Disorders of Orgasm and Ejaculation in Men

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ABSTRACT

Introduction. Ejaculatory/orgasmic disorders are common male sexual dysfunctions, and include premature ejaculation (PE), inhibited ejaculation, anejaculation, retrograde ejaculation, and anorgasmia.

Aim. To provide recommendations and guidelines concerning current state-of-the-art knowledge for management of ejaculation/orgasmic disorders in men.

Methods. An international consultation in collaboration with the major urology and sexual medicine associations assembled over 200 multidisciplinary experts from 60 countries into 25 committees. Committee members established specific objectives and scopes for various male and female sexual medicine topics. The recommendations concerning state-of-the-art knowledge of disorders of orgasm and ejaculation represent the opinion of seven experts from seven countries developed in a process over a 2-year period.

Main Outcome Measure. Expert opinion was based on grading of evidence-based medical literature, widespread internal committee discussion, public presentation and debate.

Results. Premature ejaculation management is largely dependent upon etiology. Lifelong PE is best managed with PE pharmacotherapy (selective serotonin re-uptake inhibitor [SSRI] and/or topical anesthetics). The management of acquired PE is etiology specific and may include erectile dysfunction (ED) pharmacotherapy in men with comorbid ED. Behavioral therapy is indicated when psychogenic or relationship factors are present and is often best combined with PE pharmacotherapy in an integrated treatment program. Retrograde ejaculation is managed by education, patient reassurance, pharmacotherapy, or bladder neck reconstruction. Delayed ejaculation, anejaculation, and/or anorgasmia may have a biogenic and/or psychogenic atiology. Men with age-related penile hypoanesthesia should be educated, reassured, and instructed in revised sexual techniques which maximize arousal.

Conclusions. Additional research is required to further the understanding of the disorders of ejaculation and orgasm.

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Introduction

Ejaculatory dysfunction is one of the most common male sexual disorders. The spectrum of ejaculatory dysfunction extends from premature ejaculation, through delayed ejaculation to a complete inability to ejaculate (known as anejaculation), and includes retrograde ejaculation.

The sexual response cycle can usefully be conceptualized as having four interactive stages: desire, arousal, orgasm, and resolution. During sexual activity, increasing levels of sexual arousal reach a threshold that triggers the ejaculatory response, which then typically terminates the sexual episode for the male. The perception of the striated muscle contractions and resulting semen

expelled during ejaculation, mediated through sensory neurons in the pelvic region, gives rise to the experience of orgasm, a distinct cortical event, experienced phenomenologically both cognitively and emotionally.

Specific to ejaculation and orgasm, the latency to ejaculation, that is, the time (and more importantly, the amount of stimulation) extending from the onset of penile stimulation to the moment of ejaculation, represents a continuum of time that shows variation across men, and, within men, across situations. Although the great majority of men appear to reach ejaculation and orgasm following several minutes of penile vaginal stimulation and are, along with their partners, quite satisfied with the latency of their ejaculatory response, others report dissatisfaction. Specifically, some men ejaculate very rapidly after, or sometimes even prior to, penetration and do so with minimal stimulation. Others may ejaculate only with great difficulty or not at all, even following prolonged stimulation. These conditions, as noted above, represent subsets—at opposite ends of the spectrum—that fall into the categories of male ejaculatory disorders.

The Anatomy and Physiology of the Ejaculatory Response

The ejaculatory reflex comprises sensory receptors and areas, afferent pathways, cerebral sensory areas, cerebral motor centers, spinal motor centers, and efferent pathways. Neurochemically, this reflex involves a complex interplay between central serotonergic and dopaminergic neurons, with secondary involvement of cholinergic, adrenergic, oxytocinergic, and gamma aminobutyric acid (GABA) agric neurons.

The ejaculatory process integrates actions that occur in the central (CNS) and peripheral nervous systems. Structures in the CNS that are involved in ejaculation include the medial preoptic area (MPOA), nucleus paragigantocellularis (nPGi), posteromedial bed nucleus of the stria terminalis, posterodorsal medial amygdale, and the medial parvicellular subparafascicular nucleus of the thalamus. While the MPOA is involved in stimulation of ejaculatory response, the nPGi has an inhibitory influence; specifically, descending serotonergic pathways from the nPGi to the lumbosacral motor nuclei inhibit ejaculation. The MPOA can inhibit the nPGi, which in turn results in ejaculation [1]. Several brain areas are activated after ejaculation by ascending fibers from the spinal cord and may have a possible role in satiety and the postejaculatory refractory time [2].

Table 1 The three stages of normal antegrade ejaculation

Emission	Sympathetic spinal cord reflex (T10–L2)
	Genital and/or cerebral erotic stimuli with considerable voluntary control
	Peristaltic contraction of epididymis and vas deferens
	Contraction of seminal vesicles and prostate
	Expulsion of spermatozoa/seminal/prostatic fluid into posterior urethra
	Ejaculatory inevitability sensation resulting from distension of posterior urethra
Ejection	Parasympathetic spinal cord reflex (S2–S4)
	Limited voluntary control
	Rhythmic contractions of bulbocavernous/pelvic floor muscles
	Bladder neck closure
	Relaxation of external urinary sphincter
Orgasm	Build-up and release of pressure in posterior urethra
	Smooth muscle contraction of accessory sexual organs and urethral bulb
	Sensation due cerebral processing of pudendal nerve sensory stimuli

Based upon functional, central, and peripheral mediation, the ejaculatory process is typically subdivided into three phases: emission, ejection (or penile expulsion), and orgasm (Table 1). Emission consists of contractions of seminal vesicles (SV) and the prostate, with expulsion of sperm and seminal fluid into the posterior urethra, and is mediated by sympathetic nerves (T10–L2). Ejection is mediated by somatic nerves (S2–S4), and involves pulsatile contractions of the bulbocavernosum and pelvic floor muscles, together with relaxation of the external urinary sphincter. Ejection also involves a sympathetic spinal cord reflex upon which there is limited voluntary control. The bladder neck closes to prevent retrograde flow; the bulbocavernous, bulbospongiosus, and other pelvic floor muscles contract rhythmically, and the external urinary sphincter relaxes. Intermittent contraction of the urethral sphincter prevents retrograde flow into the proximal urethra [3].

Orgasm is the result of cerebral processing of pudendal nerve sensory stimuli resulting from increased pressure in the posterior urethra, sensory stimuli arising from the verumontanum and contraction of the urethral bulb, and accessory sexual organs.

Many neurotransmitters are involved in the control of ejaculation, including dopamine, norepinephrine, serotonin, acetylcholine, oxytocin, GABA, and nitric oxide (NO) [2]. Of the many studies conducted to investigate the role of the brain in the development and mediation of sexuality, dopamine, and serotonin have emerged as

essential neurochemical factors. The dopaminergic system, particularly that in the anterior hypothalamus, exerts a sexual facilitatory role [4]. A possible sexual response regulatory role of dopamine is suggested by the observation that dopamine is released in the MPOA of male rats in the presence of an estrous female, and progressively increases during copulation, eventually triggering ejaculation [5].

