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A systematic review of the correlates and management of nonpremature ejaculatory dysfunction in heterosexual men

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Abstract

Introduction: A better understanding of ejaculatory disorders has led to an increasing interest in nonpremature ejaculatory dysfunction (non-PE EjD). Current reviews on the subject use a symptom-based classification to describe ejaculatory dysfunction even when it is a single case report. While these reviews provide important information on the disorder, a clearer picture of the prevalence of non-PE EjD in relation to the community and various pathophysiologic states is needed.

Objectives: The objective of this study was to provide a systematic review of studies of non-PE EjD excluding single case reports.

Methods: A systematic review of Medline for terms including ejaculation, orgasm or hematospermia. Association with terms delay, pain or headache was made. The search was restricted to male gender and articles written in English. Abstracts were reviewed and those mainly concerned with premature ejaculation were excluded.

Results: A total of 333 articles on non-PE EjD were identified. The condition was reported in community-based studies. In certain patient populations, non-PE EjD was commonly reported in association with antidepressant and antipsychotic treatments, in patients with chronic prostatitis/chronic pelvic pain syndrome, patients with lower urinary tract symptoms particularly in association with medical or surgical treatment, patients with retroperitoneal surgery and in patients with neurological diseases. Few articles were concerned with treatment options.

Conclusion: There is a significant prevalence of non-PE EjD in the community and in association with particular disease states or as a side effect of medical or surgical interventions. There is a need to direct efforts to prevent and treat these conditions.

Keywords: anhedonia, aspermia, ejaculation, epidemiology, headache, hemospermia, orgasm, pain, prevalence

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Background

There is an increasing interest in nonpremature ejaculatory dysfunction (non-PE EjD). The frontier of sexual medicine has shifted slowly from erectile dysfunction (ED) to premature ejaculation (PE) and now to non-PE EjD. Two factors have contributed to this shift. First is the search for new areas of research and of novel treatments and second is the better characterization of ejaculatory disorders. The development of questionnaires that better characterize the type of ejaculatory dysfunction (EjD) has helped to identify the problem with more precision in different populations.

Interest in the global sexual practice patterns gave insight into the prevalence of non-PE EjD in different areas of the world. Within the non-PE EjD itself, a shift in focus occurred over the years. Early and related to prostatic surgery and retroperitoneal lymph node dissection (RPLND) retrograde ejaculation was reported. With the development of α-blockers and finasteride, retrograde ejaculation, EjD and/or orgasmic dysfunction were reported as

adverse events. It became clear that antidepressant treatment caused orgasmic dysfunction, impaired ejaculation or delayed ejaculation. This opened an opportunity to provide treatment for the difficult problem of PE and brought it to the center of attention of clinicians and the pharmaceutical industry. The common problem of lower urinary tract symptoms (LUTS) was increasingly reported associated with sexual dysfunction, particularly the bothersomeness from non-PE EjD. This new direction led to exploration of the use of phosphodiesterase type-5 inhibitors (PDE5i) to treat both LUTS and sexual dysfunction including EjD.

In an effort to better characterize EjD, a symptom-based pathophysiologic approach has been taken. Ejaculation disorders were classified and defined according to timing of ejaculation (premature or delayed), direction (antegrade or retrograde), emission (aspermia), orgasm (lack of it), pain, hematospermia and orgasmic headache. In a clinical setting, however, these precise pathophysiologic events are overlapping and blurred by the absence of a detailed history, overlapping nonspecific terminology, lack of diagnostic tools and the presence of confounding and interacting factors. The terms EjD and orgasmic dysfunction have been used interchangeably in many studies to describe the whole spectrum of EjD.

Similarly, identification of the separate events of ejaculation and orgasm is omitted in many studies, although they might affect each other or occur in dissociation [Kobayashi *et al.* 2009; Yokoyama *et al.* 2011]. If sexual activity and erection do not occur, it is less likely that ejaculation and orgasm can occur. Identification of ED as a confounding factor for failure to ejaculate or have an orgasm was not considered in many reports.

Likewise, many reports did not indicate the ratio of subjects who are sexually active during the study.

In describing the conditions of non-PE EjD, we chose to portray the condition as prevalent in different populations. Aware that a precise pathophysiologic characterization is difficult, we are reporting non-PE EjD in the same terminology used by the studies reviewed. We think that in this way the relative importance of non-PE EjD conditions can be appraised. A precise reporting of non-PE EjD requires future studies to use specific questionnaire, well-defined terminology and to better analyze confounding factors.

Methods

A systematic search in Medline database included citations from 1945 until February 2013. The search words included ejaculation OR ejaculatory OR orgasm. The results were combined using AND with the words: pain OR delay OR dysfunction OR prevalence OR epidemiology OR headache OR retrograde OR anhedonia. An additional search was conducted separately for words: retarded ejaculation OR anejaculation OR inhibited ejaculation OR hemospermia OR hematospermia OR aspermia. The results were filtered to include only articles in English, and reporting on human, male subjects.

Abstracts and articles were reviewed for the relevance to our systematic report. Citations were excluded if the topics were mainly focused any of the subjects listed in Table 1.

Results

A total of 4258 citations were identified. Filtering for English language and only including human males, 2515 citations were found. Additional citations on hemospermia or hematospermia (195), aspermia (71) and anhedonia (5) were added. Combining the databases resulted in 2760 unique citations. Based on a review of the abstracts, 2219 citations were excluded. Full-text articles (541) were reviewed and 333 were included in this study.

