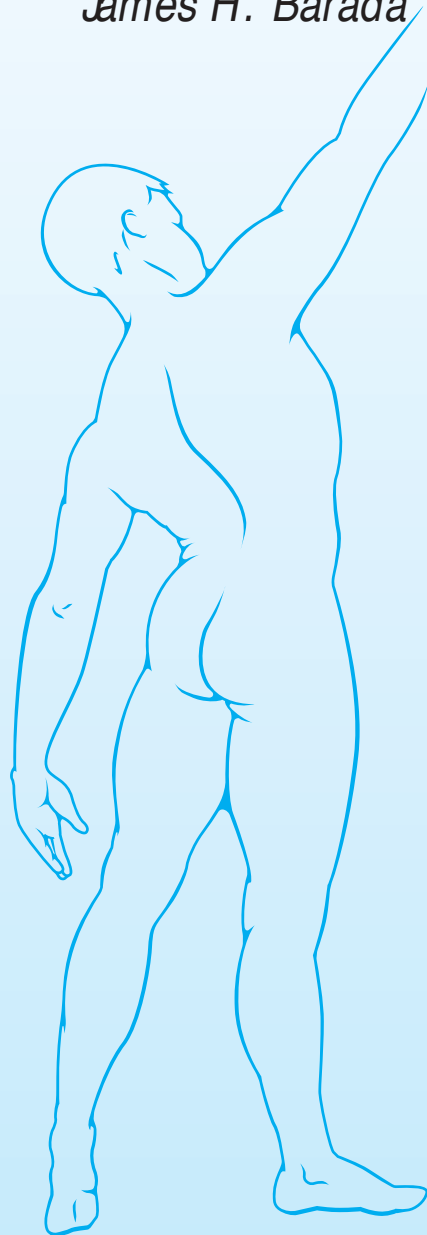


Evaluation and Treatment of the Ejaculatory Disorders

9

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Ejaculation, representing the physiologic means of semen and sperm delivery for reproduction has, until recently, received relatively little attention in the area of male sexual health. Yet, ejaculatory dysfunction, or male orgasmic disorder (MOD), is one of the most common male sexual disorders. The spectrum of MOD extends from premature ejaculation through various manifestations of diminished ejaculation: varying delays in ejaculatory latency to a complete inability to ejaculate, anejaculation, retrograde ejaculation, as well as reductions in volume, force, and sensation of ejaculation. This chapter uses a variety of conventional names describing male orgasmic or ejaculatory disorders. Although all investigators agree on what is being named, they do not necessarily agree on the names themselves.

The sexual response cycle can usefully be conceptualized as having four interactive, nonlinear phases: desire, arousal, orgasm, and resolution. The sexual dysfunctions are disruptions of any of these phases [1]. The normal male “orgasm phase” can, itself, also be described as a three-stage process: emission, ejection, and orgasm. A process of sexual arousal typically leads to this three-stage response. Orgasm is usually coincident with ejaculation, but represents a distinct cortical event that is experienced both cognitively and emotionally. This three-stage model is consistent with the overall paradigm shift within urology, where both organic and psychogenic factors are recognized and integrated into our understanding of sexual function and dysfunction. Conceptualizing three stages provides a better heuristic platform for understanding ejaculatory dysfunctions as secondary to disruptions of any stage in the ejaculatory process, leading to appropriate and specific treatments [2].

Yet, the precise mechanism of ejaculation is much less firmly elucidated than the physiology of erection. Additionally, the prevalence of ejaculatory disorders is also unclear due the lack of normative population data for defining the duration of “normal” ejaculatory latency. Therapies for ejaculatory disorders initially addressed the psychologic features, but with a progressive understanding of biogenic mechanisms, pharmacologic therapy has shown increasing clinical utility and acceptance. Combined pharmacologic and sex therapy may provide a more satisfactory treatment response in that it addresses the adverse physiologic, personal, and relationship sequelae of ejaculatory dysfunction. The presence or perception of satisfactory ejaculation is not purely a procreative requirement, but an important feature of sexual intimacy.

Despite the limitations described above, this chapter illustrates our current knowledge of ejaculation processes, mechanisms, disorders, and treatments.

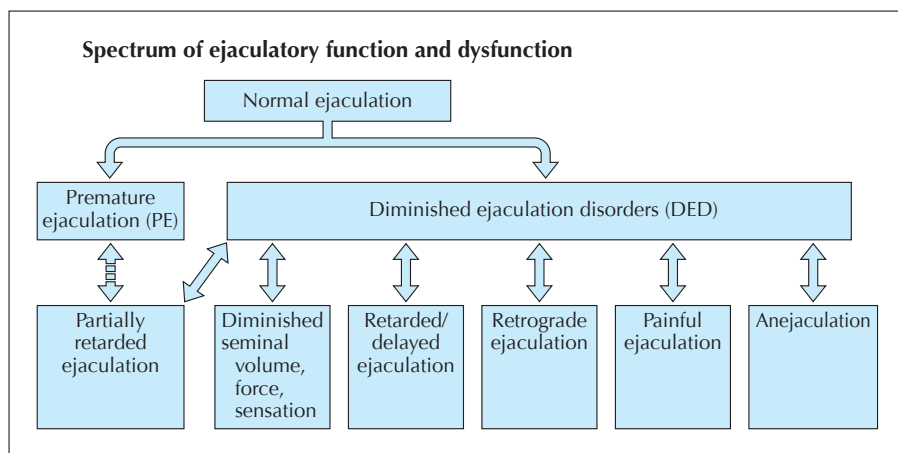


FIGURE 9-1. Spectrum of ejaculatory dysfunction, or male orgasmic disorder (MOD). MOD is a spectrum of disorders that are perceived by the individual as a deviation from an ill-defined “normal” pattern of response. This can be characterized by presence or absence, time and control, pain, volume, or

direction of ejaculation. Individuals may experience a variation in their perception of ejaculation over time or with specific sexual encounters or partners. At the very least, a persistent alteration causing distress must be present. Any of these disorders may include an alteration or elimination of the phenomenologic experience of orgasm itself. The acronym “EjD” has been suggested as a less stigmatized term for the specific disorders of ejaculation that are familiar to us at this time. However, it is potentially controversial terminology due to the risk of perceived “commercial exploitation” in a manner that the terms “ED” (erectile dysfunction) and especially “FSD” (female sexual dysfunction) have been recently criticized in the media and elsewhere.

The definitions, prevalence, mechanism of action, etiology, and treatment of these disorders is described in greater detail in the sections that follow.

ANATOMY AND PHYSIOLOGY

Stages of Normal Ejaculatory Physiology

- Emission
 - Bladder neck closure
 - Deposition of seminal fluid into posterior urethra
- Ejection
 - Expulsion of seminal fluid from the urethra
 - Relaxation of the external sphincter
 - Coordinated pelvic floor, bulbospongiosus contraction
- Orgasm
 - A sensory experience associated with these events

FIGURE 9-2. Stages of normal ejaculatory physiology. Ejaculation has been traditionally viewed as a single event comprising emission, ejection, and orgasm; however, these represent distinct events with separate neural pathways. Following a variable period of sensory stimulation represented by the plateau phase from Masters and Johnson [3], a rapid sequence of events ensue. The emission phase begins with closure of the bladder neck followed by deposition of semen from the seminal vesicles and prostate into the posterior urethra. A

sensation of “ejaculatory inevitability” arises from the distension of the bulbocavernosus and ischiocavernosus muscle contraction. Orgasm is a central sensory event that has significant subjective variation. This event can occur independent of emission, ejection, and erection. An ejaculatory bolus is not required for pleasurable orgasm, as evidenced by men with radical prostatectomy.

Volume of ejaculate, semen viscosity, and quality of the central/peripheral sexual stimulation can affect the perception of orgasm. The refractory period is a time of recovery prior to a second ejaculation. The physiologic reason for a refractory period is unknown, and unlike the female, multiple ejaculation/orgasms are rarely encountered. The refractory period lengthens with advancing age and repeated ejaculations.

Orgasm and ejaculation constitute the third phase of the sexual response cycle. Ejaculation is a reflex comprising sensory receptors and areas, afferent pathways, cerebral sensory areas, cerebral motor centres, spinal motor centers and efferent pathways. The ejaculatory reflex is predominantly controlled by a complex interplay between central serotonergic and dopaminergic neurons with secondary involvement of cholinergic, adrenergic, oxytocinergic, and GABAergic neurons. There are three basic mechanisms involved in normal antegrade ejaculation: emission, ejection, and orgasm [4,5]. Ejaculatory dysfunction can result from disruption at any point in this cascade of events. (Adapted from Gil-Vernet *et al.* [6].)

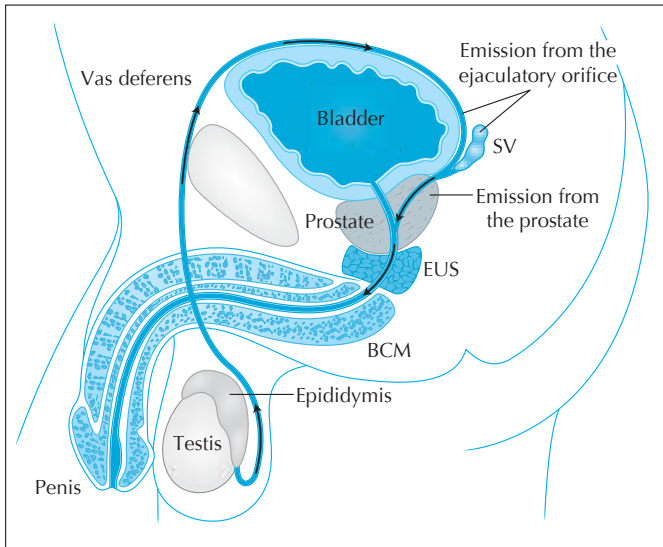


FIGURE 9-3. The physiology of ejaculation. The semen (ejaculatory) volume is derived from the seminal vesicle (50% to 80%), prostate (15% to 30%), Cowper's gland (< 5%) and the testes (< 1%). The total volume and viscosity of ejaculate demonstrates marked variation between individual men and sexual encounters. Infrequent ejaculation is generally associated with increased volumes and viscosity [7,8]. BCM—bulbocavernosus muscle; EUS—external urethral sphincter; SV—seminal vesicle (*Adapted from Mann [7].*)



FIGURE 9-4. Transrectal ultrasound during masturbation. A, Pre-ejaculatory phase (18 s). The *large arrow* is the prostate. The *small arrows* indicate the bladder neck. B, Ejaculation. This real-time transrectal ultrasound recording shows the anatomic and physiologic changes that occur during the pre-ejaculatory phase and ejaculation during masturbation. The infra-montanal urethra (*small black arrows*) filling with prostatic fluid during emission and the contracted preprostatic sphincter can be observed. The *small white arrows* indicate the prostatic urethra. (*From Gil-Vernet et al. [6]; with permission.*)

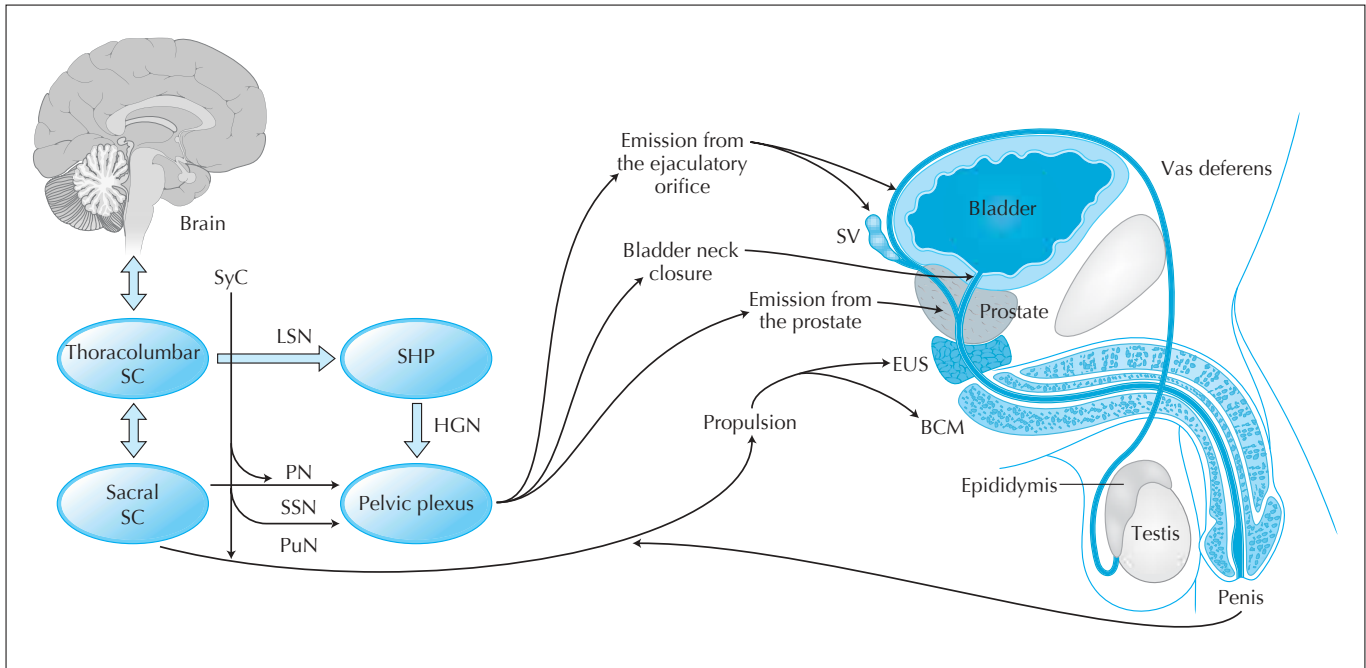


FIGURE 9-5. The neurophysiology of ejaculation. Sensory information from the glans penis travels along somatic afferent pathways within the dorsal nerve of penis to the S4 level of the spinal cord. Seminal emission and ejaculation are centrally controlled by the paraventricular nucleus (PVN) of the anterior hypothalamus and the medial preoptic area (MPOA).

Emission is controlled by the sympathetic nervous system. The cell bodies of the sympathetic neurons are located in the lateral columns of the gray matter in the thoracolumbar segments of the spinal cord. Efferent sympathetic nerves emerge from the ventral roots of the spinal column at Th12-L2 to reach the sympathetic chains bilaterally.

Ejection is controlled by the parasympathetic nervous system. Efferent somatic fibres emerge from the anterior horn of the S2-S4 spinal segments (Onuf's nucleus) and travel in the motor branch of the pudendal nerve to innervate the pelvic floor striated muscles including the bulbospongiosus and bulbocavernosus muscles. Rhythmic contractions of

the bulbocavernosus, ischiocavernosus, and other pelvic floor striated muscles propels seminal fluid into the urethra.