Whereas dopamine promotes seminal emission/ejaculation via D2 receptors, serotonin is inhibitory.

Serotonergic neurons are widely distributed in the brain and spinal cord and are predominantly found in the brainstem, raphe nuclei, and the reticular formation. Currently, at least 16 different receptors have been characterized, e.g., 5-HT1a, 5-HT1b, 5-HT2a, 5-HT2b, etc [6]. Stimulation of the 5-HT2C receptor with 5-HT2C agonists results in delay of ejaculation in male rats, whereas stimulation of post-synaptic 5-HT1A receptors results in shortening of ejaculation latency [7], leading to the hypothesis that men with premature ejaculation (PE) may have hyposensitivity of 5-HT2C and/or hypersensitivity of the 5-HT1A receptor [1,8].

PE: Definition, Epidemiology, and Pathophysiology

Definition and Classification

Definitions of premature ejaculation (PE) have provided similar though not identical conceptual frameworks for classifying an individual as having premature ejaculation, with general reference to three criteria: short ejaculatory latency, concomitant distress, or a lack of sexual satisfaction, and a lack of self-efficacy regarding the condition. Each of these criteria has been operationalized, although not always with consistency [9]. Based on the aforementioned considerations, the International Society for Sexual Medicine (ISSM) organized an international panel in 2007 to develop a consensus definition for premature ejaculation and succeeded in a definition of lifelong premature ejaculation [10]. According to this new definition, lifelong premature ejaculation is characterized by: an ejaculation that always or nearly always occurs prior to or within about 1 minute of vaginal penetration, an inability to delay ejaculation on all or nearly all vaginal penetrations, and with negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy. The panel concluded that there were insufficient data for an evidence-based definition of acquired premature ejaculation.

The population of men with PE is not homogenous and includes lifelong PE, acquired PE, natural variable PE, and premature-like ejaculatory dysfunction [11,12]. For men lifelong PE, ejaculation occurs too early at nearly every intercourse, with (nearly) every woman, and from about the first sexual encounters onwards. Based on self-selected samples, the majority of these men (80–90%) ejaculate intravaginally within 30–60 seconds, and most of the remainder (10%) between 1 and 2 minutes. The ejaculation remains rapid during life in the majority (70%) of these men or may be aggravated during the course of aging (30%). Some men ejaculate during foreplay, before penetration (anteportal ejaculation), or as soon as their penis touches the vagina. No widely accepted cure for lifelong PE is known, but various drugs (including selective serotonin re-uptake inhibitors [SSRIs]) and psychotherapy treatments may be effective in postponing the ejaculatory response [13] in these men.

For men with acquired PE, ejaculation occurs too soon beginning at some point in a man's life after experiencing normal ejaculatory latencies; the onset may be either sudden or gradual. In these men, the appearance of the PE may be due to (i) urological dysfunctions, for example, erectile dysfunction or prostatitis [14]; (ii) thyroid dysfunction [15]; (iii) psychological or relationship problems [16,17]; or (iv) a combination of these factors. Acquired PE may be overcome through the use of medical and/or psychological treatments that target the underlying cause [13].

The Prevalence and Etiology of PE

Although various epidemiological studies have shown that about 20–30% of men have complaints of premature ejaculation [18], reliable information on the prevalence of lifelong PE and acquired PE in the general male population is lacking. As the prevalence of intravaginal ejaculatory latency times (IELT) of less than 1 minute in unselected male cohorts in mainly Western countries is about 1–3%, the prevalence of lifelong PE may be rather low. With regard to the prevalence of acquired PE, data are lacking, in part related to the lack of an evidence-based definition for this condition.

Historically, attempts to explain the etiology of premature ejaculation have included a diverse range of biogenic and psychological theories. Most of these proposed etiologies are not evidence based and are speculative at best. The determinants of

PE are undoubtedly complex and multivariate, with the etiology of lifelong PE different from that of acquired PE. Although the determinants of lifelong PE are unknown, genetic and epigenetic factors may play a role in its development [19]. Ejaculatory latency time is probably a biological variable, which is genetically determined and may differ between populations and cultures, ranging from extremely rapid through average to slow ejaculation. This is supported by animal studies showing a subgroup of persistent rapidly ejaculating Wistar rats [20], an increased familial occurrence of lifelong PE [19], and a moderate genetic influence on PE in the Finnish twin study [21], and the recent report that genetic polymorphism of the 5-HTT gene determines the regulation of the IELT and that men with LL genotypes have statistically shorter IELTs than men with SS and SL genotypes [22]. In contrast, acquired PE can often be traced to either neurobiogenic (endocrine, urologic, neurobiologic) or psychogenic factors, or in some instances, both [23].

Concomitant Sexual Problems

PE and Erectile Dysfunction (ED)

PE co-exists in about one-third of patients complaining of erectile dysfunction [24]. In fact, PE correlates significantly with erectile dysfunction in all of the regions tapped by the Global Study of Sexual Attitudes and Behaviors [18]. In some instances, PE and ED may form a vicious cycle, where a man trying to control his ejaculation instinctively reduces his level of excitation (which may lead to erectile loss), or where a man trying to achieve an erection basically attempts to do so by increasing his excitation and arousal (which can lead to PE). Furthermore, erectile dysfunction may be superimposed on lifelong PE by efforts to minimize sexual excitement. Finally, PE and ED may be further linked in that lack of ejaculatory control may generate reactive ED, due to anxiety arising from poor sexual performance.

PE and Other Sexual Problems

Hypoactive sexual desire may lead to PE, due to an unconscious desire to abbreviate unwanted penetration. Similarly, diminished sexual desire can be a consequence of chronic and frustrating PE. Interesting, low sexual desire may be due to a lack of sexual arousal, such as in erectile dysfunction. Finally, female sexual dysfunctions (such as anorgasmia, hypoactive sexual desire, sexual aversion, sexual arousal disorders, and sexual pain disorders, as vaginismus [25]) may also be related to acquired PE. The female dysfunction may be secondary to the male PE with or without erectile dysfunction, and can be considered as a frequent complication of this condition. In other cases, PE may be the result of hidden female arousal difficulties [26].

The Treatment of PE

Psychological Considerations and Treatment

PE exerts a significant psychological burden on men, their partners, the male/partner relationship, and their overall relationship [9,27,28]. Men with PE show other negative effects, including a general negative affect associated with sexual situations, and more intense feelings of embarrassment/guilt, worry/tension and fear of failure [17,29]. Relative to men without PE, they indicate decreased self-confidence, increased distress and interpersonal difficulty, and mental preoccupation with their condition [17,28]. Because partner satisfaction may play a greater role in PE than ED, it is not surprising that relationship dysfunction is reported as the second most common negative effect of PE [17,30]. PE is not only associated with marital discord [31], but the insecurity of men with PE about satisfying the partner also serves as an obstacle to initiating and maintaining new relationships [30,32]. Thus, the negative psychosocial impact or burden of PE provides an essential element in the characterization of PE.

