Introduction

Historically, delayed ejaculation (DE) is probably the least common, least studied, and least understood of male sexual dysfunctions, with an estimated prevalence of 1–4% of the male population (1-6). However, according to the data from the USA National Health and Social Life Surveys (NHSLS), 7.78% of a national probability sample of 1,246 men between the ages of 18–59 years reported an inability to achieve climax or ejaculation (2). It is believed that both the overall aging of the population as well as the global increased use of biological treatments for erectile disorders are associated with increased ejaculatory latency secondary to both disease and the side effects of medications to treat them. Men using pro-erectile medications may experience DE due to confusion over their erections having emanated from increased vasocongestion as a result of pharmacotherapy rather than sexual arousal (7).

Retarded ejaculation, DE, inadequate ejaculation, inhibited ejaculation, idiopathic anejaculation, primary impotentia ejaculations, and psychogenic anejaculation have all been used synonymously to describe a delay or absence of male orgasmic response. Masters and Johnson were the first to suggest that DE in some men might be associated with orthodoxy of religious belief (8). Such beliefs may limit the sexual experience necessary for learning to ejaculate or may result in an inhibition of normal function.

DE is meant to describe any and all of the ejaculatory disorders resulting in a delay or absence of ejaculation (9). Similarly, the World Health Organization 2nd Consultation on Sexual Dysfunction defines DE as the persistent or recurrent difficulty, delay in, or absence of attaining orgasm...
after sufficient sexual stimulation, which causes personal distress (10). DSM-IV-TR defines DE as the persistent or recurrent delay in, or absence of, orgasm after a normal sexual excitement phase during sexual activity that the clinician, taking into account the person's age, judges to be adequate in focus, intensity, and duration. The disturbance causes marked distress or interpersonal difficulty. It should not be better accounted for by another axis I (clinical) disorder or caused exclusively by the direct physiologic effects of a substance or a general medical condition (11).

Difficulties in defining DE are partly related to the fact that orgasm and ejaculations usually occur simultaneously, despite being two separate phenomena. In the fifth edition of the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders (12), the definition requires one of two symptoms: either a marked delay in ejaculation or a marked infrequency or absence of ejaculation on 75–100% of occasions for at least 6 months.

**Animal model of DE**

The understanding of the neurobiology of normal and ‘pathological’ sexual functioning has been derived from animal studies in which specific brain areas have been manipulated or animals have been challenged pharmacologically. Most of the current theoretical models of animal sexual functioning have been based on copulatory behavior of laboratory rats (13). Male rats are exposed in these experiments to a receptive female and allowed to copulate for a certain period of time, or until ejaculation has occurred. Male rat sexual behavior is characterized by a series of mounts, either with or without vaginal intromission that eventually will lead to ejaculation after a number of intromissions and durations of around 5–10 min. Several parameters reflecting sexual functioning can be calculated: number of mounts, intromissions and ejaculations, in addition to latencies to first mount, intromission and ejaculation. Other parameters, such as intromission ratio, intromission interval, and postejaculatory intervals, can be calculated as well. In vivo sexual behavior of the male rat has been examined long before its characteristics became known to clinicians interested in the underlying neurobiology of sexual dysfunction. For example, Oliver et al. reported on the sexual behavior of male rats before and after specific hypothalamic lesions (14). Sexual behavior was severely disrupted if bilateral lesions were positioned in the preoptic area/anterior hypothalamus, whereas posterior hypothalamic lesions (including mammillary bodies) did not interfere with sexual behavior (15). That author also found an inverted U-shaped distribution, with relatively few animals with low or high numbers of ejaculations and a high number of animals with 2–3 ejaculations per test. Based on that study, it has been suggested that animals with low numbers of ejaculations (sluggish rats) might model human DE, whereas the high-number ejaculators (rapid ejaculators) might model human premature ejaculation (PE) (16).

**Human model of DE**

Men diagnosed with DE experience difficulties in ejaculating and reaching an adequate orgasm, both of which may occur during self-masturbation or manual, oral, vaginal, or anal stimulation by the partner. Problems with “difficulty” in ejaculating may range from varying delays in the latency-to-ejaculation interval to complete inability to ejaculate (anejaculation). Reductions in the volume, force, and sensation of ejaculation may occur as well. Although DE is commonly encountered, it can be confused with anejaculation (measured in time) and retrograde ejaculation (direction) by physicians and patients alike. Typically, the man has little or no difficulty achieving and maintaining an erection, but finds it extremely difficult, or impossible, to reach ejaculation and orgasm despite “adequate” sexual stimulation. The difficulty may occur in all situations (generalized) or be limited to only certain situations (situational). It may be primary (lifelong) or secondary (acquired). The most common clinical pattern of DE is a man who is unable to ejaculate in the presence of a partner (especially during intercourse) while he has little difficulty reaching orgasm and ejaculation during solo masturbation (5).