Ejaculatory reflexes remain intact in humans and animals with complete spinal transection between cervical level 3 and lumbar level 3.

Thus, ejaculation is mediated by a spinal control center, located in the lumbosacral spinal cord. This spinal control center has been referred to as the spinal ejaculation generator and spinal pattern generator and spinal pacemaker. There are two different afferent pathways to the spinal cord: 1) sensory fibers of the pudendal nerve (dorsal nerve of penis) up to S4, and 2) sympathetic fibers in the hypogastric nerve that transmits information to the spinal cord sympathetic ganglia. Close contact exists between these autonomic and cerebrospinal nervous pathways. BCM—bulbocavernosus muscle; HGN—hypogastric nerve(s); LSN—lumbar sympathetic nerve(s); PN—penile nerve; PuN—pudendal nerve; SC—spinal cord; SHP—septohippocampal pathway; SSN—sacral splanchnic nerve; SV—seminal vesicle; SyC—sympathetic chain.

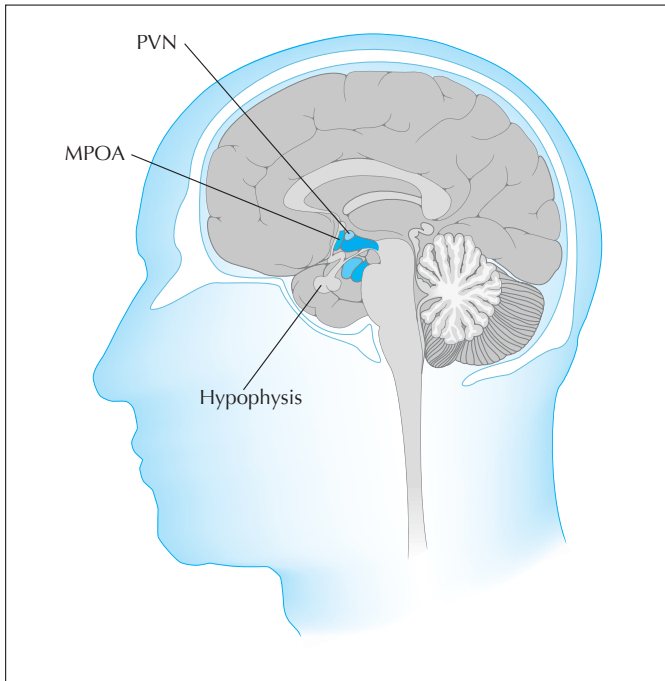


FIGURE 9-6. Cerebral receptor areas. Seminal emission, ejection, and orgasm are integrated into the complex pattern of copulatory behavior by multiple forebrain structures. The medial preoptic area (MPOA), nucleus paragigantocellularis, stria terminalis, amygdala, and thalamus are central to reproductive neurophysiology. Multiple excitatory and inhibitory neurotransmitters are involved including dopamine, serotonin, NO, oxytocin, and GABA. The interaction of individual neural tracts and transmitters has not been fully characterized. Experimental and clinical observations have identified the putative role of central 5-hydroxytryptamine (5-HT). 5-HT has an inhibitory role in sexual behavior in the male. In the rat model, a decrease in central 5-HT neurotransmission decreases the number of intromissions preceding ejaculation and shortens the time to ejaculation. An increase in central 5-HT neurotransmission produces the opposite effect. Administration of different selective serotonin reuptake inhibitors (SSRIs), which results in higher levels of 5-HT, suppresses sexual behavior in male rats [9–11]. PVN — paraventricular nucleus.

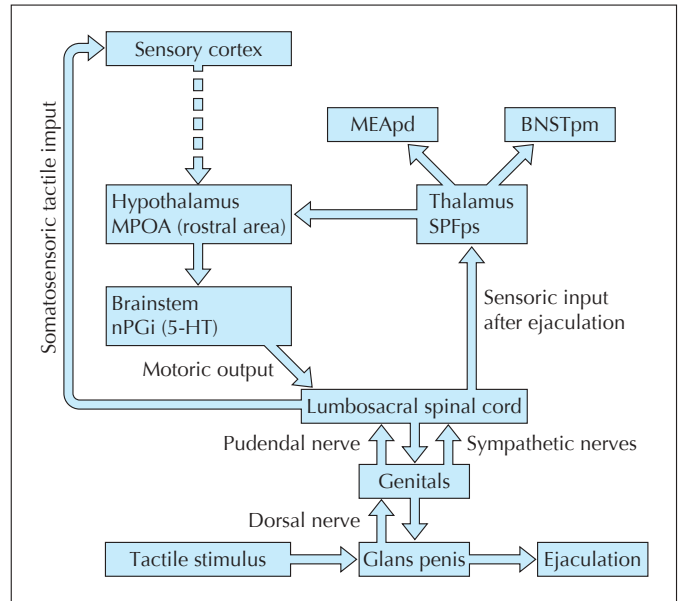


FIGURE 9-7. Central control of ejaculation. Central control of ejaculation is dependent on afferent sensory information and higher cortical areas. It has been observed that the descending serotonergic pathways from the nucleus paragigantocellularis (nPGi) to the lumbo-sacral motor nuclei tonically inhibit ejaculation; conversely, disinhibition of the nPGi by the medial preoptic area (MPOA) results in ejaculation. Several brain areas are activated after ejaculation by ascending fibers from the spinal cord—posteromedial bed nucleus of stria terminalis, lateral subarea of posterodorsal medial amygdala, and medial parvocellular subparafascicular nucleus of thalamus. These areas have a possible role in satiety and determining the postejaculatory refractory time. BNSTpm — posteromedial bed nucleus of the stria terminalis; MEApd — posterodorsal medial amygdale; SPFPs — medial parvocellular subparafascicular nucleus of the thalamus. (Adapted from Waldinger [12].)

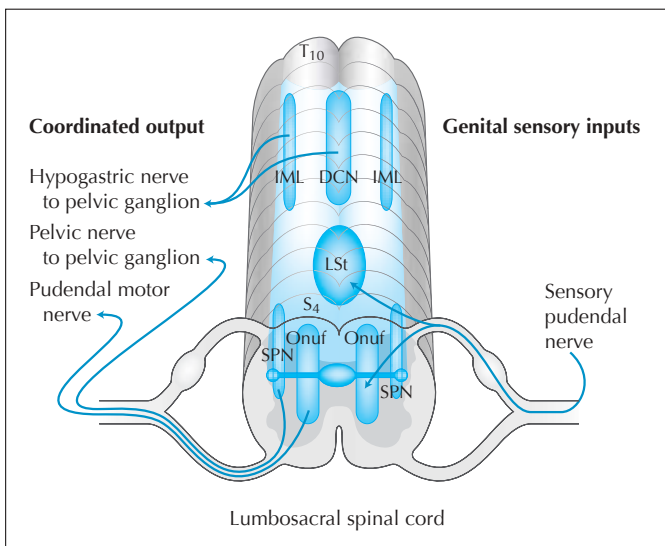


FIGURE 9-8. Efferent pathways. An important secondary ejaculatory center is present in the spinal cord. Ejaculatory reflexes remain intact in humans and animals with complete spinal transection between cervical level 3 and lumbar level 3. Thus, ejaculation is mediated by a spinal control center, located in the lumbo-sacral spinal cord. This spinal control center area has not been fully characterized and is variously referred to as the “spinal ejaculation generator,” “spinal pattern generator,” or “spinal pacemaker.”

The spinal ejaculation generator coordinates the sympathetic, parasympathetic, and motor outflow needed to induce emission and expulsion. The summation of sensory and cortical inputs activate the spinal ejaculation generator, initiating ejaculation and propagating the coordinated complex outflow patterns. McKenna *et al.* (Personal communications) have speculated on a spinal ejaculation generator that coordinates the sympathetic, parasympathetic, and motor outflow needed to induce emission and expulsion. Additionally, this generator integrates the outflow with sensory inputs during sexual activity. DCN — dorsal column nucleus; IML — intermediolateral cell column of the spinal cord; LSt — lateral striatum; Onuf — Onuf’s nucleus; SPN — sacral parasympathetic nucleus.

EVALUATION OF MALE ORGASMIC DISORDERS (MODs)

This section delineates the basic information to be obtained from the patient's history and physical examination, regardless of the specific ejaculatory dysfunction first presented. However,

a detailed algorithm for the evaluation of each specific dysfunction is presented along with treatment recommendations in the subsections that follow this one.

Modified Sexual History Outline

Medical History

- Acute or chronic illness injuries
- Surgeries
- Medications
- Drug or alcohol abuse
- Review of systems

History of the present problem

- Date and mode of onset
- Duration
- Situational context
- Exacerbations and remissions
- Effect of any attempted management

Family history

- Family attitudes toward sexuality
- Religious influences

Sexual history

- Early experience
- Level of sexual knowledge
- Past sexual practices
- Cultural myths
- Masturbatory practices: frequency, technique, etc.
- Sexual fantasy
- Homosexual experiences
- History of negative sexual experiences
- Paraphilias

Current sexual interaction or "sex status"

- Assess all four sexual response phases
- Description of recent sex experience (foreplay, intercourse, orgasm)
- Context of recent sexual experience
- Frequency of intercourse and/or orgasm
- Frequency both partners would prefer
- Presence of fatigue or pain during intercourse
- Types of contraception used
- Duration of sex experience
- Assess intrusive antisexual thoughts

Marital history

- Stability of current relationship
- Existence of communication problem
- Current stressors
- Death
- Illness
- Financial concerns
- Occupational worries

Other

- Who initiates and how
- How does symptom vary with different partners
- Awareness of premonitory sensations

FIGURE 9-9. Modified sexual history outline. The diagnostic evaluation of ejaculatory dysfunction focuses on finding potential physical and specific psychological causes of the disorder. A detailed medical and sexual history yields a significant amount of information regarding the impact of the condition on the man's sexual relationship with his partner. Outlined here is information typically contained in a sexual history. The practitioner must identify which variables are most relevant in understanding the etiology of the chief complaint, and focus the interview accordingly. Asking questions in a relaxed, supportive, and nonjudgmental manner with the opportunity for patient expression and expansion will allow global assessment. The health practitioner needs to recognize the significant anxiety that accompanies open-ended questions when exploring a topic that is generally experienced without social reference points. While open-ended questions may be useful, be wary of being too general as such questions may waste valuable professional time, as well as frustrate and embarrass the patient. However, one query provides a valuable shorthand approach to focus the sexual history taking: "Please tell me about your last sexual experience." Using this question facilitates a focused sex history or "sex status" where the critical information is obtained in a reasonable time. The patient can then elaborate upon onset (lifelong or acquired) and occurrence (global or situational). Patient/partner responses help

assess the quality of desire, degree and duration of arousal, and orgasm. They also help recognize the intimate relationship between ejaculatory dysfunction and other aspects of the sexual experience. The patient's perception of ejaculatory latency time (ELT) and stopwatch measurement have not been validated, but a good correlation is seen with progressively shorter reported ELT intervals. For many men, absolute duration is not the cause of their sexual dissatisfaction, but rather an impeded sense of ejaculatory control. Assess what previous approaches the patient has used to improve their ejaculatory responses. Many men will have attempted herbal or folk therapies for their condition and the effects of any previous treatments should be assessed. Important information can be obtained from the partner's perception of the problem and their satisfaction with the overall relationship. A significant mismatch may present therapeutic difficulties in achieving a successful outcome. It is important to remember that interviewing conducted at the professional's comfort level is the most critical variable in a successful taking of a sexual history. Therefore, it is essential that the professional monitor their own comfort level while pursuing a detailed analysis of sexual behavior, in order to instill the greatest confidence and resulting openness on the part of the patient. (*Adapted from Shenassa and Hellstrom [13] and Perelman [14].*)

Male Orgasmic Disorders: Specific Physical Examination

Physical signs of chronic systemic illness (bruits, distal pulses, neurologic findings, deep tendon reflexes)
 Neurologic examination (gait, muscle strength, reflexes, sacral reflex arc [S2–S4])
 Physical signs of endocrine dysfunction (diabetes mellitus, hypoactive or hyperactive thyroid, adrenal, pituitary disease)
 Secondary sex characteristics
 Testicular examination
 Gynecomastia
 Structural penile lesions/plaque (Peyronie's disease)
 Signs of infection in urethra, prostate, epididymis

FIGURE 9-10. Ejaculatory disorder–specific physical examination. A focused genitourinary sexual examination may identify specific physical findings associated with ejaculatory dysfunction. Additionally concomitant or contributory neurologic, endocrinologic or erectile disorders can be identified and addressed. Particular attention should be given to identifying reversible urethral, prostatic, epididymal, and testicular infections.

Drugs and Ejaculation

Drug Class	Drug	Mechanism of Action	Effect on Ejaculation/Orgasm					
			Decrease Latency	Increase Latency	Absent Ejaculation	Retrograde Ejaculation	Spontaneous Ejaculation	Other
Analgesics NSAIDs	Naproxen	Inhibition of cyclooxygenase (inhibition of prostaglandin synthesis)		X	X			
	Opioids	Methadone	μ -Agonistic activity (inhibition of activity in locus coeruleus–nucleus related with anxiety and fear)		X	X		
Morphine		μ -Agonistic activity (inhibition of activity in locus coeruleus–nucleus related with anxiety and fear)		X	X			
Antihypertensives α -blockers α - and β -blockers Centrally acting	Phenoxybenzamine	α_1 -adrenergic blockage		X	X	X		
	Labetolol	α_1 -adrenergic blockage		X	X			
	Clonidine	α_2 -adrenergic presynaptic receptors (decrease adrenergic tonus)		X	X	X		
	Guanethidine	Sympathetic blockage (by noradrenaline depletion)		X	X	X		
	Methyldopa Reserpine	Central α_2 - adrenergic agonistic action Sympathetic blockage (by noradrenaline depletion)		X X	X X			
Antiparkinsonism drugs	Bromocryptine	Antagonism of D_1 receptors		X	X			
	L-DOPA	Agonistic action in dopaminergic receptors and residual agonist in α - and β -adrenergic receptors	X X	X				
	Pergolide	Potent agonist D_2 action						X
Appetite suppressants	Mazindol	Agonistic action in α - and β -adrenergic receptors						X
Cytotoxics	Methotrexate	?		X	X			
	Vincristine	?		X	X			
Hormone antagonists	Cyproterone acetate	Antagonism of prostatic androgenic receptors		X	X			
Hypnotics and sedatives	Barbiturates (all)	Increase of GABA-ergic tonus		X	X			
Lithium		Reduction of neuron reaction to α -adrenergic stimulation (blockage of IP_3 production)		X	X			

(Continued on next page)

FIGURE 9-11. Drugs and ejaculation [15,16]. MAOI—monoamine oxidase inhibitor; SSRI—selective serotonin reuptake inhibitor.