Even though a physiological basis for some types of PE has been suspected for years [33,34], until recently, treatment options relied, quite understandably, mainly on behavioral and psychological procedures. First, psychological factors such as anxiety and negative affect have frequently been associated with sexual dysfunctions such as PE [35,36], and therefore treatment addressing such issues has represented a logically consistent approach. Furthermore, until a decade ago, few tested and well-tolerated biologically based therapeutic procedures were available for the treatment of PE. Finally, the psychological-behavioral strategies for treating PE have been at least moderately successful in alleviating the dysfunction [37].

Psychotherapy and behavioral interventions improve ejaculatory control by helping men/couples to: (1) learn techniques to control and/or delay ejaculation; (2) gain confidence in their sexual performance; (3) lessen performance anxiety; (4) modify rigid sexual repertoires; (5) surmount barriers to intimacy; (6) resolve interper-

sonal issues that precipitate and maintain the dysfunction; (7) increase communication [38,39]; and (8) come to terms with feelings/thoughts that interfere with sexual function.

Present day psychotherapy for premature ejaculation most often represents an integration of behavioral (e.g., the well-known start-stop and pause-squeeze methods) and cognitive approaches within a short-term psychotherapy model [35,40–48]. The guiding principles of treatment are to learn to control ejaculation while understanding the meaning of the symptom and the context in which it occurs.

Although the new and often more expedient pharmacological therapies are overshadowing traditional psychological–behavioral methods in the treatment of PE, the psychological–behavioral approach remains an attractive option for several reasons. The treatment is specific to the problem, is neither harmful nor painful, is less dependent on the man's medical history, produces minimal or no adverse side-effects, encourages open communication about sexuality in the couple, which is likely to lead to a more satisfying sexual relationship [49,50], and has a permanence about it. Once the techniques have been learned and incorporated into lovemaking, PE men continue to have access to strategies that help them control their ejaculation. At the same time, there are drawbacks to the psychological–behavioral approach: it is time-consuming, often requires substantial resources of both time and money, lacks immediacy, requires the partner's cooperation, and has mixed (and less well-documented) efficacy [51,52].

Because different types of treatment intervene at different stages in the dysfunctional response sequence in PE men, the choice of outcome measures depends partly on the specific treatment that is implemented. A treatment plan for PE, for example, may primarily address the end point of sexual satisfaction (e.g., with a somatically based problem in which pharmacological treatment is not an option). Alternatively, it could address ejaculatory latency which in turn affects sexual satisfaction, or it might address ejaculatory control (e.g., behavioral-cognitive techniques), which subsequently affects both ejaculatory latency and sexual satisfaction. For example, psychological–behavioral strategies instruct patients in the use of mental imagery, behavioral techniques (e.g., adjusting intercourse position, using pauses, etc.), flexible sexual repertoires, and relationship interactions to develop greater control over the timing of ejaculation. In achieving such control, IELT would be lengthened and greater satisfaction attained.

Pharmacological Treatment

The use of anesthetics to diminish the sensitivity of the glans penis is probably the oldest known form of treating PE [53]. Although the first report of successful ejaculation delay by clomipramine was published in 1973 [54], drug treatment was not used extensively in the treatment of PE until the 1990s, particularly with the introduction of the SSRIs paroxetine, sertraline, fluoxetine, citalopram and fluvoxamine. These drugs block axonal re-uptake of serotonin from the synaptic cleft of central and peripheral serotonergic neurons by 5-HT transporters, resulting in enhanced 5-HT neurotransmission and stimulation of post-synaptic membrane 5-HT2C autoreceptors. Although the methodology of the initial drug treatment studies was poor, later double-blind and placebo-controlled studies confirmed the ejaculation-delaying effect of clomipramine and SSRIs.

Daily and On-Demand Treatment with Serotonin Reuptake Inhibitors (SRIs)

Daily treatment with paroxetine 10–40 mg, clomipramine 12.5–50 mg, sertraline 50–200 mg, fluoxetine 20–40 mg, and citalopram 20–40 mg is usually effective in delaying ejaculation [55–81]. A meta-analysis of published data suggests that paroxetine exerts the strongest ejaculation delay, increasing IELT approximately 8.8-fold over baseline [55]. Ejaculation delay usually occurs within 5–10 days of starting treatment, but the full therapeutic effect may require 2–3 weeks of treatment and is usually sustained during long-term use [82].

On-demand administration of clomipramine, paroxetine, sertraline, and fluoxetine 4–6 hours before intercourse is modestly efficacious and well tolerated but is associated with substantially less ejaculatory delay than daily treatment [83–86]. The assertion that on-demand drug treatment of PE is preferable to daily dosing parallels the rationale for the treatment of ED. However, while many men suffering from PE who engage in sexual intercourse infrequently may prefer on-demand treatment, men in established relationships may prefer the convenience of daily medication.

Dapoxetine is a rapid-acting, short-life SSRI that has received regulatory approval as an on-demand treatment for PE in several parts of the world PE [87–90]. In clinical trials, dapoxetine

30 mg or 60 mg taken 1–2 hours before intercourse is more effective than placebo, resulting in a 2.5- and 3.0-fold increase in IELT, increased ejaculatory control, decreased distress, and increased satisfaction. Although daily dosing of off-label SSRIs appears to be associated with superior fold increases in IELT, direct comparator studies have not been conducted. It is likely that dapoxetine may fulfill the treatment needs of many patients, and its regulatory approval provide assurance to prescribers that expert and regulatory peer review has demonstrated drug efficacy and safety.

Topical Anesthetics

The use of topical local anesthetics such as lignocaine and/or prilocaine as a cream, gel, or spray is well established and is moderately effective in retarding ejaculation [33,91–102]. However, unless a condom is used, their use may be associated with significant penile hypoanesthesia and vaginal numbness, and resultant female anorgasmia. A recent study reported that a metered-dose aerosol spray containing a eutectic mixture of lidocaine and prilocaine (TEMPE, Plethora Solutions, London, UK) produced a 2.4-fold increase in baseline IELT and significant improvements in ejaculatory control and both patient and partner sexual quality-of-life [101].

Other Pharmacological Treatments

Given that ejaculation is a sympathetic spinal cord reflex that could theoretically be delayed by α1-adrenergic blockers, such agents have been considered for the treatment for PE [103,104]. Because subjective end points of patient impression of change and sexual satisfaction rather than actual ejaculatory latency were used in these studies, and because small sample sizes were small, additional controlled studies, are required to determine whether α1-adrenergic blockers will have a place in the treatment of PE.

Tramadol is a centrally acting synthetic opioid analgesic with an unclear mode of action that is also a weak inhibitor of re-uptake of GABA, norepinephrine, and serotonin [105]. The efficacy of on-demand tramadol in the treatment of PE was recently reported in two RCTs [106,107], but both studies had methodological limitations. Although tramadol is reported to have a lower risk of dependence than traditional opioids, its use as an on-demand treatment for PE is limited by the potential risk of addiction [108]. In community practice, dependence does occur, but appears minimal [109]. Additional flexible dose, long-term follow-up studies to evaluate efficacy, safety and in particular, the risk of opioid addiction are required.

Intracavernous self-injection treatment of PE has been reported, but is currently without evidence-based support for efficacy or safety [110]. In the absence of well-controlled studies, treatment of PE by intracavernous injection cannot be routinely recommended, but may be of value in treatment for patients wanting to prolong an erection after ejaculation.