Men with DE report less coital activity, higher levels of relationship distress, sexual dissatisfaction, lower arousal, anxiety about their sexual performance and general health issues when compared to sexually functional men (5,9, 17-19). The psychological and relational impact of DE is often significant in that it typically results in a lack of sexual satisfaction for both the man and his partner, an effect further compounded when procreation is among the couple’s goals of sexual intercourse (5).

**Pathophysiology of DE**

The pathophysiological etiology of DE should be established thorough medical, psychosexual and psychosocial history. The etiology of DE is usually multidimensional, resulting...
from the man’s biologic ejaculatory latency being affected by multiple organic biological, or psychogenic factors in varying combinations during his life. It can be of the primary (lifelong) or secondary (acquired) origin (5,19,20).

Psychogenic and biogenic etiologies of DE usually are neither independent nor mutually exclusive, with both categories overlapping and including a combination of factors involving both etiological domains (3,21).

**Psychosocial-behavioral and cultural etiology**

There are many psychological and relational factors that have been traditionally implicated as predisposing and/or confounding factors in the etiology of DE, such as fear and/or ambivalence regarding pregnancy and fertility issues, hostility and anger, fear of loss of control, fears of abandonment/rejection, fears of intimacy and loss of autonomy, paraphilic inclinations/interests, and fears of hurting/defiling the partner (6). Although some of these factors may contribute to the etiologies of individual men with DE, no well controlled studies have provided comprehensive support for any of the various hypotheses.

**Religious**

Masters and Johnson were the first to claim that DE in some men might be associated with orthodoxy of a religious belief (8). Such prohibitions may limit the male’s sexual experience necessary for learning to ejaculate or may result in an inhibition of normal function. Regardless of the specific religion (Muslim, Hindu, Jewish, etc.), many devoutly religious men may masturbated only rarely or not at all, and for some, guilt and anxiety about “spilling seed” may lead to eccentric masturbatory behavior, resulting in DE.

**Insufficient sexual arousal**

In his review on the psychological etiology of DE, Apfelbaum noted that some males appear capable of achieving erections sufficient for intercourse despite a relative absence of subjective arousal (22). He proposed that these “automatic erections” were taken as erroneous evidence by both the man and his partner that he was ready for sex and capable of achieving orgasm. With the introduction of successful medical treatment of ED with phosphodiesterase type 5, many men experience erections without adequate psycho-emotional arousal and experience difficulty achieving orgasm since they had not experienced sufficient erotic stimulation before and during coitus.

**Masturbation**

Another commonly accepted pathophysiological factor for DE is “autosexual” orientation, a term used to describe men with DE who prefer masturbation over partnered sex. Many men with DE engage in self-stimulation that is personalized in the speed, pressure, duration, and intensity necessary to produce an orgasm, and different to what they experience with a partner. They thereby precondition themselves to possible difficulty in attaining orgasm with a partner and, as a result, experience acquired DE (22).

Perelman and Rowland identified three factors that disproportionately characterized patients with DE: (I) high frequency masturbation (age-dependent, with a mean of greater than 3x/week); (II) idiosyncratic masturbatory style; (III) disparity between the reality of sex with a partner and preferred sexual fantasy during masturbation. They defined an idiosyncratic masturbatory style as a technique not easily duplicated by the partner’s hand, mouth, vagina, or anus. Furthermore, those authors noted that many men with DE engaged in a pattern of self-stimulation that was notable for its speed, pressure, intensity, duration, and specificity of focus on a particular “spot” of sensitivity in order to produce orgasm/ejaculation. In this way, they preconditioned themselves to possible difficulty in attaining orgasm with a partner and, as a result, experienced “acquired” DE (3).

Finally, the evaluative/performance aspect of a sexual encounter with a partner often creates a “sexual performance anxiety” factor that may contribute to DE. Specifically, anxiety surrounding the inability to ejaculate may draw the man’s attention away from erotic cues that normally serve to enhance arousal (3).

**Sexual orientation**

Although studies on DE apply equally well to both heterosexual and homosexual men, most of the research on DE has been based on intravaginal latency. However, Jern et al. and Bancroft et al. demonstrated that men with homosexual orientations had a significantly higher frequency of DE than heterosexual men (23,24).

