Ejaculatory Dysfunction

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Introduction

While erectile dysfunction has received much-needed publicity, ejaculatory disorders are far more common and affect over 30% of men in the age group of 40–80 years [1–3]. Ejaculatory dysfunction encompasses a spectrum of conditions, namely, premature ejaculation (PE), delayed ejaculation (DE) and anejaculation (AE) that includes retrograde ejaculation (RE). Due to the lack of standardized definitions for these problems, the clinical diagnosis and management strategies for ejaculatory dysfunctions are somewhat arbitrary. Ejaculatory dysfunction not only affects a man's sexual health but can also interfere with his fertility when conception is desired, thereby resulting in significant distress for both partners [4].

Ejaculatory Physiology

Masters and Johnson's description of the human sexual response shows that there are four distinct phases, namely, excitement, plateau, orgasm and resolution [5]. The latency period is defined as the time period from the start of sexual stimulation to the point of ejaculation and this period can greatly vary among men depending on their sexuality, habits and other factors [6, 7]. Ejaculation in itself is a distinct emotional and/or cortical event, while erection is a spino-cerebral event [4]. This is also why ejaculation occurs without a degree of voluntary control during sleep-related erections (SRE). Orgasm on the other hand is not strictly a separate phenomenon and occurs and/or overlaps with ejaculation [8].

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Ejaculation strictly has two phases: (1) emission and (2) expulsion. During the emission phase, the peristaltic smooth muscle contraction of the seminal tract propels semen into the posterior urethra via the ejaculatory duct. This process is mediated by the sympathetic nerves (T10 to L2). The ejection phase controlled by somatic nerves (S2–S4) involves the pulsatile contractions of the pelvic floor muscles and the bulbocavernosus along with concomitant relaxation of the external urinary sphincter. There is some limited degree of voluntary control in the ejection phase. In parallel the bladder neck also closes to prevent retrograde flow along with rhythmic contractions of the pelvic floor muscles that then drives the spermatozoa suspended in the seminal fluid forward. Orgasm perceived as a pleasurable experience results from the cognitive processing of the pudendal nerve stimuli due to increased pressure in the posterior aspect of the urethra along with sensory stimuli from the accessory sex organs and/or contraction of the urethral bulb. Both orgasm and ejaculations are coordinated by separate neural mechanisms and can also occur separately from one another. Animal studies have clearly shown the importance of spinal ejaculatory center in integrating signals from both central and peripheral stimuli and coordinating the ejaculatory reflex through the pelvi-perineal musculature. Mechanism to inhibit ejaculation is located at higher centers in the brain such as the posterodorsal amygdaloid nucleus, the posteromedial nucleus of the stria terminalis and the parvocellualar nuclei of the thalamus. These higher centers control and modulate the final output from all the ejaculatory stimuli [8–13].

Neurotransmitters in Ejaculation

Neurotransmitters play an important role in the control ejaculation. Of cardinal importance are dopamine and serotonin. Other neurotransmitters like acetylcholine, oxytocin, GABA, norepinephrine and nitric oxide are also involved in coordination of the complex ejaculatory process and are of secondary importance [9, 10]. Defining the exact role of each of the neurotransmitters is difficult due to the multifactorial and complex nature of ejaculation.

Dopamine promotes ejaculation by its action on D2 receptors. Dopamine levels rise in the region of the hypothalamus, and dopamine signalling has been implicated in both arousal and orgasm. Rat studies have also shown that dopamine levels increase steadily through intercourse until the point of ejaculation [10]. Serotonin is inhibitory and exhibits its effects by its action on 5HT2C and 5HT1A receptors [14]. Serotonin is the most well-studied neurotransmitter in the neurophysiology of ejaculation. Numerous seminal animal studies have shown that 5HT2C receptor stimulation is associated with a delay in ejaculation and longer latency time of ejaculation, while 5HT1A stimulation results in shorter latency time [14, 15]. The balance between receptor stimulation and inhibition may play a role in establishing a latency time point that could vary depending on the individual's sexuality, age, illness, relationship and a host of other factors. Animal studies have also suggested that oxytocin may have an important role to play in

the ejaculatory process [16]. An excess of oxytocin is associated with early ejaculation and an oxytocin deficiency is associated with delayed ejaculation [16, 17].