Definitions and assessment tools

Definitions

After reviewing the literature, it is clear that many components of non-PE EjD need more precise definitions. Although a pathophysiological classification of ejaculatory disorders can be made based on the phases of normal antegrade ejaculation of emission, ejection and orgasm, no consensus on the precise definition of ejaculatory and orgasmic dysfunction is available [McMahon *et al.* 2010] (Table 2). Delayed ejaculation (DE) received considerable attention to define the condition. *The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision* (DSM-IV-TR) defines orgasmic disorder in men as 'the persistent or recurrent delay in, or absence of, orgasm after a normal sexual excitement phase', 'The disturbance causes marked distress' and 'not accounted for by another Axis I (clinical) disorder or a substance or a general medical condition' [American Psychiatric Association, 2000]. In this

Table 1. Exclusion criteria.

Exclusions based on abstract review:
Premature ejaculation only
Female gender only
Desire disorders only
Case reports involving less than three patients
ED only
Homosexuality
Experimental animal studies
Review articles and expert opinions.
Exclusions based on full text review:
Lack of specific data presentation on EjD
Lack of definition of EjD
Patient population is not well defined
Inclusion of PE within the reported results inseparable for analysis
No separation of results between men and women
No separation of results between ED and non-ED patients (results cofounded by ED).
Full text is not available
Article has been withdrawn
Duplication of reporting
Exclusions specific to EjD as a result of a treatment or surgery:
Lack of control arm except when treatment is rare, unique or not possible to have a control group.
Early experience of a technique or rare use of a drug.

ED, erectile dysfunction; EjD, ejaculatory dysfunction.

definition, there is no clear distinction between DE and lack of orgasm, although there is a dissociation between the two events as can be found in spinal cord injury patients and in normal volunteers under silodosin treatment. Furthermore, the definition includes etiological diagnosis and requires that the problem caused marked stress. In a review of the usage of the term 'male orgasmic disorder' in publications spanning two decades since it was introduced, minimal utilization of the term was reported. A number of alternative terms were used by authors to report on orgasmic dysfunction such as anorgasmia, DE, retarded ejaculation, ejaculatory delay and ejaculatory disorder [Segraves, 2010].

A mathematical definition of DE is an ejaculation that occurs two standard deviations beyond the normal intravaginal ejaculatory latency time (IELT) [Waldinger *et al.* 2005; Patrick *et al.* 2005]. A diagnosis of DE therefore can be made for men with ejaculatory latencies beyond 25–30 minutes who report distress or men who cease sexual activity due to exhaustion or seek help for the problem [McMahon *et al.* 2010]. No precise definitions were provided for painful ejaculation, hematospermia, low-volume ejaculation and retrograde ejaculation (Table 2).

Questionnaires

The earliest objective tool to assess sexual function, the International Index of Erectile Function (IIEF) questionnaire, had two questions on ejaculation and orgasm [Rosen *et al.* 1997]: How often did you ejaculate? How often did you have the feeling of orgasm (with or without ejaculation)?

Several studies has used the more specific questionnaire, the Danish Prostatic Symptoms Score (DAN-PSS-Sex), which contains questions on EjD, pain or discomfort and their respective bothersomeness [Lin *et al.* 2009; Nickel *et al.* 2006; Li *et al.* 2005; Rosen *et al.* 2003]. Other less commonly used questionnaire for EjD included the Brief Sexual Function Inventory (BSFI) and the Utvalg for Kliniske Undersogelser (UKU) Side Effect Scale [Chung *et al.* 2004; Ekselius and Von Knorring, 2001].

Diagnostics

The most commonly reported investigations associated with Non-PE EjD are concerned with ejaculatory duct and seminal vesicle pathology. Transrectal ultrasound (TRUS) and magnetic resonance imaging (MRI) using a body coil and endorectal coil were used to investigate patients

Table 2. Definitions and description of conditions encompassed under non-PE EjD.