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Drugs and Ejaculation (continued)

Drug Class	Drug	Mechanism of Action	Effect on Ejaculation/Orgasm					
			Decrease Latency	Increase Latency	Absent Ejaculation	Retrograde Ejaculation	Spontaneous Ejaculation	Other
Psycho-pharmaceuticals Antidepressants	SSRIs	Increase of serotonergic tonus, especially by agonistic action in 5-HT ₂ and 5-HT ₃ receptors						
	Trazodone	Blockage of α_1 adrenergic		X	X	X		
	MAOIs	Increase of serotonergic and noradrenergic tonus		X	X			
	Isocarboxazid	Increase of serotonergic and noradrenergic tonus		X	X			
	Phenelzine	Increase of serotonergic and noradrenergic tonus		X	X			
	Tranlycypromine	Increase of serotonergic tonus		X	X			
	Benzodiazepines	Increase of GABA-ergic tonus		X	X			
Anxiolytics Neuroleptics	Chlorpromazine	Blockage of dopaminergic receptors and residual blockage of α_1 -adrenergic receptors		X	X	X		
	Fluphenazine	Blockage of dopaminergic receptors and residual blockage of α_1 -adrenergic receptors		X	X			
Phenothiazines	Levomepromazine	Blockage of α_1 -adrenergic receptors and residual blockage of α_1 -adrenergic receptors				X		
	Perphenazine	Blockage of α_1 -adrenergic receptors and residual blockage of α_1 -adrenergic receptors		X	X			
	Pipothiazine	Blockage of α_1 -adrenergic receptors and residual blockage of α_1 -adrenergic receptors		X	X			
	Thioridazine	Blockage of α_1 -adrenergic receptors and antagonism of muscarinic receptors		X	X			
	Trifluoperazine	Blockage of dopaminergic receptors and residual blockage of α_1 -adrenergic receptors	X	X				
	Chlorprotixene	Blockage of α_1 -adrenergic receptors and residual blockage of α_1 -adrenergic receptors		X	X			
	Thioxitene	Blockage of α_1 -adrenergic receptors and residual blockage of α_1 -adrenergic receptors				X	X	
Thioxanthenes	Zuclopendithiol	Blockage of α_1 -adrenergic receptors and residual blockage of α_1 -adrenergic receptors				X		
		Blockage of α_1 -adrenergic receptors						

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FIGURE 9-11. (Continued on next page)

Drugs and Ejaculation (continued)

Drug Class	Drug	Mechanism of Action	Effect on Ejaculation/Orgasm					
			Decrease Latency	Increase Latency	Absent Ejaculation	Retrograde Ejaculation	Spon-taneous Ejaculation Other	
Butyrophenones	Haloperidol	Blockage of dopaminergic receptors and residual blockage of α_1 -adrenergic receptors						Painful ejaculation
Diphenyl-butylpiperidines	Pimozide	Blockage of α_1 -adrenergic receptors and residual blockage of α_1 -adrenergic receptors	X	X	X			
Muscle relaxants	Baclofen	Agonistic action of GABA B receptors		X	X			
Urinary tract α -blockers	Alfuzosin	α -adrenergic blockage				X		
	Phenoxybenzamine	α -adrenergic blockage				X		
	Prazosin	α -adrenergic blockage				X		
	Tamsulosin	α -adrenergic blockage				X		
	Terazosin	α -adrenergic blockage				X		
α -reductase inhibitors	Finasteride	5- α -reductase 2 inhibition leads to decrease of prostatic DHT						Less ejaculatory volume
Recreational drugs	Alcohol	Increase of GABA-ergic tonus and blockage of NMDA receptors		X	X			
	Amphetamines	Increase of noradrenaline and dopamine activity	X	X				
	Amylnitrite (poppers)	Reduction of adrenergic tension in contractility of human seminal vesicle by NO-cGMP pathway		X				
	Cocaine	Increase of catecholamine activity by noradrenaline and dopamine reuptake		X	X			
	Heroin	μ -Agonistic activity (inhibition of activity in locus coeruleus–nucleus related with anxiety and fear)	X	X				
	Marijuana	Activation of LB1 receptors cannabinoids		X	X			
	Methadone	μ -Agonistic activity (inhibition of activity in locus coeruleus–nucleus related with anxiety and fear)		X	X			
	Tobacco	Activity in cholinergic and noradrenergic transmission		X	X			

FIGURE 9-11.

PREMATURE EJACULATION (PE)

Definitions of Premature Ejaculation (PE)

Defining Source	Definition
DSM-IV-R	Defines PE as “the persistent or recurrent ejaculation with minimal stimulation before, on, or shortly after penetration and before the person wishes it. The clinician must take into account factors that affect duration of the excitement phase, such as age, novelty of the sexual partner or situation, and recent frequency of sexual activity. The disturbance causes marked distress or interpersonal difficulty. The premature ejaculation is not due exclusively to the direct effects of a substance (eg, withdrawal from opioids).”
ICD-10	In defining PE “the general criteria for sexual dysfunction must be met. There is an inability to delay ejaculation sufficiently to enjoy lovemaking, manifest as either of the following: occurrence of ejaculation before or very soon after the beginning of intercourse (if a time limit is required: before or within 15 seconds of the beginning of intercourse); ejaculation occurs in the absence of sufficient erection to make intercourse possible. The problem is not the result of prolonged absence from sexual activity.”
WHO, 2nd International Consultation on Erectile and Sexual Dysfunction	Defines PE as recurrent ejaculation that occurs with minimal stimulation and earlier than desired, before or soon after penetration, which causes bother or distress, and upon which the sufferer has little or no voluntary control.

FIGURE 9-12. Definitions of premature ejaculation (PE). The condition named “premature ejaculation” evokes intense feeling for sufferers. Although there is constant controversy regarding nosology, PE is a well-established term, and there is no question about its meaning, which most men learn during adolescence. Perhaps it is the condition and not the specific name that causes the associated stigma. Any new name would continue to carry a “stigma” because the stigma is attached to the experience of PE. In addition, renaming would cause confusion for researchers, clinicians, and the patient population. Recently “rapid ejaculation” and “early ejaculation” had received some professional use, but historically, the condition has also been referenced in a multiplicity of ways, including ejaculation praecox. A consensus definition of major health organizations (World Health Organization [WHO], American Urological Association [AUA], and Sexual Medicine Society of North American [SMSNA]) should be forthcoming.

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-R, published by the American Psychiatric Association), the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10) and the World Health Organization 2nd International Consultation on Erectile and Sexual Dysfunction [18] provide definitions of PE. These three sources provide similar though not identical conceptual frameworks for classifying an individual as having PE. Included in these references are three general criteria: short ejaculatory latency, a lack of sexual satisfaction, and a lack of self-efficacy regarding the condition. According to ICD-10, ejaculation must occur “within 15 seconds of the beginning of intercourse.” DSM-IV-R is equivocal on duration, stating that “ejaculation occurs with

minimal sexual stimulation before, on, or shortly after penetration.” ICD-10 makes no mention of voluntary control, while DSM-IV-R notes that ejaculation occurs “before the person wishes.” All three nosologies require the man to be distressed (ICD-10 offers a time frame of 6 months; no specific time frame is defined in DSM-IV-R and the WHO definitions). Lastly, both ICD-10 and DSM-IV-R require the clinician to make a judgment regarding the independence of this condition from other mental, behavioral, or physiologic disorders.

Premature ejaculation is a multifactorial diagnosis that has both objective and subjective aspects. Diminished intravaginal ejaculatory latency time (IELT) is an objective finding on which the more subjective aspects of control and personal or relationship distress revolve. It is important to recognize that the absolute measure of IELT may be less important than identifying the distress component, because some relationships have adjusted to the condition. The measurement of time (*ie*, IELT) may be absolute, but should not be the only factor in the definition or diagnosis. In the DSM-IV-R and ICD-9/10, premature ejaculation is considered a psychosexual disorder. The WHO definition does not assign this classification.

Significant limitations of the current definition have made research in PE difficult. Men with PE are not a homogenous group, in that the condition may contain subtypes that would respond to specific therapeutic strategies. The control and distress dimension of the definition await specific validated measurement tools for characterization. As a result, much of the clinical research is often flawed in both assigning of patients and evaluating treatment responses [17–19].

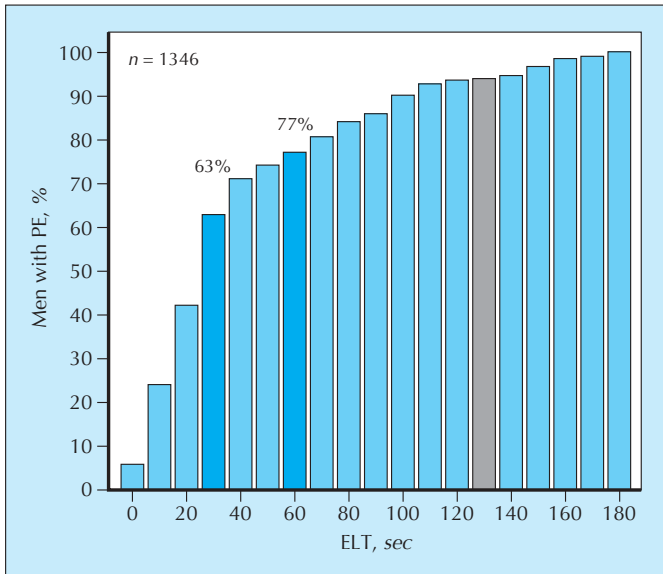


FIGURE 9-13. Intravaginal ejaculatory latency time (IVELT). IVELT is an important objective primary end point for many premature ejaculation (PE) studies. An absolute time threshold for diagnosis has not been established, but in general, a value of less than 2 minutes should provide adequate sensitivity for study inclusion. Waldinger *et al.* [20] reported IVELTs at less than 30 seconds in 77% and less than 60 seconds in 90% of 110 men with PE, respectively. McMahon [21] noted that ejaculation “ante portas” (during foreplay) occurred on the majority of occasions in 5.6% of men with PE. Secondary endpoints or domains are equally important, such as control, satisfaction, and confidence. A major obstacle to our current understanding and application is the lack of normative data for all endpoints of PE research.

Premature Ejaculation: Representative Epidemiologic Studies

Study	Type	Sample Size, PE (%)
Frank <i>et al.</i> (1976)	US couples	100 (42)
Eysenck (1983)	English students	423 (36)
Spector and Carey (1990)	Review	37
Solstad and Hertoft (1993)	Danish	439 (14)
Schiavi <i>et al.</i> (1995)	US men	20 (20)
Read <i>et al.</i> (1997)	Primary care setting	40 (31)
Lauman <i>et al.</i> (1999)	US sample (18–59 years of age)	3159 (29)
Fugl-Meyer and Syogren (1999)	Swedish (18–74 years of age)	4
Simons and Carey (2001)	Review	4
Carson <i>et al.</i> (2003)	US men (40+)	1320 (18)
Ho (2003)	Internet population	1239 (15)

FIGURE 9-14. Epidemiologic studies on premature ejaculation (PE). The epidemiology of PE has not been firmly established. A review of studies indicates a trend of decreasing prevalence.

Limitations in accuracy of these data revolve around varying ages, definitions, sample population bias, and assessment of erectile functioning. By some estimates PE is a common form of sexual dysfunction, approaching the prevalence of erectile dysfunction, a condition in which it often coexists. PE is probably under-reported and under-treated because no approved therapy exists. The true prevalence of PE is unknown and a large community-based study will be required. Design of this study will require data in the areas of comorbidities, sexual preference, ethnicity, and foreskin status. However, it is currently presumed that the vast majority of men who would meet diagnostic criteria for PE are not being diagnosed or treated [22] (Ho K, Unpublished data on file at Johnson & Johnson.) (Adapted from Simons and Carey [23].)

Types of Premature Ejaculation (PE)

Lifelong (primary)

Strong biogenic component
Putative inherited hyper-/hyposensitivity of central 5-HT receptors, interact with psychosocial factors
Variable expression of a psychogenic component

Acquired (secondary)

Psychogenic stressors
Situational
Associated with erectile dysfunction; prostatitis, urethritis; medications

FIGURE 9-15. Types of premature ejaculation (PE). Given the lack of consensus (and supporting data) regarding possible causes of PE, it is not surprising that identification of clear subtypes of PE based on cause has not been successful. Nevertheless, classification of PE into various sub-

types based on developmental histories and response characteristics has sometimes proved useful. For example, most clinicians and researchers distinguish between lifelong and acquired PE, and between PE that is limited to specific situations or partners and that which is more global. Knowing that the patient has had a lifelong history of PE not specific to one partner may argue toward a biologic and/or cognitive cause. However, the need to address interpersonal and relationship issues may be less important in these men. In contrast, knowing that the PE is secondary to a specific individual suggests the need to address relationship issues and attend less to a biologic etiology.

Metz and Pryor [25] provided a complex multilayered classification system for PE including multiple “PE types.” The physiologic types include 1) neurologic constitution, 2) acute physical illness, 3) physical injury, and 4) pharmacologic side effect. The psychologic types include 1) psychologic constitution, 2) acute psychologic distress, 3) relationship distress, and 4) psychosexual skills deficit. This hypothesized classification schemata, which is thoughtful and elaborate, has not been widely adopted by the medical community [24–25].

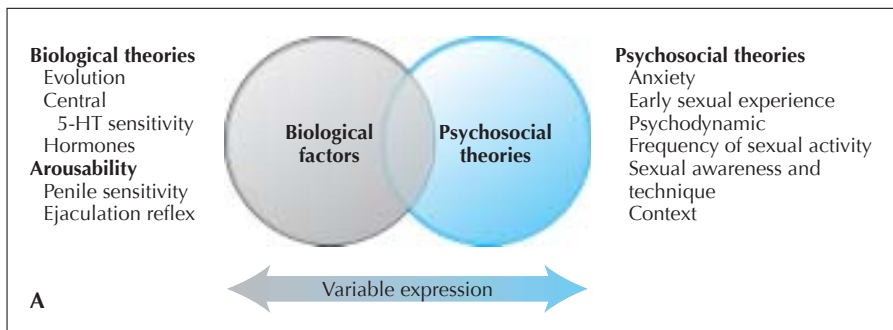


FIGURE 9-16. The multifactorial etiology of premature ejaculation (PE). This figure illustrates the importance of an improved paradigm that recognizes the overlapping interaction of both biogenic and psychosocial factors in understanding the cause of PE. Although the nature of biologic predisposition is not known, it does seem reasonable to conclude that the “threshold” for ejaculatory latency

may be distributed along the same bell-shaped normal distribution curve like so many other human variables. Determining whether the exact physiologic mechanism(s) of such a “threshold” are central, peripheral, or some combination, requires further research. However, this pattern of susceptibility presumably interacts with a variety of psychosocial, environmental, and medical risk factors, resulting in a manifest dysfunction for some men. These are many of the same issues that play a significant role in the cause of both retarded ejaculation (RE) and erectile dysfunction (ED) as well.