Premature Ejaculation

Definition and Aetiology

Premature ejaculation (PE) affects over 39% of men in the general community and data suggests that PE is the most common male sexual disorder [17]. But a certain degree of disparity exists between reported data, since the definition of PE in itself is poorly validated and/or inconsistent [18].

More importantly, PE is a self-reported symptom that occurs due to an individual distress. Thus getting exact prevalence data is difficult. The other problem is also the inconsistency of presenting symptoms.

Most previous definitions of PE are based on stopwatch studies that estimate the intravaginal ejaculation latency time (IELT), which is the time interval measured from the point of penetration till ejaculation [6]. But this data is highly inaccurate as not only does the IELT time vary between countries and study participants, but also the data is mostly based on studies done in the Western population.

The definition of PE has had numerous revisions. The first definition of PE was by Masters and Johnson; PE was defined by "the inability of a man to delay ejaculation long enough for his partner to reach orgasm in 50% of intercourse attempts" [5]. This definition was however confounded by the women's ability to reach climax.

Subsequent professional society and individual definition were more authority based rather than evidence based. The American Psychiatric Association (APA) definition was revised twice to address its vague nature and lack of standardized operational criteria. Following mounting pressure from the FDA and other regulators, the International Society of Sexual Medicine (ISSM) convened a meeting twice and a defined PE in 2008 finally as when ejaculation occurs within 1 min before or after penetration with a complete lack of control and also causing distress to one or both partners [19].

PE can be classified as either being lifelong or acquired and/or variable or subjective. The aetiology of lifelong PE is different compared to acquired PE [20, 21]. Men facing lifelong PE may have hyposensitivity at the level of the 5HT2C or hypersensitivity of the 5HT1A receptors. Genetic variations may contribute and these problems are frequently amplified by psychological factors [22]. Acquired PE on the one hand can be due to a comorbid ED or prostatitis. Many men with ED also suffer from PE; men with ED may rush through intercourse out of fear of losing erection leading to PE. These effects may also be compounded by their performance anxiety [23]. Thyroid disorders and relationship and/or psychological problems can also lead to acquired PE [24, 25].

While anxiety has been frequently stated among medical communities as a cause of PE, there is insufficient data to support the same. Authors have suggested that

anxiety-induced activation of the sympathetic nervous system reduces the threshold for ejaculation leading to PE. Acquired PE can also be caused by hypoactive sexual desire and also by female sexual dysfunctions [8]. Variable PE is considered more of a normal variation in sexual performance and occurs in situational context. Subjective PE is when the patient has a false preconceived notion that he has PE [8].

Diagnosis and Treatment

PE is best diagnosed by an in-depth psychosexual history-taking session. Table 4.1 outlines a few questions that can be asked by the clinician to help establish a diagnosis. A thorough medical history to check for other systemic health conditions should also be elicited. While it is best to have the partner involved in the sexual history-taking session, for PE this is not mandatory until or unless the patient's sexual history reveals a problem in the partner [26].

In general no specific investigations are recommended for men with PE. A physical exam is mandatory though.

Treatment of PE usually involves psychosexual counselling and/or pharmacotherapy. Integrated treatment strategies usually work best. In men with situational and/or subjective PE, a simple session of psychosexual education will correct their understanding of the problem [27, 28].

Psychosexual based behavioural therapies for PE as an isolated treatment modality include the popularly used "stop-start" manoeuvre and its modification the "squeeze-pinch technique". The advantage of these techniques is that they are free from side effects and also have greater patient acceptability, with no associated pain [29, 30]. These techniques are also highly specific to the problem in hand. The disadvantages are that there is a learning curve to the techniques and these techniques also lack immediacy and also require partner co-operation. The long-term efficacy of these techniques is unknown. Few other techniques like mental imagery, utilizing different sex positions, may increase the timing of ejaculation [31, 32].