Term	Definition or description	Source
Anejaculation	Complete inability to ejaculate	*The 3rd International Consultation on Sexual Medicine - Paris* [McMahon *et al.* 2010]
	No definition	*Merriam-Webster Medical Dictionary* [Merriam-Webster, Inc., 2013]
	No definition	*Stedman's Medical Dictionary Online* [Stedman's Online, 2013]
Anhedonia	A psychological condition characterized by inability to experience pleasure in acts which normally produce it.	*Merriam-Webster Medical Dictionary* [Merriam-Webster, Inc., 2013]
	Absence of pleasure from the performance of acts that would ordinarily be pleasurable. ICD-9-CM code: 302.72	*Stedman's Medical Dictionary Online* [Stedman's Online, 2013]
	Orgasm occurs but the patient fails to perceive pleasure	Author's comment
Anorgasmia	A perceived absence of the orgasm independent of ejaculation	*The 3rd International Consultation on Sexual Medicine - Paris* [McMahon *et al.* 2010]
	Sexual dysfunction characterized by failure to achieve orgasm	*Merriam-Webster Medical Dictionary* [Merriam-Webster, Inc., 2013]
	No definition	*Stedman's Medical Dictionary Online* [Stedman's Online, 2013]
Aspermia	No ejaculation, orgasm is present and no sperm in urine after orgasm.	Diagnostic algorithm [McMahon *et al.* 2010]
	Inability to produce or ejaculate semen	*Merriam-Webster Medical Dictionary* [Merriam-Webster, Inc., 2013]
	Lack of secretion or expulsion of semen following ejaculation. ICD-9-CM code: 606.0	*Stedman's Medical Dictionary Online* [Stedman's Online, 2013]
Delayed ejaculation (DE), retarded ejaculation, and inhibited ejaculation (IE)	Varying delays in the latency to ejaculation, or the complete inability to ejaculate (anejaculation). Reductions in the volume, force, and sensation of ejaculation may occur. At the extremes are anejaculation (time) and retrograde ejaculation (direction).	*The 3rd International Consultation on Sexual Medicine - Paris* [McMahon *et al.* 2010]
Failure of emission	No ejaculation, never orgasm	Diagnostic algorithm [McMahon *et al.* 2010]
Hematospermia, hemospermia	Presence of blood in the seminal fluid. ICD-9-CM code: 608.82; MeSH: hemospermia	*Merriam-Webster Medical Dictionary* [Merriam-Webster, Inc., 2013]
Inhibited male orgasm	No ejaculation, sometimes orgasm present	Diagnostic algorithm [McMahon *et al.* 2010]
Male orgasmic disorder (delayed ejaculation)	The persistent or recurrent delay in, or absence of, orgasm after a normal sexual excitement phase, the disturbance causes marked distress and not accounted for by another Axis I (clinical) disorder or a substance or a general medical condition.	*The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision* (DSM-IV-TR) [American Psychiatric Association, 2000]
	No clear distinction between orgasm and ejaculation. No formal distinction between delayed ejaculation and failure of ejaculation	Author's comment
Orgasmic dysfunction	The inability to achieve an orgasm or markedly diminished intensity of orgasmic sensations; marked delay of orgasm during any kind of sexual stimulation.	*The 3rd International Consultation on Sexual Medicine - Paris* [McMahon *et al.* 2010]

(Continued)

Table 2. (Continued)

Term	Definition or description	Source
Orgasmic headache	The condition of sudden onset of a throbbing or a constant headache during sexual activity and at or around the time of orgasm	Lance [1976]
Painful ejaculation	Pain related to orgasm in the penis, rectum, abdomen or testis.	Barnas *et al.* [2004]
Retrograde ejaculation	Abnormal direction of ejaculation. No ejaculation, orgasm is present and sperms are present in urine after orgasm.	Diagnostic algorithm [McMahon *et al.* 2010]
	Delivery of semen ejaculate into the bladder; seen in neurologic disease, diabetes, and occasionally after prostate surgery. ICD-9-CM code: 608.87	*Stedman's Medical Dictionary Online* [Stedman's Online, 2013]

with suspected ejaculatory duct obstruction. Vasography was used to confirm the diagnosis [Weintraub *et al.* 1993]. In patients with hemospermia, hypospermia, oligospermia, or painful ejaculation high-resolution MRI with an endorectal surface coil detected specific underlying pathologies of the prostate and seminal vesicles [Schnall *et al.* 1992]. TRUS provides excellent anatomic detail of pathologic changes in the seminal vesicles and ejaculatory ducts including seminal vesicle dilatation or cysts, ejaculatory duct cysts, or seminal vesicle or ejaculatory duct calculi [Littrup *et al.* 1988].

The demonstration of an enlarged prostatic utricle by TRUS provides etiological diagnosis of EjD in men presenting with a variety of LUTS and infertility [Coppens *et al.* 2002].

More invasive diagnostic tests include the use of endoscopy. Transurethral seminal vesiculoscopy was successfully used to diagnose and treat patients with intractable hematospermia and seminal vesicle stones [Song *et al.* 2012; Liu *et al.* 2009]

Prevalence of non-PE EjD in the general population

Non-PE EjD is a common problem that has received little attention. Follow up of men, in a population-based cohort, revealed an annual incidence of EjD (difficulty to ejaculate or the amount of semen is a problem) of 24/1000 [Gades *et al.* 2009]. In a longitudinal study of men aged 50–78 years, registered in the general practices in the Netherlands, a 6.5-year follow up showed that at baseline 40.4% of men already had EJD, with a cumulative incidence of 16.5%, 24.7% and 33.1% after follow up at 2.1, 4.2 and 6.5 years, respectively [Gan *et al.* 2007].

Ejaculatory difficulty in a nonclinical sample of men was reported as three times as prevalent as ED [Spector and Boyle, 1986]. The global study of sex behavior involved nearly 14,000 men in 29 countries [Laumann *et al.* 2005]. The prevalence of inability to reach orgasm in sexually active men was 14.4%. This is a significant prevalence compared with ED (18.5%) and PE (24.3%) in the same study population. Inability to reach orgasm was occasional in 5.5%, periodic in 6.9% and frequent in 2%. The problem varied according to the geographical location being most common in Southeast Asia (21.1%) and least in Northern Europe (9.1%) [Laumann *et al.* 2005]. In another study in a community-dwelling older Dutch men, utilizing the International Continence Society sex questionnaire which defined significant EjD as having no ejaculations or ejaculations of significantly reduced volume, the prevalence of EjD was 13% and of ED was 11% [Blanker *et al.* 2001]. Half the men with EjD had ED as well. In another survey of men 18–59 years old in the USA, the prevalence of men who are unable to achieve orgasm was 7.8% compared with 30.6% PE [Laumann *et al.* 1999]. Other population-based studies from different parts of the world reported inability to reach orgasm in men of 2%, 5%, 6.3%, 8.7% and 8.9% [Christensen *et al.* 2011b; Johnson *et al.* 2004; Richters *et al.* 2003; Herbenick *et al.* 2010; Lau *et al.* 2005].