**Biological models of DE**

In a systematic review of 333 articles, Seyam described
a variety of etiological factors that have been associated with organic DE, including age, race, infectious disorders mainly related to the prostatic diseases, diabetes mellitus, depression and other psychiatric diseases, medications, narcotics and alcohol (25). DE has also been associated with some congenital disorders (primary DE) as well as occurring after identifiable medical conditions (acquired DE) (18,19).

Rowland et al. observed that men with DE show high levels of relationship distress, sexual dissatisfaction, and anxiety about their sexual performance, and that they have significantly more general health issues than sexually functional men. In addition, along with men with other sexual dysfunctional conditions, men with DE typically report lower frequencies of coital activity (17). In another article, those authors reported that although men with DE usually have little or no difficulty attaining or keeping their erections and are often able to maintain erections for prolonged periods of time, they nevertheless report low levels of subjective sexual arousal, at least compared with sexually functional men (26).

**Age**

A progressive axonal sensory loss with age has been described by Rowland as one of the reasons for age-related DE listed in his comprehensive review on penile sensitivity. (27,28). Age-related DE was also included in the large community study performed by Feldman et al. (29). Similar findings were reported in the Olmsted Country Study by O’Leary et al. in men with urinary symptoms: 3% of men in their 40’s reported difficulty in achieving ejaculation compared with 43% men in their 70’s (30).

Contrary to the findings of these evidence-based studies on the relationship between age and DE, Waldinger and Schweitzer advocated an etiology based view of orgasmic disorders as neurobiological variants of a “normal” ejaculatory distribution curve (31).

Moreover, in a prospective, observational study on 988 subjects with one or more ejaculatory dysfunctions (EjDs) other than PE. Paduch et al. showed that there was no correlation between DE and age [odds ratios (OR), 0.67 and 95% confidence intervals (CI), 0.39–1.16 and P=0.149] (32).

**Race**

The probability of race as a pathophysiological factor in EjDs was evaluated by Paduch et al. (32). According their findings, all EjDs, including DE, are more prevalent in black populations compared to Caucasian men (OR =1.77, 95% CI, 1.52–1.57). This novel finding is currently the subject of further investigation.

**Congenital disorders that may lead to DE**

In a recently published comprehensive review on EjDs, Phillips et al. provided an excellent explanation of the physiology and pathophysiology of ejaculations, including DE, due to congenital abnormalities (33). The pathophysiology of DE in relation to congenital abnormalities is complex and is dependent upon anatomical variations of the pelvic floor and the physiological functioning of the organs located into the pelvic floor. For example, Mullerian ducts normally disappear under the influence of Mullerian inhibitory factor, which is produced by the Sertoli cells in the primitive testis. Failure of complete absorption may leave a small Mullerian duct remnant at the lower end that lies between the ejaculatory ducts. The Wolffian (mesonephric) ducts are composed of three distinct areas. The upper part forms the epididymis and distal vas deferens, while the proximal vas deferens, seminal vesicle, and ejaculatory duct are derived from the middle area. The most caudal part is the common mesonephric duct, from which the ureteric bud springs at approximately 4 weeks of development: this becomes the ureter and will induce the metanephric blastema to form the kidney. The urogenital sinus reabsors the lower end of this structure, and the ureteric orifices are thus separated from the vasa deferentia, seminal vesicles and ejaculatory ducts. If too much of the proximal vas precursor is absorbed, a variable amount of the proximal vas, seminal vesicle, and/or ejaculatory duct may be absent (33).

Congenital anomalies of the Wolffian duct may be either sporadic, with a localized defect in the proximal part of the vas deferens, or a more generalized mal-development due to a systemic genetic abnormality. A local Wolffian duct abnormality involves the loss of a variable amount of the vas deferens, seminal vesicle, and/or ejaculatory duct, and sometimes part of the ipsilateral urinary system as well (33-35). Most of the patients with prune belly syndrome have abnormal ejaculations and probably abnormal emissions. Whether the primary abnormality is retrograde ejaculation or lack of emission is not clear (33,36).

Any congenital malformation of above-mentioned anatomical apparatuses may cause DE or anejaculation. For example, incomplete regression of the Mullerian duct remnants may affect ejaculatory function and cause DE.
Woffian duct abnormalities may affect the strictures between the efferent ducts of the testis to the prostate, specifically the epididymis, the vas deference and the seminal vesicle, and also can affect ejaculation. Abnormalities of the prostate and urethra are common in prune belly syndrome, and this condition may also lead to EjD (37).

**Acquired DE**

Acquired or secondary DE is the result of an identifiable surgical procedure, a different medical condition or psychosexual changes. It may affect ejaculation by a variety of ways, such as via disruption of the chemical or nervous control of ejaculation, or directly at the site of the ejaculatory organs themselves.