Pharmacological treatment of PE includes the use of topical anaesthetics as well as selective serotonin reuptake inhibitors (SSRI). Topical local anaesthetics like lignocaine and/or prilocaine cream are moderately efficacious in PE, but unless a condom is used they can cause vaginal numbness and also penile hypoanaesthesia

Table 4.1 Questions to assess PE

Questions to assess PE
1. How much time do you last from the time you penetrate till ejaculation?
2. Are you able to control your ejaculation?
3. When did you first experience this symptom? Do you feel upset by it?
4. Does your partner feel upset by it?
5. How is your erection? Do you have difficulties in sustaining your erection?
6. Is PE affecting your relationship?
7. Have you taken any medications for this problem?
8. Does your partner complain of any specific difficulty like pain or lack of interest in sex?

[33–37]. A study suggested that the use of a metered-dose aerosol spray containing lidocaine and prilocaine produced a 2.4-fold increase in IELT and ejaculatory control [38].

Dapoxetine, a short-acting SSRI, has received regulatory approval for the on-demand treatment of PE [39–42]. The usual dose varies between 30 and 50 mg, taken 2 h before intercourse. These drugs work by blocking the reuptake of serotonin in the synaptic cleft of both the peripheral and central serotonergic neurons, thereby resulting in enhanced 5HT neurotransmission [41, 42]. When taken 1–2 h on demand, a modest increase in the IELT time ranging from 2.5- to 3.0-fold is seen. However, as compared to on-demand dosing, daily dosing has significantly better effects in delaying ejaculation as well as reducing symptoms of interpersonal distress [43]. More controlled studies though are required to find out which is better.

Different SSRIs in different dosages have been used in PE; they are namely paroxetine 10–40 mg, sertraline 50–200 mg, citalopram 20–40 mg, and fluoxetine 20–40 mg. These doses are usually well tolerated and safe. While all of them delay ejaculation, a recent meta-analysis suggested that paroxetine exerted the strongest delay in ejaculation exerting a delay of over 8.8-fold over baseline [43–45]. However, due to the lack of regulatory approval, these drugs are only prescribed off label. On a daily dosing protocol ejaculation delay usually occurs within 5–10 days of starting a treatment, but full therapeutic benefits usually occur after 2 or 3 weeks. ED is the reported side effect but it is uncommon [21].

Patients should be specifically told not to suddenly discontinue the medication as it may lead to SSRI withdrawal syndrome. PDE-5 inhibitors have been frequently used along with SSRIs in the treatment of PE; numerous systematic reviews have failed to show any benefit. PDE-5s can be used along with SSRIs when PE presents itself with comorbid ED [21].

Delayed Ejaculation and Anejaculation

Definition and Aetiology

Delayed ejaculation (DE) is the least studied and most poorly understood sexual dysfunction. The reported prevalence of DE is 1–4% [46, 47]. The WHO defines DE as the persistent difficulty or delay or complete inability to attain an orgasm after sufficient sexual stimulation leading to personal distress [48]. A well-defined operationalized criteria for DE does not exist. Assuming that most men would ejaculate in the range of 5–10 min post-penetration, a clinician can make a diagnosis of DE when men have ejaculatory latencies beyond 20 or 30 min (twice the standard deviation of the measured IELT) [6]. Anejaculation (AE) on the other hand can be orgasmic or anorgasmic. The commonest cause of orgasmic AE is retrograde ejaculation (RE) [4]. In RE semen is propelled in a retrograde fashion towards the bladder during an orgasm, rather than antegrade.

A man can also have DE if he ceases sexual activity due to exhaustion or distress. DE is of two types: primary (lifelong) or secondary (acquired). The strict definition

and/or delineation of DE into primary and secondary subtypes is difficult due to numerous external factors that play a role in causing a dysfunction. Waldinger's study on IELT found a natural variation ranging from 33 s to 44 min, and this value differed greatly across the study population [6]. This study combined with highly variable central sensitivity to both serotonin and dopamine is suggestive of DE that could be physiological rather than pathological (a type of DE that has no specific aetiology).