Anorgasmia during partnered sexual experience was 13.1% [Schick *et al.* 2010]. These data are consistent with a meta-analysis of population

based sex surveys reporting 5% inhibition of male orgasm [Nathan, 1986].

Non-PE EjD bothers many of the affected men. The Global Better Sex Survey (GBSS) focused on components important for a satisfying sexual relationship in 26 countries worldwide. The aspect that was most highly regarded by men was feeling attracted to one's partner; the ability to achieve orgasm was the next most important aspect of the sexual experience in 66% of men [Mulhall *et al.* 2008]. In men without bladder or prostate disease, EjD had a negative impact on health status domains, particularly sickness impact profile, emotions and sexual interactions [Blanker *et al.* 2002].

Several risk factors for developing non-PE EjD were identified in population-based studies. These included increasing age, ED, prostatic disease, diabetes, poor health, vascular disease, decreased thinking of sex, depression, noncommitted or nonexclusive relationship, relationship worries, less-frequent sexual encounters and drug use [Laumann *et al.* 2005; Blanker *et al.* 2001; Johnson *et al.* 2004]. The impact of age is clearly shown in the Olmsted County Study of Urinary Symptoms and Health Status among Men. Of the men in their forties, 3% reported either not having climaxed or the amount of semen ejaculated to be a big problem compared with 43% of men in their seventies [O'Leary *et al.* 2003]. In Danish younger men retarded ejaculation was reported in 2% of a community sample, whereas men older than 50 had more common prevalence reaching 8% [Andersen *et al.* 2008]. Diabetics had significantly more EjD compared with nondiabetics (31.4% *versus* 6.6) [Burke *et al.* 2007]. 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 nondiabetics [Lindau *et al.* 2010]. The use of marijuana and alcohol were identified as risk factors for EjD [Johnson *et al.* 2004].

Higher prevalence is reported in particular populations. Cultural and geographical factors affect orgasm. Japanese men with clinically localized prostate cancer were more likely than American men to report poor ability to attain orgasm [Namiki *et al.* 2008]. In a prevalence study involving secondary school teachers in Nigeria, 23% of men had an orgasmic disorder [Adegunloye and Ezeoke, 2011]. In a Canadian study in men without evidence of prostate cancer who participated in an annual prostate cancer screening event, 46% had reduced ejaculatory volume and 66% were bothered by the condition; ED and advanced age were risk factors [Walz *et al.* 2007a]. An Argentinean study of the prevalence of sexual dysfunctions in men who attended a prostate awareness week campaign showed that 14.1% had a DE and 6.8% had absence of ejaculation [Nolazco *et al.* 2004].

Few studies reported on painful ejaculation in the community. In men participating in a screening event for cancer prostate, the prevalence of ejaculatory pain was 11% and 89% were bothered by the symptom [Walz *et al.* 2007a]. In a population-based study in China, sexual problems, reported as pain, were prevalent in 4.2% of sexually active men [Lau *et al.* 2005]. In a longitudinal study of men in the Netherlands, the mean percentage of men who were bothered by reduced ejaculatory volume or painful ejaculation was 18.3% and 40.6%, respectively [Gan *et al.* 2007].

Other factors that were considered to affect EjD included circumcision, level of education, genetic influence and body mass index. In a community-based survey in Denmark, the prevalence of frequent orgasm difficulty was significantly more in circumcised men (11%) compared with the uncircumcised (4%) [Frisch *et al.* 2011]. Occasional orgasm difficulties were equally common (29–32%). A total of 12% of men with less than university education reported DE problems [Traeen and Stigum, 2010]. Genetic influence was evaluated in a population-based sample of Finnish male twins. A total of 4.1% reported ejaculation later than desired, but no genetic influence was detected [Jern *et al.* 2007]. Finally in a cohort of healthy men undergoing prostate cancer screening, elevated body mass index was associated with a lower rate of subjectively decreased ejaculate volume, lower rates of chronic pelvic pain and a lower rate of pain/discomfort on ejaculation [Bhojani *et al.* 2008].

Prevalence of non-PE EjD in patients with other medical conditions

In patients with LUTS

Several population-based studies evaluated EJD and showed a high prevalence of non-PE EjD in