Although used mainly as effective treatments for ED, phosphodiesterase type-5 isoenzyme (PDE5) inhibitors (sildenafil, tadalafil, and vardenafil) have also been used alone or in combination with SSRIs as a treatment for PE [97,111–127]. Although a review of 14 studies on the PDE5i drug treatment of PE has failed to provide robust empirical evidence to support a role of PDE-5 inhibitors in the treatment of PE, with the exception of men with PE and comorbid ED [128], recent well-designed studies do support a role for these agents suggesting a need foir further evidence based research [126].

Treating PE and Comorbid ED

Recent data demonstrate that as many as one-third to one-half of subjects with ED also experience PE [24,129]. PDE5i's alone or in combination with a SSRI may have a role in the management of acquired PE in men with comorbid ED [112,117,122]. The high correlation between improved erectile function with sildenafil and reduced severity of PE indicates that PDE5i-related reduced PE severity is due mainly to improved erectile function [122]. Men with PE and comorbid ED are less responsive to on-demand SSRIs and are best managed with a PDE5i alone or in combination with an SSRI.

The Office Management of PE: A Brief Summarization

Men with premature ejaculation should be evaluated with a detailed medical and sexual history, a physical examination, and appropriate investigations to establish the true presenting complaint, identify obvious biological causes, such as medication or recent pelvic surgery, and uncover sufficient detail to establish the optimal treatment plan (Figure 1).

Relevant information to obtain from the patient includes:

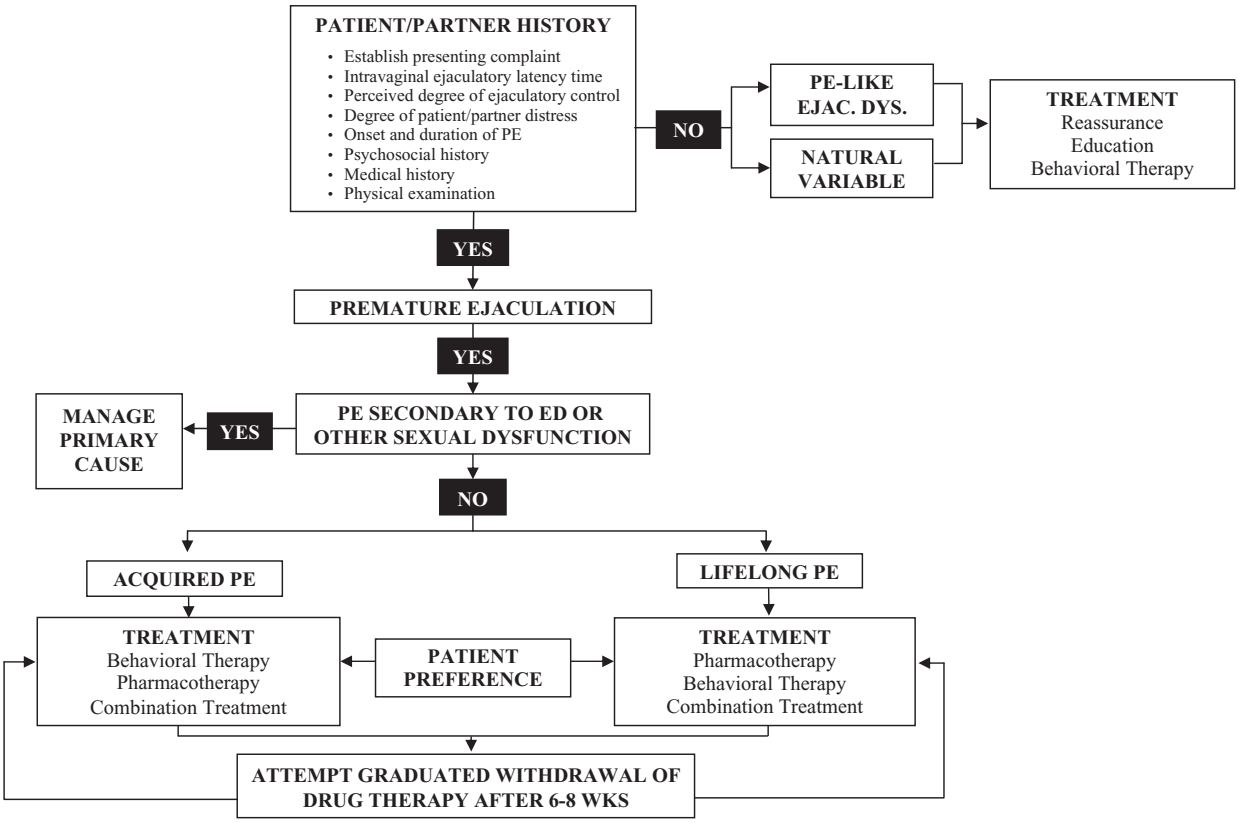

Figure 1 Management algorithm for premature ejaculation (PE).

1. a basic medical history, including the use of prescribed and recreational medications;
2. the cultural context and developmental history of the disorder, including whether the premature ejaculation is global or situational, lifelong or recent in its development;
3. measures of the quality of each of the three phases of the sexual response cycle: desire, arousal, and ejaculation, since the desire and arousal phases may impact the ejaculatory response;
4. details about the ejaculatory response, including the patient's subjective assessment of his IELT and sense of ejaculatory control, the level of sexual dissatisfaction and distress, the frequency of sexual activity, and so on;
5. the partner's assessment of the situation, including whether the partner suffers from female sexual dysfunction (FSD); and
6. assessment of the sexual and overall relationship.

Comprehensive and helpful decision trees that incorporate inclusion and exclusion criteria and that address most of the above points have recently been published in several sources [9,130]. Several paper and pencil instruments that enable the health provider to tap into some or most of the specific domains above are also available [131,132].

Men with PE secondary to erectile dysfunction, other sexual dysfunction, or genitourinary infection should receive appropriate etiology specific treatment. Men with lifelong PE are usually best managed with pharmacotherapy. Men with significant contributing psychogenic or relationship factors may benefit from concomitant cognitive–behavioral therapy [119,133,134]. Recurrence of premature ejaculation is highly likely to occur following withdrawal of pharmacological treatment. Men with acquired PE can be treated with pharmacotherapy and/or cognitive–behavioral therapy according to patient/partner preference [119,133,134]. Restoration of ejaculatory control in men with acquired PE is likely to occur following completion of treatment. Cognitive–behavioral therapy may augment pharmacotherapy to enhance relapse prevention.

Table 2 Causes of delayed ejaculation, anejaculation, and anorgasmia

Psychogenic	Inhibited ejaculation
Congenital	Mullerian duct cyst
	Wolfian duct abnormaility
	Prune belly syndrome
Anatomic Causes	Transurethral resection of prostate
	Bladder neck incision
Neurogenic Causes	Diabetic autonomic neuropathy
	Spinal cord injury
	Radical prostatectomy
	Proctocolectomy
	Bilateral sympathectomy
	Abdominal aortic aneurysmectomy
	Para-aortic lympthadenectomy
Infective	Urethritis
	Genitourinary tuberculosis
	Schistosomiasis
Endocrine	Hypogonadism
	Hypothyroidism
Medication	Alpha-methyl dopa
	Thiazide diuretics
	Tricyclic and SSRI antidepressants
	Phenothiazine
	Alcohol abuse

SSRI = selective serotonin re-uptake inhibitor.