The etiologic factors involved are outlined in A and elaborated in the accompanying table (B).
(Continued on next page)

B. Interacting Factors in the Etiology of Premature Ejaculation (PE)

Biogenic

Evolution

PE could result from natural selection. From an evolutionary perspective, copulating quickly was a superior reproductive strategy. Males who copulated more quickly could mate with more females, thus producing more offspring, and passing along a genetic basis for PE.

Central 5-HT receptors

One hypothesized theory of biogenic threshold variability is conceptualizing PE as due to central phenomena, specifically, the hypersensitivity of 5-HT_{1A} receptors or hyposensitivity of 5-HT_{2C} receptors, as supported by neuropharmacologic studies. There is alternative evidence for other possible central mechanisms.

Sex hormones

Pirke *et al.* (1979) suggested that men with sexual dysfunction have different levels of LH, free and total testosterone than men without sexual dysfunction. There were no differences between men with ED, RE, and normal controls of any of the three measured hormones.

Arousability

Men with PE might ejaculate rapidly because they become aroused more quickly than other men. Yet, Spiess *et al.* (1984) and Strassberg *et al.* (1987, 1990) found no differences between men with PE and men without PE in their subjectively or objectively measured sexual arousal in the laboratory.

Disease

A variety of diseases may be associated with PE, but chronic prostatitis is most frequently mentioned. It was suggested that possible mechanisms for prostatitis could cause PE: hypersensitive ejaculatory reflex due to chronic inflammation; intentional deferral of ejaculatory control in an attempt to reduce ejaculatory pain by reducing duration of coitus.

Psychogenic

Psychodynamic theories

Unresolved excessive narcissism during infancy could result in exaggerated importance being placed on the penis and the associated pleasure of urination. Result of an unconscious, deep-seated hatred of women. By ejaculating quickly, the man both symbolically “soils” the woman and robs her of her sexual pleasure. There are no empirical investigations of either theory.

Early sexual experiences

Men whose early sexual experiences are characterized by haste and nervousness may be conditioned to ejaculate rapidly. Men may have conditioned themselves to ejaculate quickly due to, for example, their perception that their partner was not sexually interested. No studies have compared the early sexual histories of men with PE with a non-PE control group. It is not known whether these early conditioning experiences are unique to men with PE. Many men's early sexual encounters involve haste and nervousness. Masters and Johnson did not differentiate between primary and secondary PE.

Anxiety

There are multiple theories of anxiety suggesting a relationship between high levels of sexual anxiety and PE.

It has been hypothesized that increased anxiety activates the sympathetic nervous system, the same system responsible for the emission phase of ejaculation (Kaplan, 1974; Williams, 1984; Wolpe, 1982). However, there is also research not supporting a relationship between anxiety and PE. Kockott *et al.* (1980) subdivided men with PE into high anxiety and low-anxiety groups: High-anxiety men showed PE during intercourse and more sex avoidance behavior; low-anxiety men showed PE during both intercourse and masturbation and less sex avoidance. There was no non-sexually dysfunctional control. Anxiety related to interpersonal sexual activity was not measured and there was no objective, physiological measures of anxiety to validate the subjective self-reports. Other speculated that men with high levels of anxiety are distracted during sexual activity from monitoring the level of arousal or attending to the premonitory sensations of ejaculation (Kaplan, 1974, 1989; Zilbergeld, 1978, 1992).

Frequency of sexual activity: Some researchers have found that men with PE have lower frequencies of sexual activity than men without PE (Gospodinoff, 1989; Spiess, 1984). Underlying mechanism and the direction of the correlation is undetermined. Does more frequent sexual activity lead to increased awareness of sensations premonitory to ejaculation, an increased ejaculatory threshold and decreased anxiety. Do men with PE avoid sex because of their anxiety or embarrassment about their lack of control? There is conflicting evidence, although Waldinger's research supports the accepted concept, that increased frequency of sexual activity in general, increases latency to ejaculation.

Sexual technique: ejaculatory control is a result of consciously or unconsciously learning to use techniques that are effective in delaying ejaculation (Zilbergeld, 1978). It seems that all men with primary PE lack rudimentary skill in adequately managing their bodies in response to progressively escalating levels of sexual arousal, regardless of other predisposing etiological factors [14].

FIGURE 9-16. *Continued* In conclusion, it seems clear that the causes of PE are frequently multidimensional, most importantly a given individual's biogenic predisposition to rapid ejaculatory latency, interacting with intrapsychic and interpersonal issues. The reader should conclude that

similar to ED, despite the existence of organic pathogenesis, PE always has a psychologic component—even if the PE is initially the result of constitution, illness, or treatment. 5-HT—5-hydroxytryptamine; LH—luteinizing hormone.

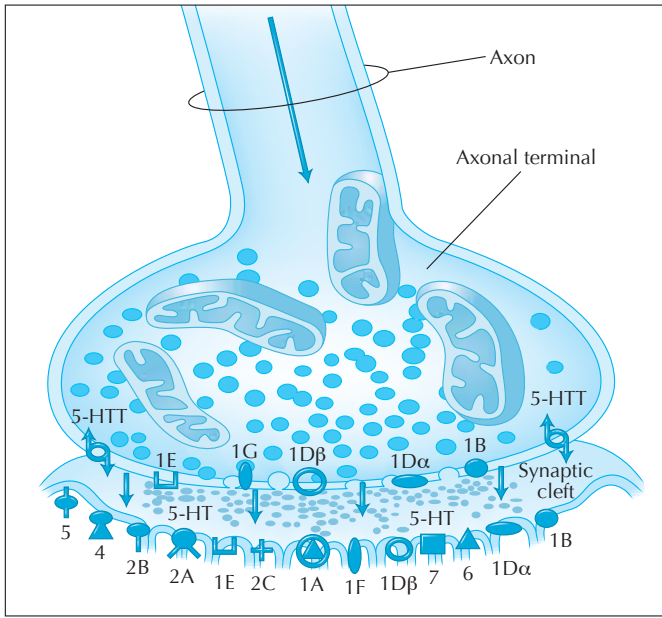


FIGURE 9-17. The central serotonergic neuron. One hypothesized theory of biologic threshold variability is conceptualizing premature ejaculation (PE) as due to hypersensitivity of 5-HT1A or 5-HT2C receptors,

as supported by detailed neuropharmacologic studies. The central serotonergic neuron has not been fully characterized, but 16 different 5-HT receptors (five classes with subtypes) have been identified with varying expression and activity to date. 5-HT activity autoregulation and neural signaling is regulated by multiple mechanisms and receptors. Among these, somatodendritic autoreceptors (5-HT1A receptors), presynaptic autoreceptors (5-HT1B, 5-HT1D receptors) and the 5-HT transporter reuptake system use a variety of different mechanisms to self-regulate their own activity. Each of these mechanisms is a negative feedback system that reduces synaptic cleft 5-HT and prevents overstimulation of the postsynaptic receptors. Additionally, activation of 5-HT1a receptors are attenuated or blocked by activation of 5-HT1C receptors. Increased levels of 5-HT in the synaptic cleft results in downregulation of neural signaling and appears to raise the ejaculatory threshold in response to sexual stimulation. The individual variability of the central 5-HT system may account for the sexual side effect profiles of the widely prescribed SSRI class of drugs.

Other neural pathways may also be involved in ejaculatory regulation. Central dopamine (DA) has a key role in sexual behavior and appears to be regulated via D1 and D2 receptors. DA agonists, *eg*, apomorphine (mixed D1/D2) and quinelorane (D2) facilitate erection and ejaculation whereas dopamine antagonists inhibit sexual responses. DA synthesis and/or release is activated by testosterone [27]. Central activation of the nitric oxide (NO)/cGMP pathway has been shown to affect dopamine (DA)-mediated behavior [28]. Thus, NO could be a bridge between testosterone and central dopamine pathways in ejaculatory regulation.

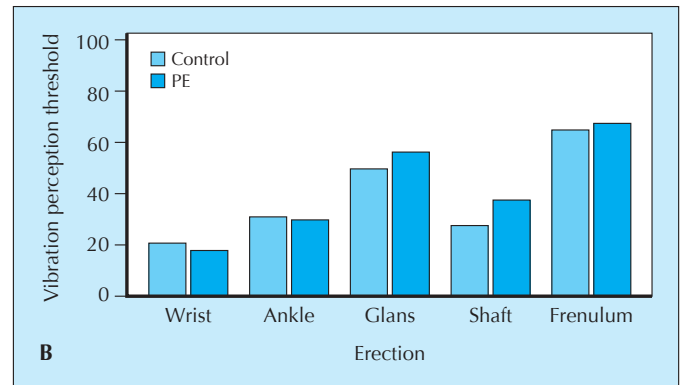
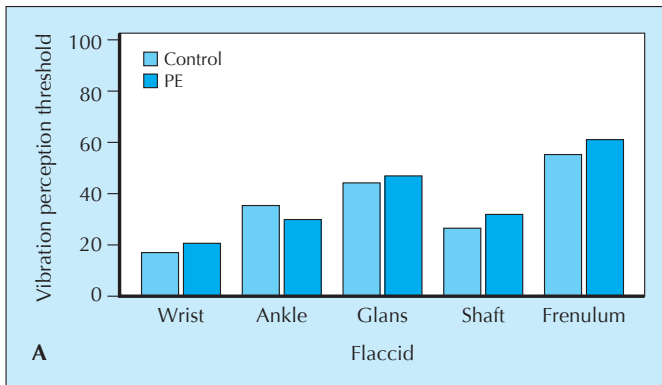


FIGURE 9-18. Glans penis hypersensitivity. It has been hypothesized that men with premature ejaculation (PE) have a greater sensitivity of the penis, glans, and foreskin to sexual stimulation and reach the ejaculation threshold earlier (Ellis, 1936; Rowland *et al.*, 1989; Schapiro, 1943; Strassberg *et al.*, 1990). However, a causal relationship between penile sensitivity has not been firmly established. Xin [29] identified a lower vibratory perception threshold of the penis and glans in men with PE. Paick *et al.* [30] showed no threshold difference in flaccidity (A) and erection (B). Quantitative somatosensory testing by Bleustein [31] showed no glans hypersensitivity difference in circumcised or uncircumcised men.

Another working hypothesis for PE etiology is the presence of a hyperexcitable ejaculatory reflex. This may correlate with a faster bulbocavernosus reflex and interfere with the process of learning to control ejaculation (Gospodinoff, 1989). Colpi *et al.* (1986) showed reduction in evoked sacral potentials in men with lifelong PE but this has not been satisfactorily replicated. Presumed ejaculatory hypersensitivity may reside centrally with a minimal peripheral component. (*Adapted from Paick et al.* [30].)

Historic Treatment for Premature Ejaculation (PE)

<u>Treatment</u>	<u>Description</u>	<u>Results</u>
Depth therapies	Sexual dysfunction as the result of unconscious fears centering around the Oedipus complex, interpersonal dynamics with expressions of anger against the female partner, and depression	Variable, no controlled research
Behavioral therapies	Systemic desensitization, anxiety-reducing techniques, drug-induced relaxation, thought stopping	Variable, no controlled research
Hypnosis	Self-explanatory	Inconclusive
Drug therapy	Afrodex (a mixture of nuxvomica extract, methyl-testosterone, and yohimbine), clomiphene (steroidal triethylene derivative), sargenor	Similar to placebo
Mechanotherapy	Artificial penis (made of flexible, firm, plastic) that fits over the man's dysfunctional penis	Inadequate data for analysis, similar to placebo
Reductive and supportive therapies	Reassurance, education, suggestions to engage in sex only under optimal conditions	Similar to placebo

FIGURE 9-19. Historical treatment for premature ejaculation (PE). (Adapted from the World Health Organization [18].)

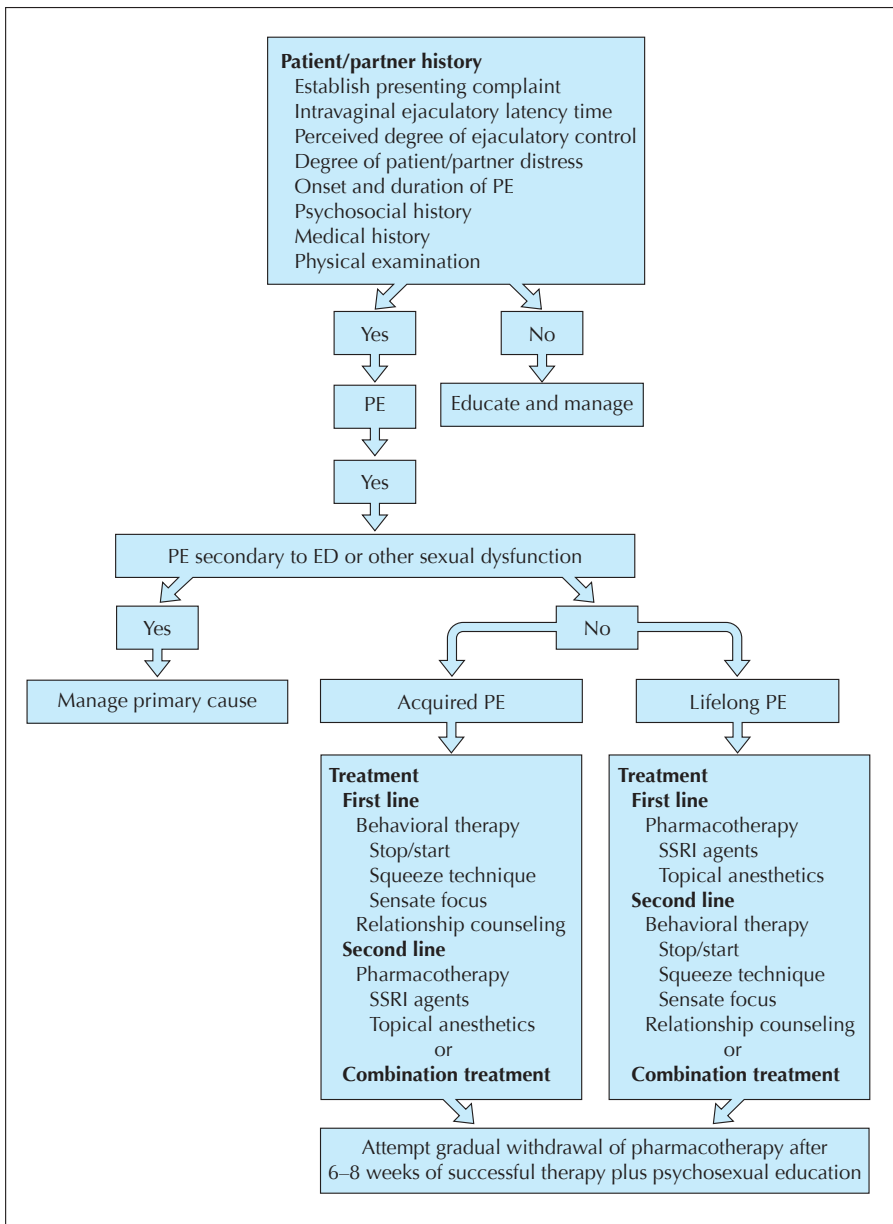


FIGURE 9-20. A diagnostic and therapeutic algorithm for premature ejaculation (PE). This algorithm combines an accurate diagnosis and differential sequential therapy based on the duration of PE. At each juncture, assessment of the patient's perception of therapy is necessary to determine a successful outcome. It may not be necessary to utilize an objective time measurement in every patient as therapy response can be ascertained globally or by patient-reported outcomes from interview or questionnaire. An empathetic, supportive approach is necessary, particularly in those who fail to achieve desired results early in the treatment course. After a period of improved ejaculatory control and latency, an attempt at withdrawal of medications can be made; however, relapse may require a long-term treatment approach. The use of combined therapy with a sex therapist (or a combination approach by a solo practitioner) can identify specific adjustment and relationship issues that may be hampering the full benefit of a pharmacologic treatment approach. Furthermore, by combining sex therapy education (including relapse prevention strategies) and pharmaceutical treatment, an optimum outcome may be obtained. A combination approach allows for titrating down the amount of medication used and potentially weaning the patient from the pharmaceutical entirely. However, this potential is limited by the predisposing effect of the individual's biological predisposition to rapid ejaculation.