Congenital DE can be caused by certain malformations like Wolffian duct abnormalities, Mullerian duct remnants and prune belly syndrome [49, 50]. Although these conditions are rare, DE frequently presents with psychological and/or behavioural components. Orthodox beliefs on "spilling the seed" outside of intercourse apart from the purpose of conception may lead to a poorer probability of achieving an orgasm outside intercourse [51]. Another common cause of DE is autosexual orientation where there is a preference to masturbation over sexual intercourse. This condition is termed as "idiosyncratic masturbation". Studies suggest that men with idiosyncratic masturbation feel that they get better arousal subjectively and are able to reach their ejaculatory threshold more quickly via masturbation as when compared to penetrative intercourse [52].

Post-surgical causes of acquired DE and/or AE usually include surgeries done to the prostate, penile cancer treatment by means of partial penectomy and/or testicular cancer treatment. Surgeries that compromise the bladder neck, such as transurethral incision of the prostate, are invariably associated with RE. RE is seen in over 45% of such patients undergoing the procedure [53–56].

Common endocrine causes of DE seen in clinical practice include hypothyroidism, hypogonadism and hyperprolactinaemia. With the widespread use of SSRIs, sexual dysfunction is a well-reported side effect after prolonged drug use. DE comprises a significant portion of these sexual dysfunctions associated with SSRI use [57, 58]. Neurogenic causes of DE commonly reported include spinal cord injury, diabetes and multiple sclerosis. Men with lower motor neuron lesions do retain ejaculatory ability, but the bigger issue is erectile dysfunction and RE especially seen in men with complete spinal cord injury [59, 60]. Table 4.2 summarizes the various known causes of DE and AE.

Diagnosis and Treatment

As is with other sexual dysfunctions, a clear pathophysiology for DE is lacking and DE should be considered as an interaction between organic and psychogenic factors [61]. Both organic and psychogenic factors work in tandem and affect a man's ejaculatory latency throughout his life. The treatment of DE should encompass a thorough understanding and assessment of these interactions.

DE evaluation starts with a thorough medical history and/or psychosexual history to rule out conditions listed in Table 4.2. Next specific history should focus on (1) age of first ejaculation, (2) masturbatory practices and also (3) ascertaining whether DE occurs with partnered sex or during masturbation only. Lifelong DE will present with global sexual dysfunction in both masturbation and partnered

Table 4.2 Various causes of DE and AE

Causes of DE and AE
Congenital and anatomical causes
Wolffian duct abnormality
Prune belly syndrome
Mullerian duct cyst
Transurethral resection of prostate (TURP)
Infective causes
Urethritis
Genitourinary TB
Neurogenic causes
Diabetes mellitus
Spinal cord injuries
Prostate surgeries
Bilateral sympathectomy
Multiple sclerosis
Endocrine causes
Hyperprolactinaemia
Hypogonadism
Hypothyroidism
Medication
Thiazide diuretics
Tricyclic antidepressants and SSRIs
Alcohol abuse
Alpha-methyldopa
Antiandrogens
Phenothiazines
Psychological causes
Relationship and life stress
Negative sex beliefs
Idiosyncratic masturbatory preferences
Chronic conditions
Increasing age
Vascular disease
Chronic pain due to other illnesses

intercourse. It is also important to ascertain information about the practices or sexual preferences of the individual that would allow him to reach the ejaculatory threshold. In addition, the patient's partner relationship should also be ascertained. The presence of a female sexual dysfunction should be ruled out.

If the patient has a small-volume ejaculate or no ejaculate and if fertility is the objective, the clinician must differentiate ejaculatory duct obstruction from congenital bilateral absence of the vasa deferentia (CBAVD). Both forms are associated with small-volume ejaculate and azoospermia [62–65]. A physical exam of the testes, epididymis and palpation of the vasa on both sides combined with an ultrasound imaging usually helps in making a diagnosis [65]. The presence of spermatozoa in the first void urine after orgasmic anejaculation is suggestive of retrograde ejaculation [65].

Other investigations like blood sugars, hormonal assessment, lipid profile and appropriate imaging studies to rule out organic causes of DE are usually recommended. The primary objective of history taking and examination in DE is to rule out all probable organic causes of DE before concluding that the DE is psychogenic in nature.

Treatment for DE can be broadly classified into two types—psychological and pharmacotherapy. Depending on the individual's receptiveness to counselling, psychotherapy is usually the first-line treatment for DE [66]. While there are numerous psychotherapeutic strategies recommended for DE, none of them have been properly evaluated in terms of efficacy through large-scale studies. "Masturbation retraining" and "sensate focus" exercises are effective psychotherapeutic treatment strategies for DE [67–69].