Delayed Ejaculation (DE), Anejaculation, and Anorgasmia: Definition, Epidemiology, and Pathophysiology

Any psychological or medical disease or surgical procedure that interferes with either central control of ejaculation or the peripheral sympathetic nerve supply to the vas and bladder neck, the somatic efferent nerve supply to the pelvic floor, or the somatic afferent nerve supply to the penis can result in delayed ejaculation, anejaculation, and anorgasmia. As such, the causes of delayed ejaculation, anejaculation, and anorgasmia are manifold (Table 2).

Definition, Terminology, and Characteristics of Men with DE

Delayed (DE), retarded ejaculation (RE), or inhibited ejaculation (IE) are probably the least common, least studied, and least understood of the male sexual dysfunctions. Yet its impact is significant in that it typically results in a lack of sexual fulfillment for both the man and his partner, an effect further compounded when procreation is among the couple's goals of sexual intercourse.

Problems with "difficulty" in ejaculating may range from varying delays in the latency to ejaculation to complete inability to ejaculate (anejaculation). Reductions in the volume, force, and sensation of ejaculation may occur as well. At the extremes are anejaculation (time) and retrograde ejaculation (direction), but more commonly encountered is inhibited, retarded, or delayed ejaculation (DE). A final disorder, anorgasmia, refers to a perceived absence of the orgasm experience, independent of whether or not any or all of the physiologic concomitants of ejaculation have taken place.

Terminology and Definition

RE, DE, inadequate ejaculation, IE, idiopathic anejaculation, primary impotentia ejaculations, and psychogenic anejaculation have all been used synonymously to describe a delay or absence of male orgasmic response. If a distinction is to be made, usually inhibited ejaculation is characterized by the complete absence of ejaculation, although no clear consensus exits. Herein, the preferred terminology delayed ejaculation (DE) is meant to describe any and all of the ejaculatory disorders resulting in a delay or absence of ejaculation.

DSM-IV-TR defines DE as the persistent or recurrent delay in, or absence of, orgasm after a normal sexual excitement phase during sexual activity that the clinician, taking into account the person's age, judges to be adequate in focus, intensity, and duration. The disturbance causes marked distress or interpersonal difficulty; it should not be better accounted for by another Axis I (clinical) disorder or caused exclusively by the direct physiologic effects of a substance or a general medical condition [135]. Similarly, the World Health Organization 2nd Consultation on Sexual Dysfunction defines DE as the persistent or recurrent difficulty, delay in, or absence of attaining orgasm after sufficient sexual stimulation, which causes personal distress [10].

There are no clear criteria as to when a man actually meets the conditions for DE, as operationalized criteria do not exist. Given that most sexually functional men ejaculate within about 4–10 minutes following intromission [28], a clinician might assume that men with latencies beyond 25 or 30 minutes (21–23 minutes represents about two standard deviations above the mean) who report distress or men who simply cease sexual activity due to exhaustion or irritation qualify for this diagnosis. Such symptoms, together with the fact that a man and/or his partner decide to seek help for the problem, are usually sufficient for a DE diagnosis.

The Prevalence of DE and Characteristics of Men with DE

The prevalence of ejaculatory disorders is unclear, partly because of the dearth of normative data for defining the duration of "normal" ejaculatory

latency, particularly regarding the right "tail" of the distribution (i.e., beyond the mean latency to orgasm). Furthermore, larger epidemiologic studies have not subdivided various types of ejaculatory disorders (e.g., delayed vs. absent), further limiting our knowledge. In general, DE is reported at low rates in the literature, rarely exceeding 3% [18,136,137]. The prevalence of DE appears to be moderately and positively related to age, which is not surprising in view of the fact that ejaculatory function as a whole tends to diminish as men age.

Failure of ejaculation can be a lifelong problem or an acquired problem. It may be global and happen in every sexual encounter or intermittent or situational. Normative descriptive data from large samples of DE men have not been available, but a recent analysis identified 25% of a clinical sample suffering from lifelong DE, with the remainder reporting a secondary problem [136]. While coital anejaculation is frequently the treatment driver (especially for extremely religious individuals referred for fertility problems), men also seek treatment when distressed by their inability to achieve orgasm in response to manual, oral, or vaginal stimulation by their partner. Many men with acquired DE can masturbate to orgasm, whereas others, for multiple reasons, will or can not. Loss of masturbatory capacity secondary to emotional or physical trauma is also seen. Approximately 75% of one clinical sample [136] could reach orgasm through masturbation, while the remainder either would not or could not.

Similar to men with other types of sexual dysfunction, men with DE indicate high levels of relationship distress, sexual dissatisfaction, anxiety about their sexual performance, and general health issues—significantly higher than sexually functional men. In addition, along with other sexually dysfunctional counterparts, men with DE typically report lower frequencies of coital activity [138]. A distinguishing characteristic of men with DE—and one that has implications for treatment—is that they usually have little or no difficulty attaining or keeping their erections—in fact, they are often able to maintain erections for prolonged periods of time. But despite their good erections, they report low levels of subjective sexual arousal, at least compared with sexually functional men [139].

Pathophysiologies Commonly Leading to Ejaculatory Disorders, Including DE

A number of pathophysiologies have been associated with ejaculatory problems. These include congenital disorders, as well as ones caused by trauma, infection, disease, and treatment for other disorders. When a medical history or symptomatology so indicates, investigation of such possible etiologies may be necessary.

Typical congenital problems include Mullerian duct obstruction, caused by failure of complete absorption of Mullerian duct remnants in the male; Wolffian duct abnormalities, which may compromise vas deferens, ejaculatory duct, and seminal vesicle functioning; and prune belly syndrome. Traumatic damage may result from prostate surgery, surgery following correction of an imperforate anus, and infection. Various cancers in the pelvic region, as well as their treatment (surgical or radiotherapy), may interfere with normal ejaculatory function. Finally, spinal injury and other neurological disorders are prime candidates for ejaculatory dysfunction.

Psychological Etiologies of DE

Like most other sexual dysfunctions, unless a clear pathophysiology has been identified, DE may be best understood as an interaction of organic and psychogenic factors. That is, a biological set point for ejaculatory latency is affected by multiple organic and psychogenic factors in varying combinations over the course of a man's life cycle. Appropriate assessment requires an appreciation of how these factors combine to inhibit ejaculatory response for any particular individual. Among those factors that are psychogenic and/or behavioral, a number of possibilities have been proposed. Although none has been identified or accepted as the primary determinant of DE, some explanations have received more support than others, and some appear more plausible than others.

Psychodynamic interpretations emphasize psychosexual development issues and have attributed lifelong DE to a wide range of conditions, including fear, anxiety, hostility, and relationship difficulties [140–142]. Although some of these factors may contribute to DE in individual men, no well-controlled studies provide broad support, at this point, for any of the various hypotheses for mentioned above [143].