**Post-surgical DE**

**Imperforate anus**

Ejaculatory duct damage may follow correction of an imperforate anus. The pull through procedure passes close to the posterior aspect of the prostate, and its partial or total injury is most likely if there has been closure of a recto-urethral fistula. Analysis of 20 subfertile males who had repair of an imperforate anus in infancy indicated that 7 had no ejaculate, 11 were azoospermic, 1 was severely oligozoospermic, and only 1 had a normal sperm concentration in a very small volume ejaculate (38).

**Prostatic surgery for BPH/LUTS**

Different surgical modalities for the treatment of lower urinary tract symptoms (LUTS) due to benign prostate hyperplasia (BPH) are associated with variable adverse effects on ejaculatory function. Antegrade (normal) ejaculation requires a closed bladder neck (and proximal urethra). Surgical procedures that compromise the bladder neck closure mechanism may result in retrograde ejaculation. Transurethral resection of the prostate (TURP) carries a higher incidence of EjDs than does transurethral incision of the prostate (TUIP). This also applies to retrograde ejaculation (39,40). Although the less-invasive procedures had a lower complication rate in ejaculatory parameters, a comparison of the efficacy of the treatments on relieving outflow obstruction was not included in the analysis and very little is known about intravaginal ejaculatory latency time (IELT) after surgical treatment of BPH/LUTS (41).

**Prostate cancer (PC)**

PC has become the most common non-skin malignancy in men in Western countries. Together with radical prostatectomy (RP), external-beam radiotherapy (EBRT) and brachytherapy (BT) are the most common and effective treatments for localized PC. RP for PC abolishes the ability to ejaculate because of complete excision of the prostate, seminal vesicles and distal vasa differentia. However, the ability to achieve orgasm in sexually active men may persist (42). Moreover, men who undergo BT only may have some ejaculatory ability. In a recently published study, Huyghe et al. evaluated ejaculatory function in 241/270 sexually active men: 81.3% had conserved ejaculatory function after treatment with BT. In addition, 84.9% who maintained ejaculatory function after implantation reported a reduced volume of ejaculate compared with 26.9% before (P<0.001), with dry ejaculation accounting for 18.7% of those cases. After implantation of the radioactive seeds, 30.3% of the patients experienced painful ejaculation compared with 12.9% before (P=0.001), and this was associated with a greater number of implanted needles (P=0.021) and with the existence of painful ejaculation before implantation (P<0.001). Moreover, 10% of patients who continued to be sexually active following implantation experienced no orgasm compared with only 1% before treatment, and more patients experienced late/difficult or weak orgasms (P=0.001) (43).

**Pelvic surgery**

Theoretically, surgery that affects either the genitalia directly or the innervation of the ejaculatory tract may lead to DE. However, unlike the sufficient amount of available information on EjD after pelvic surgery, our knowledge on DE after pelvic surgery is very limited. One publication reported that total mesorectal excision with intention to treat low rectal cancers was associated with the inability to ejaculate in 67% of sexually active men after 1 year (44). In a retrospective analysis of men who underwent pelvic surgery for rectal cancer and had no recurrence, there was a deterioration of orgasm capacity (4.1% versus 16.5%) and ejaculation ability (1.4% versus 12.4%) compared with their preoperative state (45). The preservation of ejaculation is dependent on the extent of surgery and an attempt for autonomic nerve preservation.
After total mesorectal excision for lower rectal cancer, 70% of patients without lateral node dissection and 10% of those with lateral node dissection maintained ejaculation among the patients who maintained sexual activity (46). Pelvic autonomic nerve preservation contributed to this low prevalence. Importantly, the orgasmic function score of the IIEF decreased significantly after surgery as well (47). Laparoscopic surgery for rectal cancer was similarly associated with EjD, however, with a variable range of reported prevalence. These sequelae were associated with sufficient autonomic nerve preservation for the ability to achieve orgasm and ejaculation, which was maintained by 37.8% of the patients (48).

**Testicular cancer and RPLND**

Testicular cancer is relatively rare, accounting for about 1% of all male cancers. The long-term survival for early disease approaches 100%. Because testicular cancer affects mainly young men during their sexually active and fertile periods of life, sexual functioning and ejaculatory disorders are particularly important. It is not clear how testicular cancer itself affects IELT. However, at a median follow-up of nearly 10 years, persisting sexual complications after germ cell tumor therapy included decreased orgasm (10.2%) and ejaculation (28.8%) (49). In a study involving Norwegian men, testicular cancer survivors had significantly worse scores in ejaculatory and sexual problems domains compared with the general population in both young (20–39 years) and middle-aged (40–59 years) males. EjD including DE had a prevalence of 18–19% in cancer survivors compared to 6–9% in controls (50). A long-term follow-up assessment of testicular cancer survivors in Denmark showed that 7% had ejaculatory problems (51).