Briefly, the objective of these interventions is to first destigmatize the dysfunction and remove the anxiety associated with "ejaculation on demand". First, the couples are given sex education. The man is then taught to identify pleasurable stimulation that increases his general ability to reach orgasm quicker through self-stimulation techniques. In the next step, the anorgasmia faced by the man should then be "non-stigmatized". This is achieved by allowing the man to ejaculate in a non-coital manner during partnered sex. This can be tried by incorporating different coital positions and also visualizing fantasies that can help the man improve his subjective arousal.

Next, the partner should then try to bring the male partner close to the brink of orgasm and then allow the penis to be inserted into the vagina, as this will break the mental barrier associated with partnered sexual intercourse. Subsequently, intravaginal ejaculation is then achieved. The couple is also taught to communicate specific sexual preferences to one another so that these needs can also be fulfilled in the act.

The most important clinical challenge with DE treatments is to ensure that the female partner does not feel mechanistic, due to the steps involved. The partner's sexual need should also be met. Maintaining a good couple rapport and therapeutic alliance is key. Masters and Johnson found a very low failure rate less than 18% when they used the strategies of sensate focus and intercourse modification combined with vigorous penile stimulation [5].

Drug treatment for DE/AE has had limited success. None of the drugs have regulatory approval for the treatment of DE and/or AE. Most drugs for DE are considered experimental at best and also carry significant side effects. Drugs like amantadine and cyproheptadine have been used to reverse anorgasmia induced by SSRIs. Success has been reported anecdotally. In one study on patients with spinal cord injury (SCI) and AE, daily midodrine given in doses of 7.5–12 mg helped only 50% of study participants achieve ejaculation. These drugs also cause side effects like restlessness, elevated BP and sedation which may further reduce the efficacy of treatments [70–73].

Due to the lack of randomized controlled studies, pharmacotherapy cannot be recommended for the first-line management of AE and/or DE. The scenario is different with RE though.

For RE, the aim of medical therapy is to increase sympathetic tone in the bladder neck and thus achieve antegrade ejaculation [74]. Different types and combination of medications like antihistamines, anticholinergics and alpha 1 agonists have been used. Success rates in the aforementioned medications are highly variable in terms of achieving an antegrade ejaculation.

In an RCT that involved diabetic patients with RE, the combination use of pseudoephedrine 120 mg and imipramine 25 mg twice daily helped achieve antegrade ejaculation in 62% of study participants as compared to 0% in the placebo group [75]. While there is a limited role of medical therapy in RE, where a clinical diagnosis is established, drug treatment for RE may be tried.

Where medical therapy fails and when fertility is the primary objective, the next line of treatment for RE is using a technique of sperm retrieval from the bladder [76]; here the patient is first asked to void and empty the bladder. After this, he can then proceed to collect a semen sample by masturbation; after masturbation the patient should immediately void the residual urine into a sterile container that contains physiological medium for sperm harvesting. Sperm harvested this way can then be used for fertility treatments. When this technique fails, a penile vibrostimulator (PVS) can be used. The final line of management would be resorting to use electroejaculation (EEJ) and/or direct sperm retrieval from the testis [77]. In men with spinal cord injury, prostatic massage (PM) may help in achieving antegrade ejaculation [78].

Conclusion

PE and DE significantly impair the quality of life for both the partner and the afflicted individual. The importance of a proper history taking and physical exam cannot be stressed enough. All potential organic causes of ejaculatory dysfunctions must be ruled out before coming to a conclusion. While psychotherapies and/or sex education have an important role to play in managing ejaculatory dysfunctions, the use of pharmacotherapy cannot be ignored. In the case of PE, SSRIs along with psychosexual therapies can definitely be used while in case of DE and/or RE medications have a limited role to play. Where fertility is the primary objective of the patient, efforts should be made to harvest sperm for relevant fertility-based treatments. In these scenarios, alternate methods of inducing an antegrade ejaculation with the penile vibrostimulator (PVS) and/or electroejaculation (EEJ) can be tried with medications.

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