.. TREATMENT APPROACHES ..

.. *Psychosexual* ..

Modern Sex Therapies for Premature Ejaculation

Masters & Johnson: 2-week daily therapy using sensate focus, communication exercises and the “squeeze technique” modification of the Semans (1956) procedure
 Individual or couple’s therapy: Kaplan (1974) integrated office psychotherapy + “start/stop” structured sexual exercises or homework assignments
 Majority of sex therapies prescribe 10 to 20 once-a-week sessions
 Early success was good (≈ 75%), but sustained results were modest, unless relapse prevention techniques were used
 Therapy is expensive and time consuming to patient and partner

larized by Masters & Johnson and Kaplan. During the 1970s and 1980s, treatment expanded to group approaches. All used a variety of sexual techniques and exercises teaching and emphasizing physiologic relaxation, increased cognitive awareness of level of self-arousal (eg, prodrome awareness), attentional strategies to attenuate arousal, body management techniques (stop/pause methods), masturbation training (especially useful with single men), coital positional adjustments, adjustment of partner behaviors to reduce arousal, alteration of thrusting style (eg, circular thrusting), and affectionate talking during intercourse.

By the 1990s these sex therapy approaches were criticized for having a number of limitations: their typical reliance on a supportive/cooperative partner, need for high motivation to correct the problem, and practice requiring multiple encounters over an extended period of time. Despite experimentation with alternative treatment formats in general, an experienced qualified therapist was needed and achieved benefits require continued efforts. Although case-reported “efficacy” ranged to a high of 90%, no longitudinal efficacy data supported this figure. Some researchers suggested that initial positive effects disappear after 2 to 3 years [19,32].

However, some clinicians reported that integration of relapse prevention techniques added to effectiveness and longer lasting efficacy [14,24,26].

FIGURE 9-21. Modern sex therapies. A variety of psychologic approaches were first tried during the early 20th century. The results were variable and inconclusive. In general they were similar to placebo without impressive efficacy and no controlled research. In the later half of the twentieth century, empirically supported modern sex therapies emerged. Late 20th century treatments for premature ejaculation (PE) were variations of Semans, popu-

.. *Modern Pharmacotherapy* ..

Medications for Premature Ejaculation

<i>Medication</i>	<i>Class</i>	<i>Mechanism of action</i>	<i>Dose, mg</i>	<i>Tmax, h</i>	<i>Half-life, h</i>
Clomipramine	Tricyclic antidepressant	Non-selective 5-HT reuptake inhibitor	25–50	2–6	32
Fluoxetine	Antidepressant, anti-OCD	SSRI	20–40	6–8	36
Paroxetine	Phenylpiperidine antidepressant	SSRI	20–40	5	21
Sertraline	Antidepressant	SSRI	50–200	4–8	26

*Side effects: drowsiness, tremor, dizziness, insomnia, asthenia, nausea, sexual dysfunction.

FIGURE 9-22. Medications for premature ejaculation (PE). Although the US Food and Drug Administration currently approves no drugs for the treatment of PE, physicians have attempted to control PE pharmacologically for decades. The use of antidepressive agents for managing this condition has been explored. Limited success has been observed in isolat-

ed, small, controlled trials with the tricyclic antidepressant, 5-HT-uptake inhibitor, clomipramine (anafranil, 25–100 mg). Side effects from this medication (ie, anticholinergic, dry mouth weight gain, drowsiness, reduced potency-nausea-vomiting) are problematic and have prevented its wide use. (Adapted from McCullough [33].)

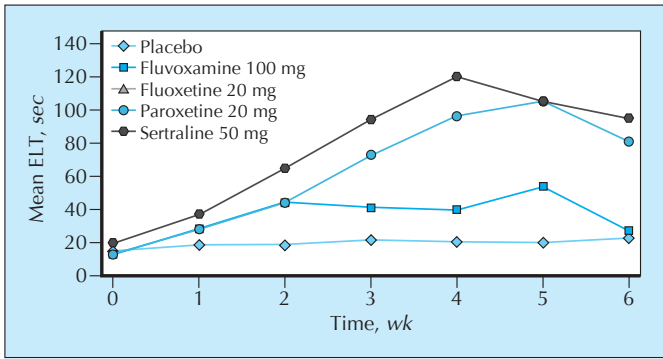


FIGURE 9-23. Effect of selective serotonin reuptake inhibitors (SSRIs) on ejaculation. Premature ejaculation (PE) may be treated pharmacologically with a variety of different medications that act either centrally or locally to retard the psychoneurologic control of ejaculation and subsequent orgasm. It is believed that the selective serotonin reuptake inhibitors enhance 5-HT neurotransmission and activate 5-HT receptors

by blocking presynaptic and somatodendritic 5-HT reuptake transporter receptors, increasing the “ejaculatory threshold set point,” causing ejaculatory delay. Results of several anecdotal case series or controlled studies indicate a role for SSRIs in the treatment of premature ejaculation. Waldinger *et al.* [20], in a 6-week placebo-controlled comparative study of fluoxetine, sertraline, paroxetine, fluvoxamine, and placebo in 60 men with severe premature ejaculation, reported significance increases in intravaginal ejaculatory latency time (ELT) compared with placebo plus fluoxetine, sertraline, and paroxetine but not with fluvoxamine.

When taken as prescribed, these agents are quite effective, although there is often a variable response in ejaculation delay both among and within individuals and medications. Additionally, adverse effects of SSRIs include fatigue, yawning, mild nausea, loose stools or perspiration, all of which present in the first week after intake. While these effects may attenuate within 2 to 3 weeks, reduced libido and mild to moderate erectile dysfunction, may often emerge. It is important to suspend gradually over 3 to 4 weeks to avoid withdrawal symptoms. Unfortunately, cessation of treatment re-establishes the previous set point within 5 to 7 days in men with lifelong PE. (*Adapted from Waldinger et al.* [20].)

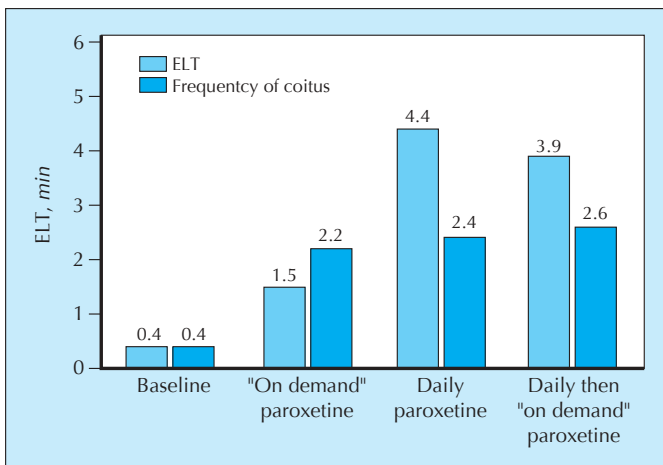


FIGURE 9-24. Chronic versus intermittent paroxetine therapy for premature ejaculation (PE). Selective serotonin reuptake inhibitors (SSRIs) for the treatment of PE are generally administered chronically in a daily dosing regimen. Use of a chronic therapy for an intermittent effect meets resistance, even if a significant benefit of therapy is achieved. Modification of the treatment to an “on-demand” basis, 2 to 6 hours prior to anticipated sexual activity, may be better accepted by patients. A comparison of treatment strategies by McMahon and Touma [34] showed equivalent improvement in ejaculatory latency time (ELT) for paroxetine given on demand only if preceded by a period of daily dosing. An increase in intercourse frequency compared with baseline was equivalent for all groups. There are a variety of explanations including a theory that reduced anxiety secondary to daily dosing increases confidence, which is then maintained with intermittent therapy. However, the exact mechanism of action is not known and this approach requires further replication. (*Adapted from McMahon and Touma* [34].)

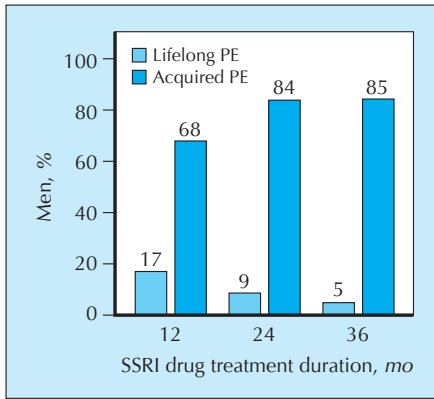


FIGURE 9-25. Restoration of ejaculatory control. McMahon [21] reported that men with lifelong premature ejaculation (PE) respond differently to selective serotonin reuptake inhibitor (SSRI) drugs than do men with acquired PE. Treatment with SSRI drugs was associated with a significantly higher intravaginal ejaculatory latency time (IVELT) in men with lifelong PE compared with acquired PE after 24 weeks of treatment. Restoration of ejaculatory control after drug withdrawal occurred in 68.2% of men with acquired PE within 12 months following treatment with combined paroxetine and ejaculatory control “re-education” using Seman’s stop-start technique. The average duration of treatment was 4.7 months and the prospect of restoration was directly related to the frequency of intercourse and inversely related to age. Only 17.1% of men with lifelong PE achieved restoration of ejaculatory control within 12 months, and rapid ejaculation recurred in 50% of this group over the following 12 months. This variance in response to treatment suggests that the etiology of lifelong PE is different from that of acquired PE, which is consistent with Waldinger’s [35] hypothesis that lifelong PE is a biologic variance of ejaculatory function with a lower ejaculatory threshold “set-point” possibly due to 5-HT receptor malfunction. (Adapted from McMahon [21] and Waldinger [35].)

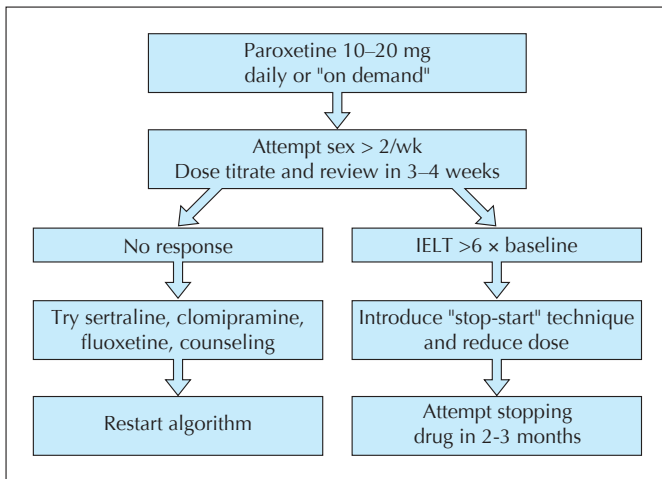


FIGURE 9-26. Use of paroxetine. The integrated treatment of premature ejaculation (PE) is initiated with paroxetine administered either daily at a starting dose of 10 mg or “on demand” 20 mg, depending on relationship status, patient preference, and planned frequency of intercourse. Patients are advised to engage in coitus at least twice a week and to titrate the daily dose of paroxetine up to 20 mg if their intravaginal ejaculatory latency time has not increased to at least 2 to 3 minutes by day 12 to 14. Patients are reviewed at 4 weeks. Patients with poor responses are prescribed another SSRI or clomipramine. Patients satisfied with their response are instructed in the “stop-start” technique of ejaculatory control and paroxetine is slowly withdrawn over the next 2 to 3 months in an attempt to restore ejaculatory control.

PDE-5 Inhibitors and Premature Ejaculation: Possible Mechanisms

Reduced performance anxiety due to better erections
 PDE-5 inhibitors may re-set the erectile threshold to a lower level of arousal
 Possible central effect involving increased NO and reduced sympathetic tone
 Possible peripheral effect involving smooth muscle dilatation in vas deferens and seminal vesicles may oppose sympathetic vasoconstriction and delay ejaculation

FIGURE 9-27. The role of phosphodiesterase-5 (PDE-5) inhibitors in treatment of premature ejaculation (PE). Although not encouraging for primary PE, there has been some experimentation using sildenafil alone or in

combination with other drugs to treat PE. Nitric oxide (NO) is recognized as an important intracellular messenger both peripherally and centrally. Machtens *et al.* [36] reported that the adrenergic tone of seminal vesicle strips “in vitro” was attenuated by NO donors in a dose dependent manner. Proposed mechanisms for a sildenafil effect in the treatment of PE include possible central effect involving increased NO and reduced sympathetic tone; PDE-5 inhibitors may centrally reset the erectile threshold to a lower level of arousal; reduction in the amount of sexual stimulation required for erection, reducing anxiety and allowing distraction; and possible peripheral effect involving smooth muscle dilatation in vas deferens and seminal vesicles to oppose sympathetic vasoconstriction and delay ejaculation.

In an open-label comparison trial, Abdel-Hamid *et al.* [37] showed superiority of combining sildenafil with a start-stop technique over SSRI therapy. The magnitude of effect has not been replicated and may have been due to a significant number of men with combined PE and erectile dysfunction. (*Adapted from Abdel-Hamid et al.* [37].)