men with LUTS [Rosen *et al.* 2003; Chung *et al.* 2004; Li *et al.* 2005; Lin *et al.* 2009]. These studies revealed that there was a significant association between the prevalence of EjD with increasing age and the severity of LUTS [Rosen *et al.* 2003; Chung *et al.* 2004; Li *et al.* 2005]. A significant portion of men with EjD were bothered particularly by painful ejaculation reaching up to 90%. LUTS are quite common in older men. A population-based survey involving a sample of men aged 50–80 years in the USA and six European countries showed that 90% had LUTS [Rosen *et al.* 2003]. Reduced semen or no ejaculation, in men who could achieve erection, occurred in 46.2%. The bothersomeness of ejaculatory problems ranged between 50.2% and 58.4%, and increased significantly with LUTS severity up to 80.1%. Painful or uncomfortable ejaculation in men able to ejaculate occurred in 7.2% with a high percentage of bothersomeness of 88.3%. Painful ejaculation was associated with increasing age and with severity of LUTS [Rosen *et al.* 2003]. In a cross-sectional population study in the USA, the UK and Sweden, 6.7% of men with LUTS reported ability to ejaculate less than half or none of the time. Significant associations with EjD were increasing age, prostate cancer, depression, urine leaking during sex and urgency with fear of leaking [Wein *et al.* 2009]. Another population-based study reported similar findings. A cross-sectional study of subjects in The Olmsted County Study of Urinary Symptoms and Health Status among Men found a significant association between LUTS and non-PE EjD [Chung *et al.* 2004]. The median score of EjD as evaluated by the BSFI was 8 in men with LUTS. Among the sexual dysfunction domains, EjD score had the strongest association with the severity of LUTS [Chung *et al.* 2004]. These findings were reiterated in reports from population-based studies in Asian countries [Li *et al.* 2005]. A survey in selected cities in five countries, involving men aged 50–80 years, showed that the prevalence of LUTS ranged from 14% to 59%. Ejaculation disorders were present in 68% of respondents and 52% reported bothersomeness. Painful ejaculation was experienced by 19% of men in the study and 88% reported bothersomeness. Lower bothersomeness was reported in another study. A survey showed that reduced or no ejaculation and pain upon ejaculation were found in 76.6% and 6.1% of men with LUTS [Lin *et al.* 2009]. However, only 22.1% and 4.4% were bothered by the sexual dysfunction, respectively.

In a clinical setting, patients presenting for the management of LUTS reported EjD. In a registry of men with benign prostatic hyperplasia (BPH) treated conservatively in the United States EjD at baseline was found in 63% (mild to moderate 34%, severe 29%) [Rosen *et al.* 2009]. In an observational study of men with LUTS suggestive of BPH, 77.9% had decreased force of ejaculation and 74.4% had decreased amount of semen [Rosen and Fitzpatrick, 2009]. EjD was bothersome to 35.6-64.1% of men. In a multinational study in men reporting LUTS suggestive of BPH the prevalence of ejaculatory pain was 18.6% and 88% considered it as a problem [Nickel *et al.* 2005]. Reduced ejaculation was significantly associated with older age, LUTS severity and previous BPH surgery [Vallancien *et al.* 2003]. EjD was highly bothersome in 82–91% of patients younger than 60 years old. Another study involved a mixed population of community subjects in the UK and urology clinic attendees in 12 countries [Frankel et al., 1998]. In the community, the prevalence of reduced ejaculation was 47% and the prevalence of painful ejaculation was 5%; in the clinic, the prevalence of reduced ejaculation was 62% and the prevalence of pain on ejaculation was 17%. In patients referred to hospitals for the management of clinical BPH, 54% noted that the amount of semen had decreased and pain/discomfort during ejaculation occurred in 15% [Schou *et al.* 1996]. The bothersomeness was low for the low-volume ejaculation and high for pain [Schou *et al.* 1996]. Other studies reported 66% reduced ejaculation, 18% painful ejaculation, 38% EjD, 38% inability to reach orgasm and 35% bothersomeness [Li *et al.* 2008; Namasivayam *et al.* 1998].

Interestingly, obesity was associated with EjD in men with LUTS [Lee *et al.* 2012]. The prevalence of EjD increased from 21.4% to 64.7% as waist circumference increased from < 90 to ≥ 100 cm [Lee *et al.* 2012]. Two other conditions not attributable to BPH were associated with non-PE EjD. In a series of men with cystoscopically confirmed interstitial cystitis, sexual dysfunction occurred in 60% of patients with a primary complaint of painful ejaculation [Forrest and Schmidt, 2004]. In a cross-sectional, population based study, overactive bladder was associated with an increased risk of inability to ejaculate. Continent and incontinent men reported 4.7% and 8.5% inability to ejaculate all the time, respectively, compared with 1.1% in the control group [Coyne *et al.* 2011].

In patients with chronic prostatitis/chronic pelvic pain syndrome

Attention has recently been directed to the condition of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) [Litwin *et al.* 1999]. Painful ejaculation is included in the symptoms associated with this syndrome. Utilizing the questionnaire developed by the National Institutes of Health (NIH) a clear distinction is not provided between perineal pain and ejaculatory pain. In this section of the review, we report on EjD as defined by the NIH CP/CPPS-like symptom index as perineal and/or ejaculatory pain and a total pain score of 4 or greater.

The prevalence of CP/CPPS-like symptoms in the community. In community based studies in different geographical areas of the world the prevalence of CP/CPPS-like symptoms varied. In the United States, the incidence of type III prostatitis is 3.3 per 1000 person-years. Ejaculatory pain was reported in 8.5% of those patients [Clemens *et al.* 2005]. Among Canadian men at risk, the prevalence of CP/CPPS-like symptoms was 9.7% [Nickel *et al.* 2001], while the reported prevalence in Japanese men was 4.9% [Kunishima *et al.* 2006]. In another USA community sample the reported prevalence was 6.3% [Daniels *et al.* 2007]. The condition was often associated with ejaculatory pain. A strong association between this condition and urinary tract infection (UTI) particularly recurrent infection was reported [Daniels *et al.* 2007]. Pain during ejaculation was reported in a similar study in 1.2% of Australian men [Ferris *et al.* 2010].