Retroperitoneal lymph node dissection (RPLND) following orchiectomy has been introduced either before chemotherapy or after it, in cases if residual retroperitoneal mass is found on the follow up CT. Retroperitoneal surgery for testicular cancer might affect the superior hypogastric plexus, which is responsible for ejaculation. It is a fenestrated network of fibers anterior to the lower abdominal aorta, and it is mediated by the sympathetic system. The hypogastric nerves exit bilaterally at the inferior pole of the superior hypogastric plexus, and have connections with the S1–S2 roots. Normal emission requires integrity of this system. During RPLND, these nerves are difficult to recognize and might be damaged, resulting in decreased semen volume or dry ejaculation (52). In addition, several factors affect the impact of RPLND on ejaculation, such as the stage of the tumor, associated chemotherapy and attempted nerve preservation. Dry ejaculation occurs in the majority of the patients in non-nerve-sparing techniques. As a result of improvement of surgical technologies, techniques and careful anatomical studies, the original RPLND approach has been modified and is now a nerve-sparing one that allows the maintaining of antegrade ejaculations in 80–100% of patients (53).

**Effect of circumcision on ejaculatory function**

Circumcision has been considered to affect ejaculation by changes in penile sensitivity. Masood et al. reported improvement in penile sensitivity and DE in 38% (P=0.01) of their patients who underwent circumcision, a worsening of those conditions in 18%, and no change in 46% (54). Fink et al. demonstrated a worsening of erectile function from 12.4 to 10.5 on IIEF score (P=0.01), decreased penile sensitivity and, as a consequence, DE from 9.5 to 9 (P=0.08) in 123 men aged 18 years and older (55). In contrast, the results of Senel et al. prospective study demonstrated that circumcision performed by a plastic clamp technique in adult men does not affect ejaculation (56).

**Neurological disorders**

**Stroke**

Neurological disorders, either functional or organic, that affect the brain and spinal cord may cause DE, depending on the level and extent of the pathology. Cheung et al. found that 45.9–64.5% of men in a stable condition and with mild or no disability after a stroke reported diminished ejaculatory latency time or absent ejaculation (57). Tämam et al. showed that the side of the hemispheric lesions did not affect latency of ejaculation (58).

**Multiple sclerosis**

Multiple sclerosis is associated with ED (63.2%), EjD and/or orgasmic dysfunction (50%) and reduced libido (39.5%) (59). In a community-based study in Australia, Redelman evaluated 283 patients with multiple sclerosis, of whom 74% were male responders. Men with multiple sclerosis reported masturbation difficulties, difficulty with achieving vaginal orgasms, DE and PE (60).
**Spinal cord injury (SCI)**

The ability to ejaculate is severely impaired by SCI. Bors and Comarr highlighted the impact of the level and completeness of SCI on post-injury erectile and ejaculatory capacity (61,62). Unlike erectile capacity, the ability to ejaculate increased with descending levels of spinal injury. Fewer than 5% of patients with complete upper motor neuron lesions retained the ability to ejaculate. Ejaculation rates were higher (15%) in patients with both 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 retained the ability to ejaculate. The sensation of orgasm may be absent or diminished in patients capable of successful ejaculation, and this can cause DE (62). Kamischke et al. conducted a meta-analysis of 560 men whose direct cause of DE was SCI in 68.9%, RPLND in 21.6%, diabetes in 2.1%, multiple sclerosis in 0.4%, bladder neck surgery in 0.2% and idiopathic in 7.1% (63).

**Congenital neurological anomalies**

Congenital neurological anomalies affecting the lower segment of the spinal cord are associated with a lesser degree of EjD. Shiomi et al. showed positive rates of 88% and 65% for ejaculation and orgasm, respectively, in young male patients with spina bifida. Some of the patients, however, complained of decreased penile sensitivity and DE (64).