Masters and Johnson were the first to suggest that DE in some men might be associated with orthodoxy of religious belief [144]. Such beliefs may limit the sexual experience necessary for learning to ejaculate or may result in an inhibition of normal function. Many devoutly religious men

have masturbated only minimally or not at all, and for some, guilt and anxiety about "spilling seed" may have led to idiosyncratic masturbatory patterns, which in turn resulted in DE. Such men often had little contact with women prior to marriage, and, although they may have dated, were less likely than their secular counterparts to experience orgasm with a partner, especially through intercourse.

Apfelbaum coined "autosexual" orientation to describe men with DE who prefer masturbation to partnered sex [145]. Many men with DE engage in self-stimulation that is idiosyncratic in the speed, pressure, duration, and intensity necessary to produce an orgasm, yet dissimilar to what they experienced with a partner. Thus, they precondition themselves to possible difficulty attaining orgasm with a partner, and, as a result, experience acquired DE. These men appear able to achieve erections sufficient for intercourse despite a relative absence of subjective arousal [145], and their erections are taken as erroneous evidence by both the man and his partner that he was ready for sex and capable of achieving orgasm. Finally, disparity between the reality of sex with the partner and the use of sexual fantasy (whether unconventional or not) during masturbation is another potential cause of DE. This disparity may take any number of forms: body type, orientation, and sex activity performed [146].

In summary, delayed or absent ejaculation can be a lifelong or an acquired problem. Many psychodynamic explanations have been offered for DE, and these may account for the problem in specific individual cases. More likely, men with DE derive greater arousal and enjoyment from masturbation than from intercourse, an "autosexual" orientation that may involve an idiosyncratic and vigorous masturbation style that interferes with the ability to attain orgasm [147–152]. In fact, masturbatory frequency and style may be predisposing factors for DE, since a substantial portion of men who present with coital DE report high levels of idiosyncratic masturbatory activity [148–152]. Disparity between the reality of sex with the partner and the sexual fantasy used during masturbation may inhibit sexual arousal and thus represent another contributor to DE [146,153]. And finally, the evaluative/performance aspect of sex with a partner often creates "sexual performance anxiety," a factor that may contribute to DE. Specifically, anxiety surrounding the inability to ejaculate may draw the man's attention away from erotic cues that normally serve to enhance arousal [147].

Treatment of DE, Anejaculation, and Anorgasmia

Evaluation and Assessment of DE

Treatment should be etiology specific and address the issue of infertility in men of a reproductive age. If a man has difficulty with ejaculation, or has a small volume or absent ejaculate, it should first be established whether the problem is congenital or acquired, and whether organic factors are implicated. Assessment begins by reviewing the conditions under which the man is able to ejaculate, for example, during sleep, with masturbation, with partner's hand or mouth stimulation, or infrequently with varying coital positions. The course of the problem is documented, and variables that improve or worsen performance are noted. Questions concerning the man's ability to relax, sustain, and heighten arousal and the degree to which he can concentrate on sensations are posed [130]. If orgasmic attainment had been possible previously, the life events/circumstances temporarily related to orgasmic cessation are reviewed. The events in question maybe pharmaceutical, congenital problems, illness, trauma, or a variety of life stressors and other psychological factors—for example, following his wife's mastectomy, the man is afraid of hurting her and therefore only partially aroused. Societal/religious attitudes that may interfere with excitement are noted, such as the spilling of seed as a sin. Finally, questions concerning the quality of the nonsexual relationship are posed and problems explored. This assessment in conjunction with appropriate physical examination and laboratory results will provide understanding and determine an appropriate treatment path.

Before considering a psychological/behavioral approach toward the treatment of DE, clinicians first need to exclude probable iatrogenic and pathophysiological causes. They should, for example, be alert to various medical conditions, as well as medications that might delay ejaculation, and, in the case of antidepressants, consider a reduction in dose or use of antidote [154]. Vascular or neuropathic damage that causes DE is usually irreversible and therefore the patient might be counseled to seek alternative methods to achieve mutual sexual satisfaction with his partner. Whether a clear pathophysiological cause is present or absent, patients might be counseled to consider lifestyle changes, including enjoying more time together to achieve greater intimacy, minimizing alcohol consumption, making love when not tired, and practicing techniques that maximize penile stimulation, such as pelvic floor

training [143]. Patient education regarding existing factors that can exacerbate their delayed ejaculation is an important first step and may represent a segue into either short-term or long-term counseling.

Investigating and Alleviating Organic Factors in DE or Anejaculation

Along with a medical history, physical examination may help establish whether organic factors play a role in the DE, including whether the testicles and epididymes are normal, and whether the vasa are present or absent, on each side. It is also important to establish whether ejaculation is retrograde or absent, with the presence of spermatozoa in urine indicating retrograde ejaculation.

If the etiology is unclear, organic factors such as hemospermia may require investigation. Culture of expressed prostatic secretion and urine will define the nature of an infective process such as prostatitis [155] and urine cytology, and serum prostate specific antigen should be assayed to exclude bladder or prostatic cancer. Ultrasound scan of the testicles and epididymes may define any local disease.

Patients with ejaculatory duct obstruction usually present with infertility. Seminal analysis may simply be reported as showing azoospermia or oligozoospermia, but the characteristic biochemical changes should be sought. When vasa are absent, it is important to establish whether the condition is unilateral or bilateral. With unilateral absence of the vas deferens, the urinary system must also be checked by ultrasound scanning, as coexisting renal anomalies may be present [156]. With bilateral absence or malformation of the vasa, it is essential to consider whether the anomaly may be part of a genetic defect associated with carriage of the potentially harmful cystic fibrosis chromosome anomaly [157].

In addition to the general investigation, more focused investigations may be warranted when a medical history or symtomatology suggests. These may include such procedures as imaging for ejaculatory duct obstruction, electrophysiological evaluation of neural pathways controlling ejaculation, pudendal somatosensory and motor evoked potentials, sacral reflex arc testing, and sympathetic skin responses.

Psychological Strategies in the Treatment of DE

Beneficial effects through psychotherapy depend on the severity of the DE and the individual's receptiveness to engage in counseling and adhere to the counselor's recommendations. Indeed, for DE that has its probable roots in psychological and behavioral issues, psychotherapy is probably the only effective treatment, as effective drug treatment is limited and poorly tested. The man who presents with DE for whom organic and pharmacologic causes have been eliminated requires thorough psychosexual assessment. His partner and the quality of the relationship also warrant exploration. Numerous psychotherapeutic processes are described for the management of delayed or inhibited ejaculation [140,144,145,158], and some appear to be effective, but none has been properly evaluated in large scale samples [159]. Among these strategies are: (i) sex education; (ii) reduction of goal-focused anxiety; (iii) increased, more genitally-focused stimulation; (iv) patient role-playing an exaggerated ejaculatory response on his own and in front of his partner; (v) masturbatory retraining; and (vi) re-alignment of sexual fantasies and arousal strategies.