In a managed care population, the prevalence of CP/CPPS-like symptoms in men was 5.9% [Clemens *et al.* 2006].

The prevalence of CP/CPPS-like symptoms was determined in men concerned about their health. In a large cohort of men participating in a health screening project, the overall prevalence of symptoms suggestive of chronic pelvic pain syndrome was 2.7% with no age dependence [Marszalek *et al.* 2007]. In men during a male-health promotion event, the presence of CP/CPPS-like symptoms was found in 10.5% and painful ejaculation in 5.9% of all respondents [Walz *et al.* 2007b].

CP/CPPS-like symptoms have also been reported in a younger population. In young men 20 years old in a conscription program in South Korea, the prevalence of prostatitis-like symptoms was 6% [Ku *et al.* 2001]. Higher education and a longer time in sunlight were associated with less likelihood of CP/CPPS-like symptoms. In a Canadian study among community-dwelling African males aged 16–19 years, attending secondary school, the prevalence of CP/CPPS-like symptoms was 13.3% [Tripp *et al.* 2012].

In patients diagnosed to have CP/CPPS. CP/CPPS has a negative impact on sexual function. A significant association between the two conditions was shown in a cross-sectional study of older men in Olmsted County [Lutz *et al.* 2005]. 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 [Litwin *et al.* 1999]. There was a significant increase in baseline CP/CPPS Symptom Index total score for patients with always having ejaculatory pain *versus* no pain at all. Mental and physical quality of life were also progressively lower. There were no significant differences in white blood cell count or bacterial growth in urine, prostate fluid or semen among subgroups. Men with ejaculatory pain were younger, more likely to live alone, had lower income and a greater variety of sexual practices than those with no ejaculatory pain [Shoskes *et al.* 2004].

In Turkish patients with CP/CPPS types IIIa and IIIb, pain on ejaculation was detected in 37.2%, while none of the control group had pain on ejaculation [Sönmez *et al.* 2011]. Similar results were reported in another study from USA. Men diagnosed with CPPS type III were compared with healthy controls. Of men with CPPS, 36% 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 [Aubin *et al.* 2008]. In a randomly selected cohort of white men 47–90 years old from Olmsted County, Minnesota, 1.7% reported a physician diagnosis of prostatitis in the preceding 2 years. Ejaculatory pain was prevalent in 7.4% of men with prostatitis compared with 1.3% without prostatitis symptoms [Roberts *et al.* 2004]. The association of CP/CPPS, ED and EjD was reported. Of patients seeking treatment for CP/CPPS, 72.3% reported sexual dysfunction. Of these patients 25.0% complained of ED only, 33.4% complained of ejaculatory difficulties only, and 41.6% complained of both ED and ejaculatory difficulties [Lee *et al.* 2008].

Certain radiological findings were sometimes reported in patients with CP/CPPS and EjD. In a

group of patients with CP/CPPS, 55% had EjD. Investigations showed 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 [Trinchieri *et al.* 2007]. In another study of men with CP/CPPS-like symptoms, the presence of a medial prostatic cyst was associated with reduced ejaculation volume in 35%, painful ejaculation in 24%, hemospermia in 24% and infertility in 12%. After marsupialization of the cyst, symptoms resolved completely in 78% or improved in 94% [Dik *et al.* 1996].

In patients receiving medical treatment of LUTS

A significant number of men on medical treatment for LUTS associated with BPH report EjD. In particular, α_{1A}-selective adrenoceptor blockers impair ejaculation. Tamsulosin in doses ranging from 0.2 to 0.8 mg daily causes different problems with ejaculation. Tamsulosin 0.2 mg daily for the treatment of LUTS in men with an International Prostatic Symptom Score (IPSS) >8 after 12 weeks was associated with 13.4% EjD [Song *et al.* 2011]. Incidences of decreased frequency, delay, dryness, decreased strength/force, decreased volume, decreased pleasure and pain at ejaculation were 2.4%, 3.1%, 3.9%, 3.9%, 6.3%, 7.1% and 3.1%, respectively. In another study comparing tamsulosin 0.2 mg with other α-adrenergic blockers for the treatment of LUTS, *de novo* decreased volume of ejaculation developed in 2.6% of patients [Yokoyama *et al.* 2011]. A prospective study of the more widely used dose of tamsulosin 0.4 mg daily was carried out involving men above 50 with LUTS [Goktas *et al.* 2006]. The study aimed at assessing the effect of intermittent treatment on ejaculatory complications. On daily dosing, abnormal ejaculation developed in 7.4% of men. Retrograde ejaculation was reported by 4.4% patients, decreased volume by 1.7% and absent ejaculate by 1.2%. Ejaculatory function recovered during intermittent tamsulosin treatment in 63.3% of affected men [Goktas *et al.* 2006]. At a maximum dose of 0.8 mg tamsulosin daily, 90% of volunteers developed decreased ejaculate volume and 35% had anejaculation [Hellstrom and Sikka, 2006]. Interestingly enough, none of the patients had retrograde ejaculation, indicating an inhibition of seminal emission as the cause for EjD [Hellstrom and Sikka, 2006]. In contrast, men in the placebo and alfuzosin control groups did not have significant difference in ejaculate volume and none had anejaculation [Hellstrom and Sikka, 2006].