**Hormonal disorders**

Although hormonal regulation of all aspects of male reproduction is well established, the role of endocrine control on the ejaculatory process is still not completely clarified. Correlations between EjDs and endocrine disorders has recently been investigated in several studies (1,65-69). In one study on 2,652 patients, Corona et al. found that 674 (25%) patients complained of PE and 194 (7%) patients suffered from DE. After adjustment for age and other parameters, the authors performed calculations with a regression model and concluded that prolactin, TSH and SSRIs were independent causes of prolonged IELT. Current thought favors the effect of prolactin on ejaculation via its effect on the serotonergic system (68,69), while the opposite was observed for testosterone levels (32,65,67). An inverse relationship has been reported between thyroid hormone levels and ejaculatory latency. Hypothyroidism was strongly associated with longer ejaculatory latency (DE), while hyperthyroidism was accompanied by shorter ejaculatory latency (PE) (1,65).

Paduch et al. and Corona et al. demonstrated a lower predisposition to ejaculate in men with low testosterone levels and hypogonadism in several studies (32,65,67). This finding is noted by other authors as well (66).

Schmidt et al. pharmacologically induced hypogonadism in healthy volunteers, and demonstrated diminished orgasmic function which was corrected to normal after androgen replacement (70). Free testosterone and sex hormone-binding globulin (SHBG) levels were significantly correlated with the orgasmic dysfunction domain of the IIEF after correction for age (71). The prevalence of reported PE and DE was 25.9% and 4.4%, respectively, in a consecutive series of male patients with sexual dysfunction. Lower total testosterone and free testosterone levels were observed in older DE subjects. Patients with PE showed the lowest (12%) and subjects with DE showed the highest (26%) prevalence of hypogonadism (72).

**DE in prostate and pelvic infections**

UTI, pelvic inflammation and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) have all been recognized as etiologic factors for EjD, including DE. Men with recurrent infections are predisposed to more frequent occurrences of EjD, painful ejaculation and hematospermia. Tuncel et al. reported EjD disorders in 67.7% of men with evidence of prostatic inflammation compared to 30.2% of men with ED (73). CP/CPPS was significantly associated with EjD in a cross-sectional study of older men in Olmsted County (MN, USA) (74). The NIH Chronic Prostatitis Cohort (CPC) study reported ejaculatory pain in 58% of patients with prostatitis versus 17% of patients with BPH and 4% of controls. The baseline CP/CPPS symptom index total score was significantly higher for men who always had ejaculatory pain versus men who never had ejaculatory pain. Mental and physical quality of life was also progressively lower for the former group (75).

In another study from the USA, men diagnosed with CPPS type III were compared with healthy controls: 36% CPPS men reported never having painful ejaculation, 51% reported having had it only sometimes, and 13.5% reported having pain at ejaculation most of the time or always. Analysis of factors related to sexual function in CPPS subjects included pain status and psychological adaptation,
and the results showed that frequency of sexual activity decreased with increasing depression, whereas arousal/erectile function decreased with increasing pain symptoms and stress appraisal. Additionally, orgasm function decreased with increasing depression, and pleasure/satisfaction decreased with increasing pain symptoms, stress appraisal, and decreasing belief of an association between emotion and pain (76).

Certain pathological radiological findings have been reported in some patients with CP/CPPS and EjD. For example, 55% of a group of patients with CP/CPPS also had EjD. Investigations have shown that painful ejaculation was significantly associated with the sonographic demonstration of enlargement, asymmetry or inflammatory changes of the seminal vesicles, whereas hemospermia was significantly associated with asymmetry or inflammatory changes of the seminal vesicles (77).

In spite of the extensive information existing on EjD and UTI, CP/CPPS and pelvic inflammation, there is no definitive evidence of the actual frequency of DE in patients with pelvic inflammatory disorders or of the true pathophysiological role of these inflammatory disorders in DE.

**Medical treatment and DE**

**Medical treatments that cause DE**

The medical treatment for many conditions can be the reasons for DE. McMahon introduced a list of the main drug groups can cause DE, including alpha methylidopa, diuretics, tricyclic antidepressants, SSRIs, and phenothiazines as well as alcohol abuse (78).

**α adrenoceptor blockers**

A significant number of men on medical treatment for LUTS associated with BPH report EjD. The possible explanation on way that α adrenoceptor blockers affecting ejaculation is there effect on the receptors in bladder neck, prostate urethra, seminal vesicles and vas difference all together impairs ejaculation at the level of seminal emission.

**Tamsulosin**

One of the frequently used medications today is α1A-selective adrenoceptor blocker tamsulosin. Tamsulosin in daily doses ranging from 0.2 to 0.8 mg causes various types of problems with ejaculation. Even low doses of tamsulosin (0.2 mg daily) after 12 weeks of treatment were associated with 13.4% EjD, with a 3.1% incidence of DE (79).