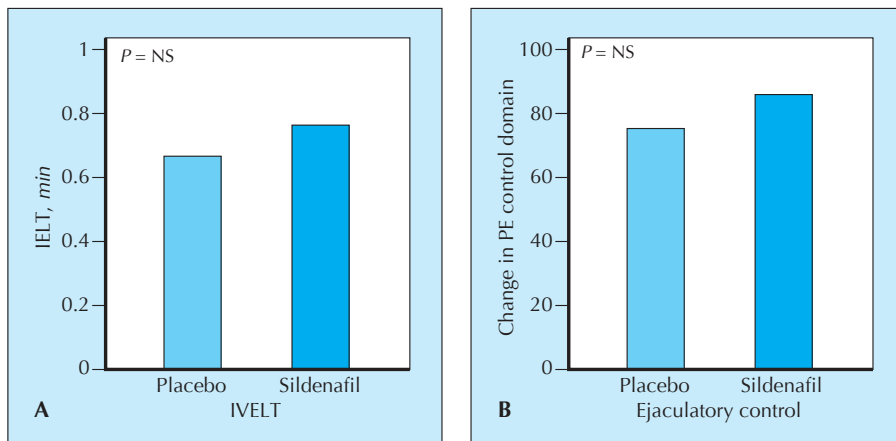


FIGURE 9-28. Sildenafil for premature ejaculation (PE). (A) and (B), The results of a manufacturer-sponsored double-blind placebo-controlled multicenter study show no significant difference in the intravaginal ejaculatory latency time (IVELT) of sildenafil compared with placebo but do

demonstrate significant improvements in the ejaculatory control domain and the ejaculatory function global efficacy question. The latter is possibly consistent with the erectile response of sildenafil. McMahon [38] has demonstrated no benefit of sildenafil over placebo for prolonging IVELT or vibrotactile stimulation. However, a significant reduction in the refractory time following ejaculation was identified, perhaps allowing the use of a secondary erection for intercourse during the same sexual encounter. There is no high level of evidence to support the use of PDE-5 inhibitors in the treatment of rapid ejaculation except in those men who have an indication for concomitant erectile dysfunction. It is unlikely that phosphodiesterase inhibitors have a significant role in the treatment of PE with the exception of men with acquired PE secondary to comorbid ED.

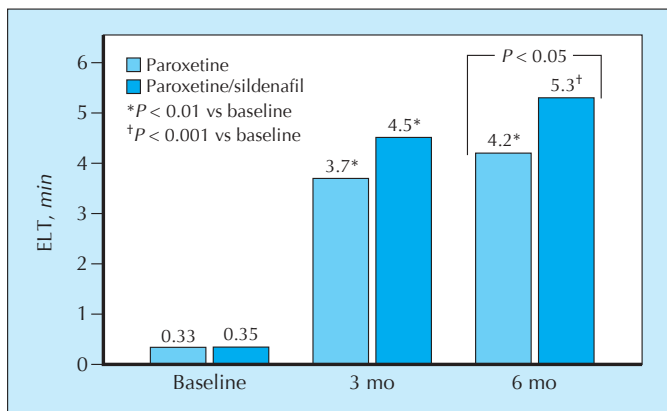


FIGURE 9-29. Intravaginal ejaculatory latency time (IVELT) with paroxetine and sildenafil. In an open-label study of 80 potent men, Salonia *et al.* [39] compared treatment with paroxetine alone, using initial chronic and then “on demand” dosing, with a combination of paroxetine and sildenafil, using the same dosing regimen for paroxetine and sildenafil administered 1 hour prior to intercourse. Both treatments significantly improved the ejaculatory latency time and intercourse satisfaction domain of the IIEF. The combination of paroxetine and sildenafil produced superior results in both end points at 6 months treatment. Additionally, intercourse frequency was higher in the combined treatment group and the authors suggested a possible role of sildenafil in the treatment of rapid ejaculation. The use of combination therapy may have a role in the treatment of PE but comes with an increase in the cost, complexity, and acceptance of therapy. In addition there is exposure to the side effect profile of two drugs along with their specific drug-drug interactions.

Topical Local Anesthetics

Aycokk (1942): dibucaine
 Shapiro (1943): nupercaine
 Damarau (1963): benzocaine
 Berkowicz (1995): lignocaine/prilocaine
 Morales *et al.* (2003): Lignocaine/prilocaine
 Xin *et al.* (1998): SS cream (royal Chinese remedy)

Limitations

- Difficulty in dosing (easy overdosing)
- Anesthesia to the partner
- Messy

FIGURE 9-30. Topical local anesthetics. Use of penile/glans topical local anesthetic sprays or gels as well as barriers (condoms) are widely used therapies for premature ejaculation that have few controlled studies with evolving efficacy data. The proposed mechanism of action is to lessen penotactile sensations felt during intercourse. This has been demonstrated by decreased amplitude of sensory evoked potentials in a laboratory setting. More recent application of potent prescription topical anesthetic desensitizing creams (Lidocaine, EMLA) and a proprietary SS cream have shown moderate effectiveness in uncontrolled studies. Use of the agents may be limited by penile hyposensitivity and transvaginal absorption leading to vaginal numbness. Additionally, the use of creams and barriers is cumbersome and may increase anxiety with a corresponding decrease in erectile capacity.

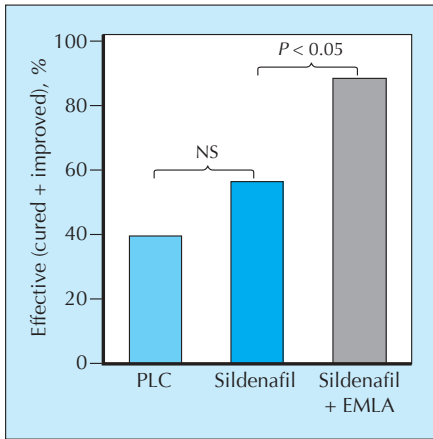


FIGURE 9-31. Sildenafil plus topical EMLA cream treatments for premature ejaculation (PE). Combination therapy of sildenafil has been used in patients. In an open-label study, Tuncel noted no difference in effectiveness between sildenafil and placebo. Combination of sildenafil and EMLA was better than sildenafil monotherapy, but erectile functioning or the effect of EMLA monotherapy was not assessed. (*Adapted from Tuncel, European Society for Sexual Medicine, PS4-5, Istanbul, Turkey, 2003.*)

Level II and III Treatments for Premature Ejaculation

Level II

Intracavernous Injection Therapy for PE

Self injection

Alprostadil monotherapy (Caverject, Edex)

Papaverine, phentolamine, alprostadil in combination

Mechanism of action in PE

Augmented erection and improved ejaculatory control in men with PE secondary to ED

Sustained erection postejaculation allowing continued thrusting

Decreased erectile recovery time allowing rapid achievement of second erection before ejaculatory recovery

Risks

Pain

Priapism

Intracavernous fibrosis and penile curvature/deformity

Intraurethral procedures

Level III

Penile prosthesis

Surgery (dorsal neurotomy)

FIGURE 9-32. Level II and III treatments for premature ejaculation (PE). This figure describes the “second line” use of injection therapy for PE. Intraurethral approaches could also be used in this manner, but some of the same risks and limitations apply and the efficacy is probably even poorer. These approaches are not highly recommended.

Level III interventions are equally ill-advised when treating premature ejaculation, albeit researchers and clinicians have reported using such approaches.

Combination Treatment: Integrating Cognitive-Behavioral Psychosexual Strategies with Pharmaceuticals to Manage Premature Ejaculation

- Pharmaceuticals plus psychosocial education
 - Individual procedures
 - Physiologic relaxation training
 - The pubococcygeal muscle control technique
 - Cognitive and behavioral pacing technique
 - Behavioral stop-start technique
 - Sensual awareness training: entrancement arousal vs partner involvement
 - Cognitive arousal continuum technique
 - Pharmaceuticals plus psychosocial education
 - Couple procedures
 - Couples sensate focus pleasuring exercises
 - The partner genital exploration relaxation exercise
 - Couple use of the behavioral pacing method: stop-start technique
 - The intercourse acclimatization technique, *eg*, “quiet vagina”

FIGURE 9-33. Integrating cognitive-behavioral psychosexual strategies with pharmaceuticals to manage premature ejaculation (PE). A combination drug and behavioral protocol may best produce the necessary learning needed for a cure, with less medication continuously required. Such an approach would integrate pharmaceuticals with sex therapy; combining multiple strategies such as physiologic relaxation, pubococcygeal muscle training, and cognitive behavioral pacing strategies (stop-start technique) and partner involvement (including intercourse accommodation techniques, *eg*, “quiet vagina”). Relapse prevention strategies should also be incorporated to minimize the amount of medication needed long term and to extend the benefits of treatment. (*Adapted from* Perelman [14], Metz [25], and McCarthy [25a].)

Future Goals for the Treatment of Premature Ejaculation

- Effective new therapies are needed
- Demonstration of clinical effectiveness
- Develop ideal oral pharmacologic agents
- “On demand” treatments
- Further development of a combined pharmaceutical and sex therapy algorithm

FIGURE 9-34. Future goals for the treatment of premature ejaculation (PE). There is a significant need to develop effective new therapies for PE. Further basic research may provide novel therapeutic approaches.

More important will be demonstrating clinical effectiveness in all primary and secondary endpoints of PE therapy. An ideal oral pharmacologic agent should have a rapid onset of action and a short half-life without accumulation on repeated dosing. The quantitative increase in IELT should demonstrate significant improvement in the domains of control and satisfaction and be corroborated by both patient and partner. This pharmacokinetic and therapeutic profile provides for “on demand” therapy, which has demonstrated patient acceptance in erectile dysfunction therapy. A number of companies are looking at “on demand” treatments. In fact, Johnson and Johnson have indicated they are currently developing a novel serotonergic agent with rapid onset of action for the treatment of PE that may be used for as needed dosing (Personal communication). These new drugs will provide even greater opportunity for combining both pharmaceutical and sex therapy techniques and procedures in the treatment of PE.

DIMINISHED EJACULATORY DISORDERS (DED)

Diminished Ejaculatory Disorders (DED)

Retarded (delayed/inhibited) ejaculation
Anejaculation
Retrograde ejaculation
Diminished seminal volume, force, sensation
Partially retarded ejaculation
Anorgasmia
Painful ejaculation

FIGURE 9-35. Various types of diminished ejaculatory disorders (DED). DED is a collective term for an alteration of ejaculation that involves a delay in time, pain, reduction in sensation, force, or direction of semen. At the extremes are anejaculation (time) and retrograde ejaculation (direction), but more commonly encountered is delayed ejaculation or

“Retarded Ejaculation” or Delayed Ejaculation/inhibited (RE)

WHO, 2nd Consultation definition: The persistent or recurrent difficulty, delay in, or absence of attaining orgasm, following sufficient sexual stimulation, which causes personal distress.

DSM-IV (1994) definition: Persistent or recurrent delay in, or absence of, orgasm following 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.

Incidence: RE was considered a clinical rarity reportedly at less than 2%. However, some clinical practices report higher rates in settings of religious orthodoxy.

FIGURE 9-36. The DSM-IV-R definition of retarded ejaculation (RE) or delayed ejaculation/inhibited. Multiple terms are used to describe a delay or absence of male orgasmic response. RE, delayed ejaculation, and inhibited ejaculation as well as idiopathic anejaculation, primary impotentia ejaculations, and psychogenic anejaculation have all been used essentially synonymously to describe this problem in men. Like the term “premature ejaculation,” the most commonly used term—retarded ejaculation—is often avoided because of its pejorative associations.

According to the DSM-IV-R, male orgasmic disorder is defined as persistent or recurrent delay in, or absence of, orgasm following a normal sexu-

men volume reduction. Each of these disorders represent some manner in which the normal stages of ejaculatory physiology are disrupted. While defined independently, these conditions may overlap each other. For instance, diminished seminal volume, force, or sensation may be related to aging or may also be a manifestation of a somatic illness such as diabetes.

Partially retarded ejaculation is sometimes observed in men who attempt to control a rapid ejaculation by suppressing the muscular contractions associated with ejaculation. These men experience diminished pleasure and sensation as semen is released during emission, but the ejaculatory sensations are dulled through over control of striated muscle. This may be observed in men who prematurely ejaculate when they attempt to consciously delay their orgasm but end up experiencing a partially retarded ejaculation.

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.

al excitement phase during sexual activity that the clinician, taking into account the person's age, judged to be adequate in focus, intensity, and duration. The disturbance causes marked distress or interpersonal difficulty. The clinician is to note if the orgasmic dysfunction is not better accounted for by another Axis I disorder and is not due exclusively to the direct physiologic effects of a substance or a general medical condition. Failure of ejaculation can be a lifelong primary event (eg, congenital anorgasmia) or an acquired or secondary problem. It can happen in every sexual encounter or it may be intermittent or situational. It may be caused by organic, psychogenic, or combined factors. Some men can masturbate to orgasm; others, for a multiplicity of reasons, would or could not masturbate. Loss of masturbatory capacity secondary to emotional or physical trauma can be identified. Affected men may report intermittent nocturnal emissions, and others are either unaware of or do not have nocturnal emission/orgasm. Coital anorgasmia is the driver for extremely religious individuals referred for fertility problems, although this is not the case for other men distressed by their inability to achieve orgasm in response to manual or oral stimulation by their partner. Retarded ejaculation has been reported in men utilizing therapies for erectile dysfunction [43]. The presence of a surgically or pharmacologically enhanced erection may reduce the need for fantasy or the pleasure awareness normally required for maintaining the erection and experiencing ejaculation. These men experience an unpleasant prolonging of the ejaculatory interval, particularly if associated with anxiety [2]. There is no standard definition of what length of time constitutes RE, but it is not unusual for sexual irritation or exhaustion to be a primary complaint from prolonged intercourse for the man or his partner.

Etiology of Diminished Ejaculatory Disorders

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; retroperitoneal lymph node dissection

Endocrine: hypogonadism; hypothyroidism

Medications (iatrogenic): α -methyl dopa; thiazide diuretics; tricyclic and SSRI antidepressants; phenothiazine

Psychosocial causes: psychodynamics, interpersonal, cultural, behavioral, contextual, cognitive

FIGURE 9-37. Causes of diminished ejaculatory disorders (DED). The organic causes of DED are varied but can be placed in several broad categories: anatomic causes, neurogenic causes, endocrine, and medications (iatrogenic). Disruption in bladder neck competence from surgical therapy for prostatic obstruction is a significant long-term side effect that requires careful preoperative discussion. Pathologic lesions of the sympathetic innervation of the coordinated ejaculatory reflex may result in a variable effect on the quality of ejaculation or orgasm. Commonly used medications, particularly the antidepressants, may cause a central inhibition of ejaculation.