Another α_{1A}-specific adrenoceptor blocker more recently introduced for the treatment of LUTS is associated with similar ejaculatory complications as tamsulosin. Silodosin 4 mg BD was associated with inability to have antegrade ejaculation in 7.2–28.1% of men with LUTS [Miyakita *et al.* 2010; Marks *et al.* 2009a, 2009b; Yokoyama *et al.* 2011]. More patients receiving *de novo* (7.5%) *versus* continuing treatment (1.9%) discontinued study participation because of retrograde ejaculation [Marks *et al.* 2009b]. Silodosin, similar to tamsulosin, 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 [Kobayashi *et al.* 2008]. All participants felt orgasm indicating dissociation between the mechanisms of orgasm and ejaculation [Kobayashi *et al.* 2009].

Another α_1 adrenoceptor blocker not selective to the α_{1A} subtype is uncommonly associated with ejaculatory complications. In a pooled analysis of three double-blind, placebo-controlled studies of alfuzosin treatment for LUTS, abnormal ejaculation was reported in only 0.6% [Roehrborn *et al.* 2003]. A 3-year follow up of European men treated with alfuzosin 10 mg once daily for LUTS suggestive of BPH in 'real-life practice' showed that ejaculatory disorders were uncommon (0.4%) [Vallancien *et al.* 2008]. In a prospective study evaluating the effect of alfuzosin on sexual function in men with LUTS, after 1 month of treatment, men had no adverse effect on ejaculatory function [Rosen *et al.* 2007]. On the other hand, alfuzosin treatment in men with LUTS was associated with improvement in ejaculatory function. A prospective, open-label study showed that alfuzosin caused a significant improvement in the ejaculatory function score after 6 months [Leungwattanakij *et al.* 2010]. In 'real-life' practice men with LUTS at baseline had 63.2% reduced volume of ejaculate and 20.2% pain/discomfort on ejaculation. After 1 year of treatment with alfuzosin, there were significant improvements in sexual function scores related to volume and pain [van Moorselaar *et al.* 2005].

The 5α-reductase inhibitors are another class of medications used for the treatment of LUTS

suggestive of BPH, which have some adverse effects on sexual function. In a prospective double-blind randomized 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 2-year follow up [Nickel *et al.* 1996]. In a meta-analysis on the effect of finasteride on sexual function, a significant ejaculatory disorder developed in 2% of men in the treatment group *versus* 0.6% in the control group [Edwards and Moore, 2002]. Combination medical treatment for LUTS was compared with surgery and monotherapy. In men with LUTS suggestive of BPH, dry ejaculation occurred in 67.4% of men with previous BPH-related surgery, 57.2% in men treated with a 5α-reductase inhibitor plus an α_1-blocker and 52.3% treated with tamsulosin alone compared with controls (31.6%) [Rosen and Fitzpatrick, 2009]. Alfuzosin treatment was associated with significantly lower EjD symptoms than in controls [Rosen and Fitzpatrick, 2009].

Finasteride treatment for conditions other than LUTS is associated with EjD. In men treated with finasteride for male pattern hair loss, and developed sexual dysfunction including orgasmic problems, the side effects persisted after cessation of treatment for an average of 40 months [Irwig and Kolukula, 2011]. A follow-up study of those subjects, 9–16 months later showed that persistent sexual side effects continued to be present in 96% [Irwig, 2012].

In patients on drug treatment for other conditions

Several psychological, hormonal and neurological factors and associated medications contribute to EjD.

In men who were seeking medical help for sexual dysfunction, severe DE was associated with the use of serotoninergic drugs, mild and moderate DE were associated with hypogonadism and with serotoninergic drugs which increased risk for DE by 10-fold [Corona *et al.* 2006a].

Antidepressants. Depression itself has a significant impact on the sexual life of affected patients. In men with untreated major depression ejaculatory or orgasm difficulties occur in 15–20% [Kennedy *et al.* 1999]. Antidepressant treatment, in addition, is associated with sexual adverse effects impairing ejaculation and orgasm. A meta-analysis of studies of patients treated for major depression with antidepressants, reported a DE rate of 20–22% [Furukawa *et al.* 2001].

Selective serotonin reuptake inhibitors. Early reports observed strong relation between selective serotonin reuptake inhibitors (SSRIs) antidepressants and the adverse effect on sexual function [Seppälä *et al.* 1988; Herman *et al.* 1990; Zajecka *et al.* 1991]. In healthy volunteers, the only adverse effect attributable to indalpine was EjD which was spontaneously reported by 67% of the subjects [Seppälä *et al.* 1988]. In men treated for depression, delay in ejaculation and orgasmic dysfunction are the most significant sexual complications [Labbate *et al.* 1998]. Initiation of treatment results in worsening of orgasm delay, orgasm satisfaction and overall sexual functioning [Piazza *et al.* 1997]. The reported prevalence of orgasmic dysfunction may reach up to 51.2% in men treated [Safarinejad, 2010]. Patients receiving antidepressant monotherapy experienced significant dysfunction in the orgasmic phase of the Changes in Sexual Functioning Questionnaire (CSFQ) [Clayton *et al.* 2006]. The use of fluoxetine in depressed outpatients was associated with 7.8–8.3% treatment-emergent orgasmic dysfunction (anorgasmia and/or delayed orgasm) [Herman *et al.* 1990; Zajecka *et al.* 1991].