Treatment strategies for DE have typically been based upon the etiologies previously described, and most benefit from cooperation of the sexual partner. Successful treatment approaches typically begin by recognizing the importance of de-stigmatizing the dysfunction, providing appropriate sex-response education to the couple, and defusing dyadic tension that might have evolved in response to the dysfunction. For example, discussion of a potential biologic predisposition is often helpful in reducing patient and partner anxiety and mutual recriminations, while simultaneously assisting the formation of a therapeutic alliance with the health care professional [136].

Most current sex therapy approaches to DE emphasize the importance of masturbation in the treatment of DE, with most of the focus on "masturbatory retraining" integrated into sex therapy [136,160]. Masturbation retraining is, however, only a means to an end, and the true goal of most current therapeutic techniques for DE (either lifelong or acquired) is to both provide more intense stimulation and induce higher levels of psychosexual arousal so the man can attain orgasm within the framework of a satisfying partnered experience. A number of strategies have been utilized to achieve the end points of increased arousal and satisfaction.

Men with lifelong anorgasmia (a complete lack of ejaculatory response), like their female counterparts, typically need help determining their sexual arousal preferences through self-exploration and

then in communicating that knowledge to their partner. Masturbation training may use a modification of the model described by Barbach [161] for women. Progressing from neutral sensations to the ability to identify and experience pleasurable sensations is encouraged whether or not ejaculation should occur.

Typically, self-stimulation techniques incorporating fantasy can be used to achieve incremental increases in arousal that eventually enable orgasm. Fantasy can serve the purpose of increasing arousal and blocking inhibiting thoughts that might otherwise interfere. Once the man's ejaculatory ability is established through masturbation, the same skill set can be incorporated into sex with the partner. Although some cultures and religions forbid masturbation, temporary religious dispensation is sometimes available, especially when procreation is a goal of treatment.

An important component in the treatment of any type of DE is the removal of the "demand" (and thus anxiety-producing) characteristics of the situation [145]. "Ejaculatory performance" anxiety can interfere with the erotic sensations of genital stimulation and may result in levels of sexual excitement insufficient for climax (although they may be more than adequate to maintain an erection). To reduce anxiety, treatment may include recognition of DE men's overeagerness to please their partners, validation of (though not necessarily encouragement of) the man's autosexual orientation, removal of stigmas suggesting hostility or withholding toward their partner, and general anxiety reduction techniques such as relaxation and desensitization. By normalizing the anorgasmia, therapy can then explore factors that increase the man's arousal (similar to treatment of anorgasmia in women). Finally, like a previously anorgasmic woman, the man is taught to effectively communicate his preferences to his partner so that both their needs are incorporated into the sexual experience.

As with counseling for other kinds of problems, men with DE may resist the recommendations of the therapist. For example, a therapeutic suggestion to temporarily discontinue masturbation may be met with resistance by the patient. In addition to suspending masturbation, the patient might be encouraged to use fantasy and bodily movements during coitus that help approximate the thoughts and sensations previously experienced in masturbation. This process is facilitated and resistance minimized when the man's partner is supported by the practitioner and understands that the alteration in coital style is part of a series of steps designed to reach a long-term goal of coital harmony and satisfaction for them both.

The partner also needs to collaborate in the therapeutic process, finding ways that not only enhance the man's arousal, but to accept the use of erotica and various (harmless) sexual fantasies that also might be incorporated into the couple's lovemaking. Furthermore, because interventions used in the treatment of DE may be experienced by the female partner as mechanistic (e.g., using a stepwise program) and insensitive to her sexual needs, the therapeutic challenge is to facilitate the rapport between the partners, while maintaining a therapeutic alliance with both partners and simultaneously optimizing his response to her manual, oral, and vaginal stimulation.

Finally, issues surrounding reproduction/conception may need to be addressed, as this issue is often an initial driver for treatment. If discordance exists in the couple's reproductive goals, the practitioner must find an acceptable way to refocus the treatment, at least temporarily, on the underlying issues responsible for the discordant goals in order for DE treatment to succeed. This process may require individual sessions with the man and occasionally with the partner as well.

The success of treating DE is difficult to assess from the literature [159], as the evidence on the effectiveness of various treatments is limited [52,143], and both successful and unsuccessful case reports have been cited [145,150]. Although many treatments for DE have been suggested in the psychotherapy literature [140,144,162–166], few have been subject to rigorous testing. Masters and Johnson [144] reported a low failure rate of 17.6% using a treatment combination of sensate focus, vigorous noncoital penile stimulation, and modifications of intercourse technique. Other studies have reported success rates in the neighborhood of 70–80% using a variety of treatment approaches [167]. However, these analyses represent, for the most part, uncontrolled reports with treatment ranging from a few brief sessions of sex education to nearly 2 years of multiple-modality treatment in more complex multiple etiologic cases.

Drug Treatment for DE and IE

Treatment of delayed or inhibited ejaculation with pharmaceuticals has met with limited success. No drugs have been approved by regulatory agencies for this purpose, and most drugs that have been identified for potential use have limited efficacy,

impart significant side-effects, or are yet considered experimental in nature. In some instances, the drugs may only indirectly affect ejaculatory latency by affecting other components of the sexual response cycle; in other instances, the drugs have been used primarily to counter effects of other pharmaceuticals that iatrogenically induce delayed or inhibited ejaculation.

Alpha-1 adrenergic receptor agonists such as imipramine, ephedrine, pseudoephedrine and midocrine may eventually have a role in the pharmacological treatment of inhibited ejaculation. A recent study reported that midocrine reverses organic anejaculation in non-SCI subjects in more than 50% of patients, but further study is needed before any conclusions can be drawn [168].

The antihistamine cyproheptadine, which increases cerebral serotonin levels, is anecdotally associated with the reversal of anorgasmia induced by the SSRI antidepressants, but no controlled studies are known [169–174]. These studies suggest an effective dose range of 2–16 mg., with administration on a chronic or "on demand" basis [170], Its sedative effects are likely to diminish its overall efficacy.

Amantadine, an indirect stimulant of dopaminergic nerves both centrally and peripherally, has been reported to stimulate sexual behaviour, ejaculation, and other sexual reflexes in rats [175,176]. Several authors have reported an effect for amantadine (100 mg) in the reversal of SSRI antidepressant induced anorgasmia [170,177–181] when administered 5–6 hours before coitus.

A variety of other pharmacological agents, including yohimbine, buspirone, apomorphine, quinelorane, and oxytocin purportedly increase the likelihood of ejaculation in men with DE. For these agents, large sample studies have not been carried out, and their use has been primarily experimental, limited, or anecdotal. As a result, findings are not sufficiently robust to recommend their use in the treatment of DE.

Office Management of DE and Anejaculation: A Summary

Men with delayed ejaculation, anejaculation, and/or anorgasmia should be evaluated with a detailed medical and sexual history, a physical examination, and appropriate investigations to establish the true presenting complaint, identify obvious biological causes, such as medication or recent pelvic surgery, and uncover sufficient detail to establish the optimal treatment plan (Figure 2).