In addition to psychodynamic and interpersonal causes for retarded ejaculation, a biologic etiology should also be considered. There is strong likelihood of biologic variability in the threshold of arousal necessary before experiencing orgasm. Furthermore, it seems likely that the dispersal pattern of ejaculatory latency should resemble the same bell-shaped distribution as do so many other human characteristics. Perelman extrapolated from Waldinger's animal model that individuals experiencing either premature ejaculation (PE) or retarded ejaculation (RE) were likely to be biologically predisposed to their symptom [43]. The dysfunction becomes manifest given certain external factors: medications, sexual circumstances, and intra- and interpersonal dynamics, etc. [18,43]. Rowland *et al.*'s [40] data showed that men with RE reported the lowest levels of sexual arousal in the laboratory, compared with men who reported rapid ejaculation, erectile dysfunction, or were normal controls. Their findings suggest that inhibited arousal may be more common among men with RE, who do not manifest other apparent somatic pathology. Perelman [43] speculated that normal variation in the function of the nervous systems responsible for ejaculation could result in a somatically determined variation between men's ejaculatory latency and capacity. He noted that exploration of biologic predisposition is often helpful by itself in reducing patient and partner anxiety and mutual recriminations, while simultaneously assisting the formation of a therapeutic alliance with the health care professional [43].

Masters and Johnson [3] first indicated that RE was associated with orthodoxy of religious belief. Beliefs may limit sexual experience necessary for developing the knowledge necessary to learn to ejaculate or may result in an inhibition of normal function. Perelman [43] observed that regardless of specific religion involved (*eg*, Muslim, Hindu, Jewish), many devout religious men have masturbated only minimally or not at all. Some of these men masturbated for a period of years like their secular counterparts, but guilt and anxiety about "spilling seed" often resulted in idiosyncratic masturbatory patterns, which in turn resulted in RE. These men often had little contact with women prior to marriage. These very religious men may date, but were less likely than their secular counterparts to experience orgasm with a partner, especially through intercourse. Some of these men did sexually experiment with women who they did not marry; however, their cognitions about these women often reflected a "Madonna-whore" split [43].

Multiple explanations for RE have been offered, with unconscious aggression and unexpressed anger recurring as themes in the RE literature.

Additionally, pregnancy fears received emphasis, since the reason for professional referral is often the female partner's wish to conceive. Finally, Bancroft's [41] model of psychogenic factors in erectile dysfunction depends on a delicate balance between central excitatory and inhibiting mechanisms

would seem to have potential applicability to the understanding of RE as well.

An excellent critical review of the psychological etiology of RE was provided by Apfelbaum [42], who provocatively first noted the sexual politics surrounding RE and female anorgasmia: "Like the woman who has inappropriately been castigated for willfully depriving her husband of the pleasure of bringing her to orgasm. The retarded ejaculator's own belief that he is withholding is widely endorsed, understandably by his partners and less justifiably by most therapists." Not only psychoanalysts, but sex therapists and behavior therapists as well, seemed to assume the RE patient's orgasm is blocked, rather than the patient's level of arousal being insufficient [43].

Apfelbaum [42] observed that some men appeared able to achieve erections sufficient for intercourse despite a relative absence of subjective arousal. He felt these "automatic erections" were taken as erroneous evidence by both the male and his partner that the man was ready for sex and capable of achieving orgasm. Perelman believed this same process was the likely cause of increased anecdotal clinical reports of RE for patients using popular urologic-based treatments for erectile dysfunction. Urologists received a few early complaints of RE, secondary to successful penile prosthesis surgery and intracavernosal injections (ICI). However, sildenafil brought huge numbers of patients to physicians' offices. Many of these patients experienced restored erections and coitus with ejaculation. Although sildenafil has been used with some success to facilitate reversal of the antidepressant sexual adverse effects, the effect of PDE-5 inhibitors may be bimodal. The phenomena of erection without adequate psychoemotional arousal occurred in some men using sildenafil when they did not experience sufficient erotic stimulation before and during coitus. These men confused their erect state as an indication of sexual arousal when it merely indicated vasocongestive success [2,43].

Apfelbaum [42] coined autosexual orientation to describe men with RE who prefer masturbation to partnered sex. Perelman [43] discussed the role of fantasy, as well as masturbation frequency, motivation, and idiosyncratic technique in the etiology and maintenance of RE. Many men with RE engage in stimulation that was striking in the speed, pressure, duration, and intensity necessary to produce an orgasm, and dissimilar to what they experienced with a partner. In this manner, they have preconditioned themselves to likely difficulty with a partner and experience secondary RE. Disparity between the reality of sex with the partner and the sexual fantasy (whether unconventional or not) used during masturbation is another cause of RE. This disparity takes many forms: body type, orientation, sex activity performed, and so on. Many men and women remain inhibited about using their masturbatory fantasies when with their partner. Yet like their female counterparts, when anorgasmic men integrate their masturbation fantasies into sex with their partner, orgasm is more likely [43].

It would seem that DED, like other sexual dysfunctions, is best understood as being caused by an interaction of both organic and psychogenic factors. A biologic 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 each of these factors determines the endpoint dysfunction for a particular individual, at a particular moment in time.

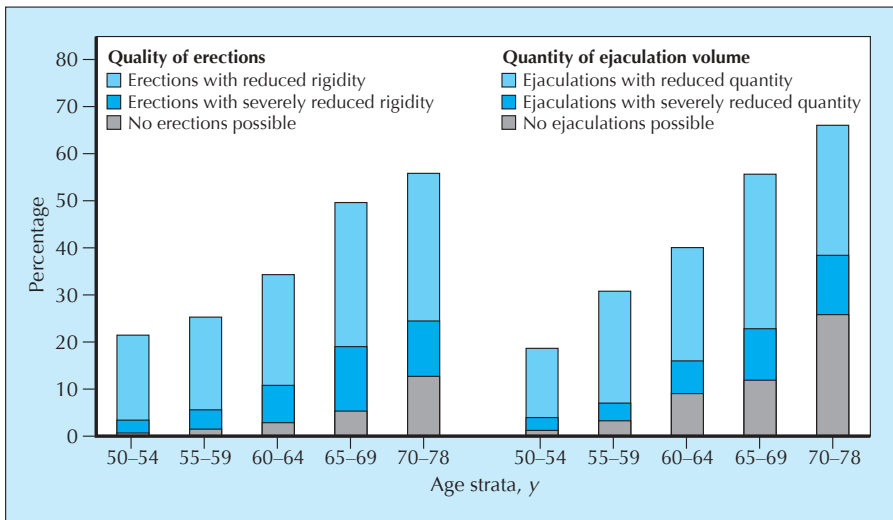


FIGURE 9-38. Ejaculatory dysfunction (ED) and diminished ejaculatory disorders (DED) in the aging man. While controversy exists regarding the labeling of normal age-related phenomena as pathologic, it is clear that increasing age is highly associated with diminished ejaculatory function. All types of DED show an age-related increase in prevalence. Although this may represent a normal aspect of aging, the applied definition factors in personal or relationship distress before the diagnosis is applied. (Adapted from Blanker *et al.* [44].)

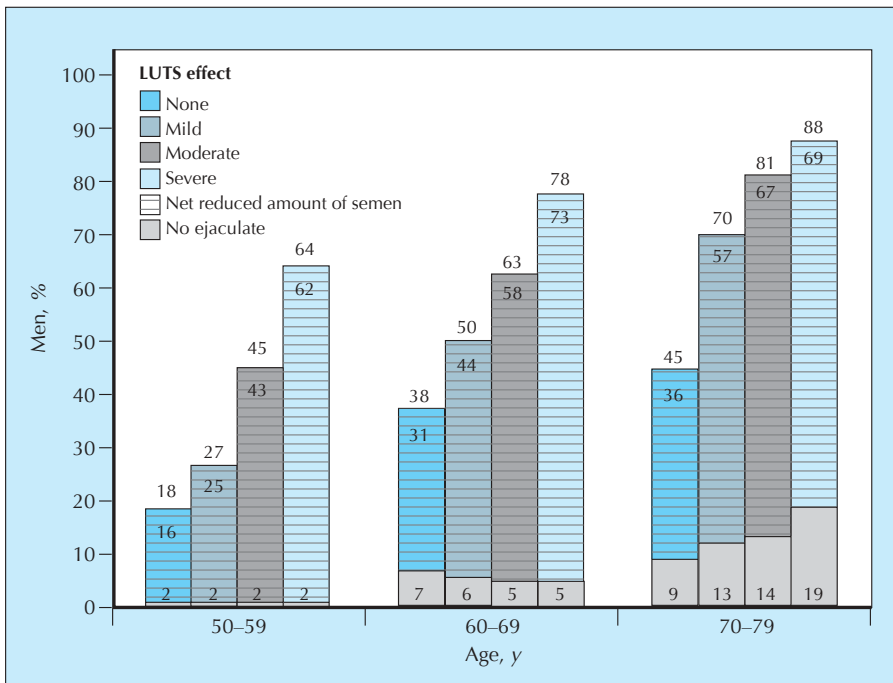


FIGURE 9-39. Prevalence of ejaculatory dysfunction increases with severity of lower urinary tract symptoms (LUTS) independent of age. As demonstrated in a large population-based study by Rosen (Presented at the Annual Meeting of the American Urological Association in Orlando, May 2002), there is an increase in the incidence of diminished ejaculation with increasing age. A validated questionnaire (DAN-PSSex) for determining diminished ejaculation or anejaculation in men with varying degrees of LUTS. Within each age group the number of men who experience diminished ejaculation increases significantly with increasing severity of identified LUTS. (Adapted from Rosen *et al.* [45].)

Evaluation and Assessment of Diminished Ejaculatory Disorders

- Medical history, medication history
- Global or situational, lifelong or acquired
- Quality of desire, arousal, and orgasm
- Patient's assessment of latency time in various sexual situations
- Quantity and quality of semen volume and force
- Partner's assessment
- Overall relationship
- Physical examination

FIGURE 9-40. Evaluation and assessment of diminished ejaculatory disorders (DED). Assessment begins by reviewing the conditions under which the man is able to ejaculate, *eg.* 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. If orgasmic attainment had been possible previously, the life events/circumstances temporarily related to orgasmic cessation are reviewed. The events in question may be pharmaceutical, illness, or a variety of life stressors and other psychologic factors previously highlighted in the section on etiology. This examination in conjunction with appropriate physical examination and laboratory results will provide understanding and determine an appropriate treatment path.

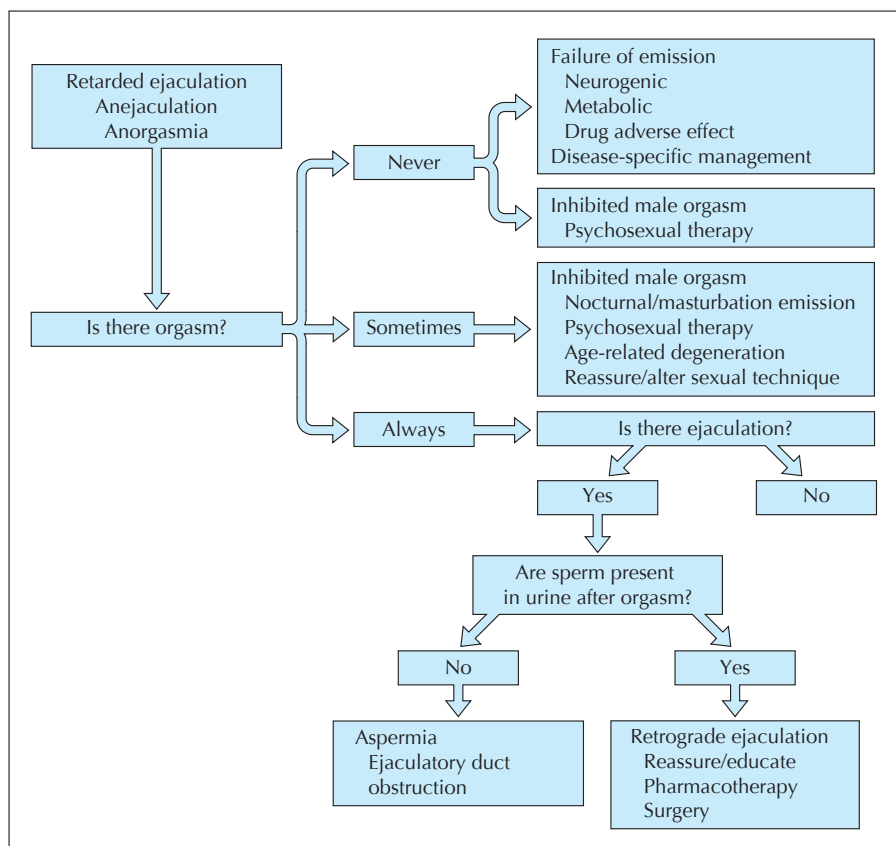


FIGURE 9-41. Diagnostic algorithm for diminished ejaculatory disorders (DED). (Adapted from the WHO 2nd Consultation, Paris, 2003.)

Adjunctive Drug Therapy for SSRI-Induced Sexual Dysfunction				
Drug	Mechanism	Symptom	Dosage, mg	
			As Needed	Daily
Amantadine	Dopamine agonist	Anorgasmia Decreased libido Erectile dysfunction	100–400 (for 2 d prior to coitus)	75–100 bid/tid
Bupropion	Mixed 5-HT, NE, dopamine reuptake inhibitor	Anorgasmia	75–150	75 bid/tid
Buspirone	Partial 5-HT _{1A} receptor agonist, dopamine adrenergic stimulant	Anorgasmia Decreased libido ED	15–60	5–15 bid
Cyproheptadine	Serotonin and histamine antagonist	Anorgasmia Decreased libido ED	4–12	Not applicable
Yohimbine	Central/peripheral α_2 agonist	Anorgasmia Decreased libido ED	5.4–10.8	5.4 tid

FIGURE 9-42. Adjunctive drug therapy for selective serotonin reuptake inhibitor (SSRI)-induced sexual dysfunction. Sexual side effects are commonly seen with SSRI therapy. Decreased libido, erectile dysfunction, and ejaculatory disorders (ED) are seen with all of the current therapies and may be lead to treatment discontinuation, particularly in younger men. Treatment strategies take into account the underlying indication for therapy and the current or expected response. Early in the course of therapy, reassurance is necessary, because improvement may take 4 to 6 weeks. Continued difficulties and distress may prompt consideration of a treatment strategy to counteract the pharmacologic ejaculatory effects of SSRIs. Significant indi-

vidual variegation in therapeutic response is seen with different drugs within the SSRI class and in a similar fashion, ejaculatory improvement may be seen with an alternative medication. Dosage adjustment, timing alteration, or brief (2 day) “holiday” may be of benefit. Recent interest in “SSRI antidotes” are primarily anecdotal and are based on activating proejaculatory dopaminergic pathways, while maintaining 5-HT neuromodulation. This table provides suggested medications and can be used with daily dosing or on demand 2 to 6 hours prior to anticipated sexual activity. PDE-5 inhibitors may also be of benefit as a durable erection may provide a “scaffold” for sufficient stimulation to achieve ejaculation/orgasm.