In a prospective study of the more widely used 0.4 mg daily dose of tamsulosin, Goktas et al. assessed the effect of intermittent treatment on ejaculatory complications. On daily dosing, abnormal ejaculation developed in 7.4% of the men and DE in 1.2%. Ejaculatory function recovered during intermittent tamsulosin treatment in 63.3% of affected men (80).

**Silodosin**

Another α1A-specific adrenoceptor blocker more recently introduced for the treatment of LUTS is associated with ejaculatory complications similar to those as tamsulosin. Silodosin 4 mg daily was associated with inability to have antegrade ejaculation in 7.2–28.1% of men with LUTS (81,82). Similar to tamsulosin, silodosin impairs ejaculation at the level of seminal emission. Compared with placebo in a group of male volunteers, silodosin caused complete lack of seminal emission and expulsion, with none of the subjects having post-ejaculation sperm in their urine (83).

**Alfuzosin**

Alfuzosin, one of the popular α1 adrenoceptor blockers not selective to the α1A subtype is rarely associated with ejaculatory complications. In a pooled analysis of three double-blind and placebo-controlled studies of alfuzosin treatment for LUTS, abnormal ejaculation was reported in only 0.6% of the men (84).

In contrast to other α1 adrenoceptor blockers, alfuzosin treatment in men with LUTS was associated with improvement in ejaculatory function. Rather, in a prospective, open-label study, Leungwattanakij et al. showed that alfuzosin caused a significant improvement in the ejaculatory function score after 6 months (85). Additional studies are needed to confirm these findings and to understand this reversal effect of alfuzosin.

**5α-reductase inhibitors**

Dihydrotestosterone (DHT) is the androgen responsible for prostate growth and enlargement. Inhibition of the enzyme 5α-reductase that catalyzes the formalization of DHT from testosterone is another class of medications used for the treatment of LUTS suggestive of BPH.
**Finasteride**

Both finasteride (Proscar) and dutasteride (Avodart) have some adverse effects on sexual and ejaculatory function. In a prospective, double blind randomized study (PROSPECT study) of the efficacy and safety of finasteride in the treatment of BPH, EjD occurred in 7% of the treatment group versus 1.7% in the placebo group after a 2-year follow-up (86). The first long-term combination trial, MTOPS, which was performed only in the United States on 3,047 men with moderate symptoms of BPH and a PSA <4, lasted for 5.5 years and compared monotherapy with doxazosin, finasteride, or placebo to the combination of doxazosin and finasteride. Finasteride treatment for conditions other than LUTS was associated with EjD. Men treated with finasteride for male pattern hair loss reportedly developed sexual dysfunction, including orgasmic problems (87).

**Dutasteride**

Dutasteride is a 5α-reductase inhibitor that blocks both type 1 and 2 isoenzymes and provides a greater blockade of DHT production than finasteride. Dutasteride monotherapy trials were performed in which the long-term effects of dutasteride were compared with placebo. The results of the 4-year extended monotherapy trial (CombAT IV) showed an 80% better symptom response, a 56% PSA reduction, a 27% volume reduction, and a 70% risk reduction in either AUR or the need for surgery. However, in three randomized, double blind clinical trials, there were significantly greater incidence rates of EjD in the men with benign prostatic hyperplasia and treated with dutasteride (2.2%) than the placebo group (0.8%) (P<0.001) (88,89).

**Combination therapy**

In the combination alpha blocker and 5-alpha-reductase inhibitor dutasteride trial, sexual and ejaculatory adverse events were the most commonly reported class of drug-related side effects. The only adverse events considered to be at least possibly drug-related and that occurred in at least 5% of patients in either treatment group throughout the 36-week treatment period were ejaculation disorders. The majority of those disorders were related to sperm volume (9% DT36 group; 8% DT24 + D12 group), decreased libido (5% DT36 group; 6% DT24 + D12 group), impotence (5% DT36 group; 4% DT24 + D12 group), and malaise and fatigue (5% DT36 group; 1% DT24 + D12 group). The drug-related adverse event profiles for combination therapy were comparable to those predicted for the individual drugs, and there was no evidence of synergistic interaction. These data suggest that dutasteride and tamsulosin combination treatment is well tolerated over a 36-week period (91).

Unlike the ample evidence of a negative effect of both 5α-reductase inhibitors on EjD, there is a paucity of studies for indicating whether or not these medications cause DE, and if they do, what is the true prevalence of this disturbance in men who are treated with 5α-reductase inhibitors.

