychosocial factors is the goal of both the patient and the clinician in helping achieve the desired outcome whether they suffer from premature ejaculation, delayed ejaculation, or anorgasmia [55, 133]. The sexual tipping point has been embraced as a holistic approach to ejaculatory dysfunction as it incorporates all aspects of the disorder to help find solutions [50].

Painful Ejaculation

Etiology

Painful ejaculation is perhaps the least well-studied and characterized of the ejaculatory disorders discussed in this chapter. This condition can have a dramatically negative impact on relationships, leading to the avoidance of sexual intimacy with one's partner, sexual distress, sexual dissatisfaction, and ultimately, marital problems [134, 135]. A variety of causes have been cited, but the underlying etiology is not well understood. Some authors suggest spasm of the bladder neck or dystonia of the pelvic floor musculature during orgasm [136], and others note that ejaculatory duct obstruction may be the underlying cause [26, 137]. This obstruction could arise from ejaculatory duct calculi, intrinsic stenosis, or external compression by a prostatic cyst leading to ejaculatory duct compression and blockage. Antolak et al. have suggested that pudendal nerve compression and neuropathy may be the cause of ejaculatory pain in some men [138]. Finally, some authors have suggested that antidepressant medications may induce painful ejaculation as a side effect [139–143].

The true incidence of painful ejaculation is unclear. Most studies assessing this condition employ retrospective questionnaires, and are thus subject to some form of bias. In 2003, Rosen et al. reported that 6.7 % of men participating in a large multinational survey of aging males noted pain or discomfort on ejaculation [2]. Roberts et al. found that 1.5 % of the 2115 respondents from Olmsted County, Minnesota experienced ejaculatory pain [144]. Another US study reported that 9.7 % of respondents (age 20- to 74-years-old) noted perineal pain or discomfort with ejaculation [67, 145]. Finally, the authors who developed the National Institutes of Health Chronic Prostatitis Symptom Index found that ejaculatory pain was present in 58 % of men with prostatitis, 17 % of men with BPH, and 4 % of controls [146].

Diagnosis

The diagnosis of ejaculatory pain is largely based on subjective complaints; objective diagnostic information can be gathered in some instances. For example, in men with ejaculatory duct obstruction, transrectal ultrasound imaging can be utilized to visualize ejaculatory duct anatomical abnormalities (such as calculi or a compressing cyst) and/or seminal vesicle dilation (a possible sign of distal ejaculatory duct obstruction). Antidepressant medication-related symptoms may be clarified by converting to another medication or ceasing this therapy (in conjunction with the prescribing physician). In patients with suspected pudendal neuropathy, neurophysiological tests may help delineate pudendal neuropathy associated with perineal pressure [147]. Most of the purported causes of ejaculatory pain, however, are more challenging to diagnose and not associated with clear physical findings or alterations in laboratory values. This fact can make pursuit of a clear therapeutic plan challenging for both the patient and the treating physician.

Treatment

The treatment of painful ejaculation should be based on objective findings from the examination and laboratory workup. Prostatitis and urinary tract infections should be treated. Patients with ejaculatory duct obstruction should be considered for transurethral resection of the ejaculatory duct. Patients with seminal vesicle anomalies (i.e., seminal vesicle stone) suspected of being the root cause of the pain should be informed of the option of laparoscopic seminal vesicle excision, as this has been reported as providing durable relief in the setting of ejaculatory pain [148]. Finally, consideration should be given for enlisting the assistance of physical therapists specializing in pelvic floor physical therapy. Anderson et al. reported encouraging results with trigger

point release and paradoxical relaxation training in 133 men with refractory chronic pelvic pain syndrome and sexual dysfunction (ejaculatory pain [56 %], decreased libido [66 %], erectile and ejaculatory dysfunction [31 %]) [149]. The authors noted significant improvement in the above categories of sexual dysfunction, with 70 % of patients reporting markedly or moderately improved symptoms after trigger point release/paradoxical relaxation training. Thus, physical therapists can help elicit and treat underlying musculoskeletal anomalies, which may be the root cause of many patients' complaints of ejaculatory pain.

Conclusions

The physiology of ejaculation is highly integrated and relies on both the sympathetic and parasympathetic neural pathways. Ejaculatory dysfunction is fairly common and is a source of significant bother for many of those affected. Ejaculatory dysfunction can entail a wide array of anomalies, including premature ejaculation, inhibited ejaculation (consisting of delayed ejaculation and absent ejaculation), and painful ejaculation. Patients should be evaluated through a thorough medical history, physical examination, and laboratory testing to help ensure proper diagnosis. Finally, with directed therapy, many disorders of ejaculation can be successfully treated.

Appendices

Appendix 25.1

Algorithm of Disordered Ejaculation in Men. $^{\Psi}$=See Collaboration of Clinician and Sexual Therapist (Appendix 25.2). *=Medications in Table 25.3 can be tried in treatment of Retrograde Ejaculation (see Table 25.3). ^ = If patient on SSRI consider use of SSRI Antidote types of medications (see Table 25.3). †=Medications in Table 3 can be used for Prolactin abnormalities (see Table 25.3).

(Used with permission from Sadowski DJ, Butcher MJ, Kohler TS. Delayed Ejaculation: Medical and Psychological treatments and Algorithms. Current Sexual Health Reports. September 2015; 7(3): 170–179. Created using data in Rowland D, McMahon CG, Abdo C, Chen J, Jannini E, Waldinger MD, et al. Disorders of orgasm and ejaculation in men. The journal of sexual medicine. 2010;7(4 Pt 2):1668–86.)

Appendix 25.2

Collaboration of Clinician and Sexual Therapist (Used with permission from Sadowski DJ, Butcher MJ, Kohler TS. Delayed Ejaculation: Medical and Psychological treatments and Algorithms. Current Sexual Health Reports. September 2015; 7(3): 170–179. Created using data from Perelman, MA. Delayed ejaculation in: Principles and practice of sex therapy. Fifth edition. Binik YM, Hall KSK. (eds). New York, NY: The Guilford Press; 2014. 138–55.)

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