Treatment of Retarded Ejaculation

There is low-level evidence recommending sex therapy for RE
 Numerous drugs, herbs, and medication dosing strategies exist for treatment of antidepressant-related RE (level 3)
 Following the pattern seen in the treatment of ED—integration of pharmacotherapy and sex therapy—will become the likely treatment of choice

FIGURE 9-43. New optimism for using a combined sex therapy and pharmaceutical approach in treating ejaculatory disorders. Heiman and Meston's [46] summary of sex therapy treatments concluded that "inadequate data" on the topic of delayed orgasm in men prevented any conclusion regarding efficacy of treatment. However, many treatments for RE have been suggested in the psychotherapy literature, including early psychodynamic and sex therapy approaches. Masters and Johnson [3] reported a low failure rate of 17.6% using a treatment combination of sensate focus, vigorous noncoital penile stimulation, and modifications of intercourse technique. Apfelbaum [42] treated almost all of his RE cases with "body work" using sexual surrogates. Perelman [2] reported retrospective chart review success rates of over 80% in treating RE using a cognitive-behavioral sex therapy. However, these were uncontrolled case reports with treatment ranging from a few brief sessions of sex education to the nearly 2 years of multiple-modality treatment in more complex multiple etiologic cases.

Numerous drugs, herbs, and medication dosing strategies have been reported to offset an iatrogenic induced, antidepressant-related RE. Widespread use of selective serotonin reuptake inhibitors (SSRIs) in the last decade has triggered tremendous interest in the effect of these antidepressants on sexual function [47]. Additionally, case reports indicated successful use of sildenafil to treat SSRI-induced orgasmic latency problems in men and women, with clinical trials currently investigating this phenomenon. Recently, Nurnberg *et al.* [48] published a prospective, parallel-group, randomized, double-blind, placebo-controlled multicenter study to assess the efficacy of sildenafil citrate in men with sexual dysfunction associated with the use of selective and nonselective serotonin reuptake inhibitors. In this study, sildenafil effectively improved erectile function and other aspects of sexual function in men with sexual dysfunction asso-

ciated with the use of SSRI antidepressants. Although the endpoints used were very limited, regarding the question of ejaculatory latency, this is one of the few randomized controlled trials to address this question and accordingly becomes important. It remains to be seen whether sildenafil will be shown to be an orgasmogenic agent; however, it is probable that multiple compounds will be developed to reduce orgasmic threshold and assist us in treating people who have difficulty reaching orgasm. Indeed, some speculate that a dopaminergic pathway might facilitate orgasm.

There is a need for integrated pharmacotherapy and sex therapy approaches. It seems likely that the most effective treatments for RE will follow the pattern seen in the treatment of ED, where an integration of pharmacotherapy and sex therapy is becoming the treatment of choice [18,43]. 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 (*eg*, retrograde ejaculation secondary to prostatic surgery). Further, 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 psychologic issues that otherwise may destabilize treatment success. There are published case reports integrating sex therapy and pharmacotherapy when treating a couple's multiple dysfunctions (including RE), but large controlled prospective studies are needed in order to define an appropriate treatment algorithm [43]. The development of new pharmaceuticals will only refine such an algorithm and improve our opportunity for enhancing orgasmic function.

Sexual Dysfunction in Men with Lower Urinary Tract Symptoms

	Community > 40 y, % (n = 423)	Community > 45 y, % (n = 1271)
ED	53	60
Decreased ejaculation	47	62
Painful ejaculation	5	17
Sex life decreased by LUTS	8	46

FIGURE 9-44. Sexual dysfunction in men with lower urinary tract symptoms (LUTS). As shown previously, sexual function is adversely affected by LUTS. Frankel *et al.* [49] compared a community population with LUTS to those men presenting for LUTS to a urology clinic. The rate of erectile dysfunction (ED) was similar but a higher incidence of diminished ejaculatory disorders (DED) was identified in the clinic patients. It is commonly held that patients present for the bother of their voiding complaints, but may also consider the associated DED as a contributory reason for seeking therapy. A reduction in the enjoyment of sexual activity may be driven more by the DED than the underlying LUTS associated erectile dysfunction and should be considered carefully in treatment selection.

Arai *et al.* [50] evaluated 173 men with LUTS and normal ejaculatory function treated with four surgical modalities (transurethral resection of the prostate [TURP], transurethral microwave thermotherapy of the prostate, transurethral laser ablation of the prostate, and transurethral needle ablation). All therapies improved symptoms with a similar incidence of ED and no change in sexual desire. Postoperative DED (including retrograde ejaculation) was 48.6% in the TURP group and similar in the less invasive treatment groups (21%–28%). More importantly, 46% of men with postoperative DED reported deterioration in their sexual enjoyment compared to 3.5% with unchanged ejaculation. These data indicate that preoperative or surgically induced DED has an adverse impact on sexual activity and enjoyment.

Pathophysiology of Retrograde Ejaculation

Ejaculation backwards into bladder due to incompetence of the bladder neck mechanism
Transurethral resection of the prostate
Open prostatectomy
Diabetic neuropathy
Retroperitoneal lymph node dissection
Drug adverse effect
Usually experience orgasmic sensation
Retrograde ejaculation and failure of emission can be distinguished by examination of a postmasturbatory specimen or urine for the presence of spermatozoa and fructose

FIGURE 9-45. The pathophysiology of retrograde ejaculation.

Treatment of Retrograde Ejaculation

Surgical
Bladder neck reconstruction results remain consistently poor
Pharmacotherapy
Sympathomimetic agents: pseudoephedrine, ephedrine, phenylpropanolamine
Stimulate release of noradrenaline from axon terminals but may also directly stimulate both α - and β -adrenergic receptors
Imipramine
Tricyclic antidepressant
Blocks noradrenaline reuptake by sympathetic axon

FIGURE 9-46. Treatment of retrograde ejaculation. Retrograde ejaculation can be surgically treated with bladder neck reconstruction, but results remain consistently poor [51]. Drug treatment is the most promising approach. The α -adrenergic sympathetic nerves mediate both bladder neck closure and emission and sympathomimetic agents such as pseudoephedrine, ephedrine, and phenylpropanolamine, as have been described as useful with mixed results [52]. These agents work by stimulating the release of noradrenaline from the nerve axon terminals but may also directly stimulate both α - and β -adrenergic receptors. The tricyclic

antidepressant, imipramine, which blocks the reuptake of noradrenaline by the axon from the synaptic cleft, is also occasionally useful [53]. The usual dose is 25 mg twice daily. Whereas medical treatment may not always produce normal ejaculation, it may result in some prograde ejaculation. In patients who do not achieve antegrade ejaculation with either surgery or medication, sperm retrieval and artificial insemination is an alternative approach. (*Data from* Abrahams *et al.* [51], Kedia and Markland [52], and Nijman *et al.* [53].)

Definition of Painful Ejaculation

Persistent pain or discomfort associated with or following ejaculation/orgasm that causes personal distress

FIGURE 9-47. Painful ejaculation is a relatively rare disorder that is usually a concomitant manifestation of an underlying urologic disease and/or a post-ejaculatory muscle spasm. At this time, there is no empirical evidence for incidence, prevalence, diagnostic evaluation or therapy.

However, any pain syndrome may be the result of a variety of potential etiologies, including, but not limited to: spasm, irritation, obstruction, infection, neurological, musculoskeletal or psychosomatic. The assessment of painful ejaculation follows the guidelines for other male orgasmic disorders, both in terms of the specific physical examination and the sexual history. Any underlying disease must be treated. Additionally, in the case of post-ejaculatory muscle pain, attention would be paid to both pharmaceutical and psycho-educational treatment for reducing muscle cramping in addition to analgesics and warm baths for symptomatic relief. In fact, masturbation in a warm bath can sometimes be useful diagnostically, to distinguish muscle spasm from other etiology.

Spinal Cord Injury

Cord Lesion		Reflexogenic Erections*	Psychogenic Erections	Successful Coitus	Ejaculation
Upper motor	Complete	92	9	66	1
	Incomplete	93	48	86	22
Lower motor	Complete	0	24	33	15
	Incomplete	0	1	100	100

*All numbers are percentages.

FIGURE 9-48. Spinal cord injury (SCI). The ability to ejaculate is severely impaired by SCI. Unlike erectile capacity, the ability to ejaculate increases with descending levels of spinal injury [54,55]. Fewer than 5% of patients with complete upper motor neuron lesions retain the ability to ejaculate. Ejaculation rates are higher (15%) in patients with both a lower motor neuron lesions and an intact thoracolumbar sympathetic outflow. Approximately 22% of patients with an incomplete upper motor neuron lesion and almost all men with incomplete lower motor neuron lesions will retain the ability to ejaculate.

In those patients who are capable of successful ejaculation, the sensation of orgasm may be absent and retrograde ejaculation often occurs. Several techniques for obtaining semen from spinal cord injured men

with ejaculatory dysfunction have been reported. Electroejaculation of efferent sympathetic fibers of the hypogastric plexus is effective and safe. Seventy-one percent of men with spinal cord injury who underwent electroejaculation achieved ejaculation [56]. Sperm density and motility is higher in those with incomplete lesions [57]. Vibratory stimulation is successful in obtaining semen in up to 70% of men with SCI [58]. There is a significantly higher risk of autonomic dysreflexia than electroejaculation. Pretreatment with a fast-acting vasodilator such as nifedipine will minimize the risk of severe hypertension should autonomic dysreflexia occur with either form of treatment [59]. Another technique is sperm harvesting by percutaneous aspiration of semen from the vas deferens [60].

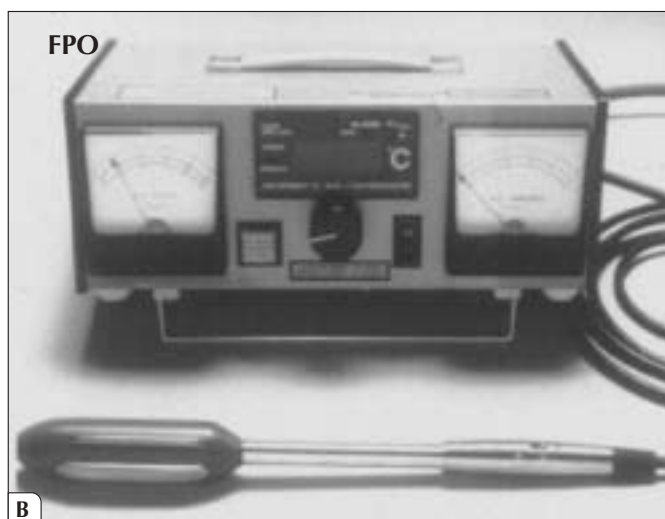
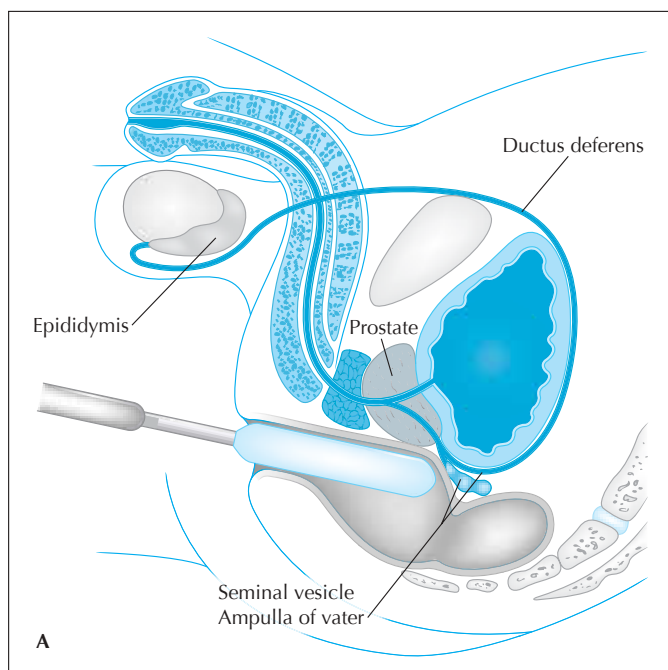


FIGURE 9-49. Electroejaculation technique in patient with spinal cord injury (SCI). A, Anatomic position of electroejaculator. B, Electroejaculator unit. Semen collected from men with SCI is often initially senescent and of poor quality with a low sperm count and reduced sperm motility due to chronic urinary tract infection, sperm content with urine, chronic use of various medications, elevated scrotal temperature due to prolonged sitting, and stasis of prostatic fluid. Testicular dysfunction is also present, including hypospermatogenesis, maturation arrest, atrophy of seminiferous tubules,

germinal cell hypoplasia, interstitial fibrosis, and Leydig cell hyperplasia. Prostatitis secondary to prolonged catheterization, epididymitis and epididymo-orchitis can precipitate obstructive ductal lesions and testicular damage. Sperm quality may improve with subsequent ejaculations.

Perelman [43] has noted that some otherwise healthy men (non SCI), who have previously conceived children via electroejaculation, were later able to father children through normal coitus, subsequent to successful sex therapy. (Courtesy of Dana Ohl, MD.)

Conclusions

Ejaculatory dysfunction is a common and distressing entity that deserves further critical research and clinical awareness. Increased clinician awareness and patient advocacy for ejaculatory disorders is needed to improve patient/partner/relationship quality of life. A detailed understanding of sexual pharmacology will guide further development of ejaculatory dysfunction therapies. Psychosexual behavioral therapy has an important adjuvant role in the treatment of PE. Combination models of treatment that integrate psychosexual therapy and sexual pharmaceuticals should be developed and validated for the treating physician. Further research is required including, but not limited to, studies to establish normative epidemiologic and ejaculatory latency data; to clarify the neurochemical control of ejaculation and the hypothesized biogenic basis of lifelong PE; and to identify the cerebral events that occur during ejaculation in normal men and in men with ejaculatory dysfunction using brain imaging studies.

FIGURE 9-50. Conclusions. The most effective treatments for premature ejaculation (PE) and diminished ejaculatory disorders (DED) will follow the pattern seen in the treatment of erectile dysfunction (ED), where an integration of pharmacotherapy and sex therapy is becoming the treatment of choice [14]. 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 combination of sexual counseling and pharmacotherapy is likely to be of assistance to patients seeking adjustment and rehabilitation from multiple medical conditions (eg, 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. Perelman [61] recommended research on integrating pharmacologic treatments with behavioral treatments to reduce the dosage of medication necessary to provide symptomatic improvement, enhance learning, and minimize relapse potential. An integrated model allows for resolving and balancing significant intra- and interpersonal psychologic issues that otherwise may destabilize treatment success. There are published case reports integrating sex therapy and pharmacotherapy when treating a couple's multiple dysfunctions (including male orgasmic disorder), but large controlled prospective studies are needed in order to define an appropriate treatment algorithm.

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