**Medications and chronic medical conditions**

**Chronic medical conditions**

Several medications and chronic medical conditions can cause DE. Chronic pain following various injuries or as a sequela of illnesses or medical treatment for illnesses such as chronic pain among cancer patients, can all cause EjD and DE (92). In a study Lew-Starowicz and Gellert, 539 patients suffering from chronic pain were requested to answer questions on sexual and ejaculatory function: 34.5% of testicular cancer survivors complained of reduced sexual desire, and sexual activity was reduced in 41.6% of them. ED was present in up to 31.5% of those patients. Ejaculatory disorders (premature, delayed, retrograde, or anejaculation) were recorded in 84.9% of testis cancer survivors. Patients with poor overall health, vascular diseases, and chronic kidney diseases were strongly associated with sexual dysfunction, with more than 50% of men on hemodialysis suffering DE or lack of ejaculation (93).

**Selective serotonin reuptake inhibitors (SSRIs)**

Durable relations were found between selective SSRIs and an adverse effect on sexual function. The only adverse effect attributable to indalpine in healthy volunteers was EjD, which was reported by 67% of the subjects. In men treated for depression, DE and orgasmic dysfunction were the most significant sexual complications (94,95).

In their pilot study, Piazza et al. reported that treatment with SSRI resulted in worsening of orgasm delay, orgasm satisfaction and overall sexual functioning in more than 10% of patients (96). Different SSRIs, however, had significant variations in their adverse effect on sexual function. In a prospective study on 152 men aged 39.6±11.4 years,
Montejo-Gonzalez et al. showed that paroxetine provoked more delay of orgasm or ejaculation and more impotence than fluvoxamine, fluoxetine or sertraline (P<0.05) (97).

The reported adverse effect of SSRIs on ejaculation may subside in a significant number of patients that continue treatment. Out of 108 patients treated with SSRIs, 34.3% developed orgasm delay and, after 6 months, 30.8% reported complete remission, 15.4% noted a marked improvement, while 15.4% continued to describe severe orgasm delay (98).

Other antidepressants

Similar to SSRIs, tricyclic antidepressants and monoamine oxidase inhibitors were associated with significant adverse effects in sexual function among patients treated for depression. In one double blind, placebo-controlled study, imipramine and phenelzine were associated with a high incidence of adverse changes in sexual function, particularly impaired orgasm and ejaculation (99).

Narcotics and alcohol

Addiction to narcotics or alcohol was associated with sexual dysfunction and EjD, including DE. A telephone survey on cannabis use and its effect on sexual function was conducted on 8,656 Australian men and women aged 16–64 years. Frequency of cannabis use was unrelated to sexual problems in the women, but daily use vs. no use was associated with increased reporting of an inability to reach orgasm among the men (3.94, 1.71–9.07; P<0.01) who described reaching orgasm too quickly (2.68, 1.41–5.08; P<0.01) and too slowly (2.05, 1.02–4.12; P=0.04) (100).

In another study by Zhang et al., 24.5% of 612 male age 22–50 years who were addicted to heroin complained of DE. After withdrawal treatment with methadone, the DE improved, with the rate dropping to 6.9% (101).

As in narcotics, alcohol addiction was also linked to sexual dysfunction. Men on outpatient treatment in a county alcoholism program showed an association between quantity, frequency and duration of drinking and sexual dysfunctions. During heavy drinking, 59% of the men experienced ED, 48% reported DE and 84.4% had experienced at least one kind of sexual dysfunction (102).

Diabetes

Autonomic neuropathy and microvascular disease of the ejaculatory apparatus are common sequelae in patients with long-standing diabetes mellitus and may play a major role in the development of the secondary EjD in general and DE in particular. The vas deferens and seminal vesicles may lose their ability of contraction due to replacement of the smooth muscle by fibrotic calcified tissue (103). In a national population-based study that evaluated the effect of diabetes on sexual function, the inability to climax during partnered sex in men with diagnosed diabetes was 26.1%, undiagnosed diabetes 28.5% and no diabetes 15.9%. Inability to reach orgasm with masturbation was slightly less prevalent, involving 21.1% in diabetics, 9% in undiagnosed diabetics and 14.9% in non-diabetics (104).

Conclusions

DE is one of the least common and least understood part of the EjD spectrum. Many men and their partners are often distressed by this disorder. The pathophysiology of DE involves cerebral sensory areas, motor centers, and several spinal nuclei that are tightly interconnected. The biogenic, psychogenic and other factors strongly affect the pathophysiology of DE. Despite the many publications on this disorder, there still is a paucity of publications dedicated to the subject. The diagnosis of DE should be based on patient self-reporting, clinical history, sexual history and finding of physical and laboratory examination. In addition, evaluation and treatment of this disorder requires a more holistic approach, and the collaboration between urologists, psychologists and specialists in other medicine is critical for optimal management.

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Footnote

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