Relevant information to obtain from the patient includes:

1. a basic medical history, including use of prescribed and recreational medications;
2. the cultural context and developmental history of the disorder, including whether the ejaculatory dysfunction is global or situational, lifelong or recent in its development;
3. measures of the quality of each of the three phases of the sexual response cycle: desire, arousal, and ejaculation, since the desire and arousal phases may impact the ejaculatory response;
4. details about the ejaculatory response, including the presence or absence of orgasm, the prodromal sensation of ejaculatory inevitability and prograde ejaculation, the level of sexual dissatisfaction and distress, the frequency of sexual activity, and so on,
5. a careful physical examination to establish whether the testicles and epididymes are normal, and whether the vasa are present or absent, on each side
6. the partner's assessment of the situation, including whether the partner is suffers from FSD; and
7. assessment of the sexual and overall relationship

Treatment should be etiology specific and address the issue of infertility in men of a reproductive age. Men who never achieve orgasm and ejaculation, or who are suffering from either a biogenic failure of emission and/or psychogenic inhibited ejaculation may require fairly extensive medical evaluation. Men who occasionally achieve orgasm and ejaculation are usually suffering from psychogenic inhibited ejaculation or penile hypoanaesthesia secondary to age-related degeneration of the afferent penile nerves and may respond well to various cognitive–behavioral strategies that include education, enhanced stimulation, and other sexual techniques designed to maximize arousal.

Finally, the majority of men who regularly achieve orgasm but never experience prograde ejaculation or have a greatly reduced prograde ejaculatory volume should be investigated for retrograde ejaculation. The presence of spermatozoa and fructose in centrifuged postejaculatory voided urine confirms the diagnosis. Management involves education and reassurance of the patient, pharmacotherapy or, in rare cases, bladder neck reconstruction. The absence of spermatozoa suggests congenital absence or agenesis of the testis or

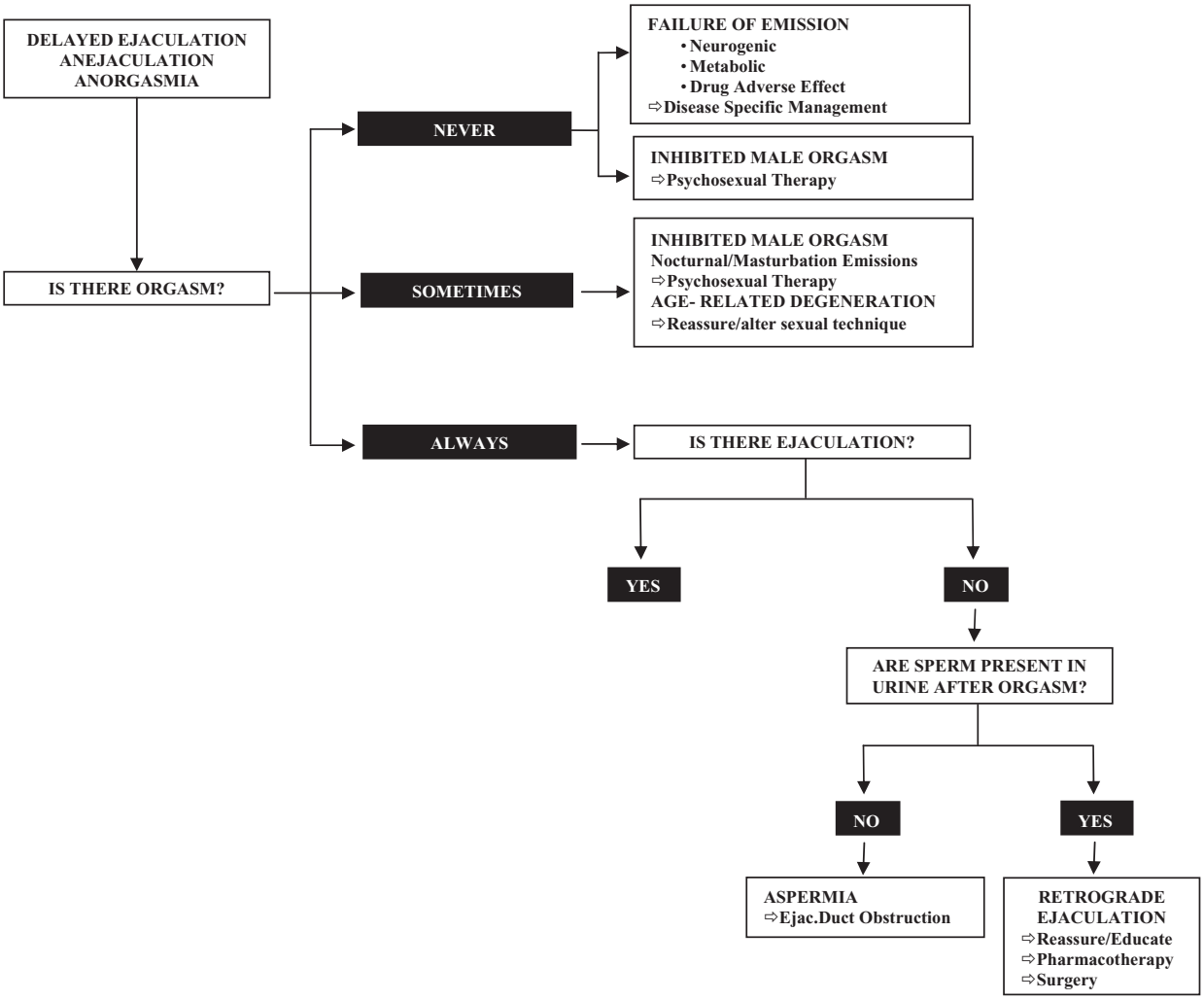

Figure 2 Management algorithm for delayed ejaculation, anejaculation, and anorgasmia.

vas/vasa or acquired ejaculatory duct obstruction. Management involves investigation by ultrasonic or radiological imaging to identify the site of obstruction and disease specific treatment.

The Future

Combined treatment—need for integrated pharmacotherapy and sex therapy approaches—has been gaining acceptance within both medical and counseling circles, and although evidence is yet limited, preliminary research suggests that the patient has much to gain from this more holistic approach [2]. It seems likely that the most effective treatments for PE and DE will follow the pattern seen in the treatment of ED, where an integration of pharmacotherapy and sex therapy is becoming the treatment of choice [182–193]. These recent articles by urologists and sex therapists have advocated a multidisciplinary approach for the treatment of ED, emphasizing the importance of follow-up in providing opportunity for necessary patient education and counseling. Additionally, the integration of sexual counseling and pharmacotherapy is likely to be of assistance to patients seeking adjustment and rehabilitation from multiple medical conditions (e.g., retrograde ejaculation secondary to prostatic surgery). Furthermore, couples presenting multiple sexual dysfunctions are likely to benefit from a model incorporating additional sex therapy with pharmacotherapy. An integrated model allows for resolving and balancing significant intra and interpersonal psychological issues that otherwise may destabilize treatment success. Although large controlled studies are lacking, a number of published case reports inte-

grating sex therapy and pharmacotherapy attest to the efficacy of this approach [194]. The development of new pharmaceuticals will only refine such existing treatment algorithms and improve the opportunity for achieving satisfactory ejaculatory function.

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