Different SSRIs, however, have significant variation in their adverse effect on sexual function [Montejo-González *et al.* 1997]. A prospective study showed that paroxetine provoked more delay of orgasm or ejaculation and more impotence than fluvoxamine, fluoxetine or sertraline [Montejo-González *et al.* 1997]. Paroxetine treatment for moderate to severe depression is associated more commonly with abnormal ejaculation than treatment with fluoxetine [Chouinard *et al.* 1999]. Sertraline and citalopram, in a prospective randomized study evaluating the treatment of men with depression, produced *de novo* orgasmic dysfunction in 18.9% and EjD in 25% of patients after 24 weeks. No significant difference between adverse sexual side effects in the two drugs [Ekselius and von Knorring, 2001].

A particular type of EjD is associated with non-SSRI treatment of men diagnosed with major depressive disorder [Clayton *et al.* 2003]. Sexual function during treatment with the selective noradrenaline reuptake inhibitor reboxetine, the SSRI fluoxetine and placebo was assessed [Clayton *et al.* 2003]. Patients receiving reboxetine reported

painful ejaculation in 20%, while only 2% receiving fluoxetine reported the side effect [Clayton *et al.* 2003].

Genetic predisposition might be an underlying factor for developing sexual adverse effects in patients treated for depression with SSRIs [Perlis *et al.* 2009]. Genotyping revealed and association between single nucleotide pleomorphism in one glutamatergic gene (GRIA1) and a serotonergic gene (SLC6A4) and difficulty of orgasm [Perlis *et al.* 2009].

The reported adverse effect of SSRIs on ejaculation may subside in a significant number of patients that continue treatment [Haberfellner and Rittmannsberger, 2004]. In patients treated with SSRIs, 34.3% developed orgasm delay [Haberfellner and Rittmannsberger, 2004]. After 6 months, 30.8% reported complete remission, 15.4% noted a marked improvement and 15.4% continued to describe severe orgasm delay. Lack of remission correlated with high severity of orgasm delay [Haberfellner and Rittmannsberger, 2004].

Several treatments may alleviate SSRIs induced EjD. Treatment with the antiserotonergic medication cyproheptadine for fluoxetine-induced anorgasmia reverses the adverse effect and this was associated with relapse of depressive symptoms [Feder, 1991]. The addition of bupropion, an atypical antidepressant, in the treatment of patients on SSRIs for major depressive disorder is associated with significant improvement of orgasmic function [Safarinejad, 2010]. Treatment with PDE5i was shown to benefit some patients with SSRI-associated sexual dysfunction [Nurnberg *et al.* 2003]. Patients randomized to placebo or sildenafil citrate treatment showed a significant improvement in ejaculation and orgasm in the treatment group [Nurnberg *et al.* 2003]. In a trial with men who had SSRI-induced ejaculatory delay, 67% had associated ED [Seidman *et al.* 2003]. Low-dose sildenafil corrected ED in most of these patients and recovered ejaculatory function in a third of them [Seidman *et al.* 2003]. High-dose sildenafil was effective in reducing ejaculatory latency in most patients without significant ED [Seidman *et al.* 2003]. Other patients benefited from correction of testosterone level [Amiaz *et al.* 2011]. In depressed men with low or low–normal testosterone levels on serotonergic antidepressants, treatment with exogenous testosterone was associated with a significant improvement in ejaculatory ability [Amiaz *et al.* 2011].

Other antidepressants. Similar to SSRIs, tricyclic antidepressants and monoamine oxidase inhibitors are associated with significant sexual adverse effect in patients treated for depression [Harrison *et al.* 1986]. In a 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 [Harrison *et al.* 1986]. The risk for mild, moderate and severe perceived ejaculatory volume reduction (PEVR) was studied with different medications. A mild PEVR was associated with the use valproic acid and SSRIs. The use of the latter, along with benzodiazepines, was also associated with a moderate PEVR [Corona *et al.* 2011].

Painful ejaculation following the administration of imipramine and clomipramine has been described in four patients. The phenomenon occurred in all patients during the first 3 weeks of treatment and disappeared within several days when the tricyclic dosage was reduced or the medication was withdrawn [Aizenberg *et al.* 1991]. Desipramine treatment was associated with anhedonic ejaculation (ejaculation without orgasm) [Rosenbaum and Pollack, 1988].

Alternative medications to treat depression are sometimes associated with fewer side effects on sexual function [Coleman *et al.* 2001]. In a comparison of sexual dysfunction reported by men treated with SSRIs, benzodiazipines or non-SSRIs, there was a seven-fold risk for developing DE in SSRI users [Corona *et al.* 2009]. In a randomized, double-blind study, patients with recurrent major depression were treated with bupropion, fluoxetine, or placebo for up to 8 weeks [Coleman *et al.* 2001]. Both bupropion and fluoxetine were equally effective and well tolerated. Bupropion, however, was less frequently associated with sexual dysfunction and may prove useful for the treatment of depression in patients concerned about sexual function [Coleman *et al.* 2001].

Another antidepressant causing less sexual dysfunction is nefazodone acting on both adrenergic and serotoninergic receptors [Ferguson *et al.* 2001]. Patients who had recovered from sexual dysfunction (ejaculatory and/or orgasmic difficulty) induced by treatment with sertraline, were randomized to retreatment with sertraline or nefazodone in a double blind study [Ferguson *et al.* 2001]. Significantly more sertraline-treated

patients (76%) experienced re-emergence of sexual dysfunction than did nefazodone-treated patients (26%) [Ferguson *et al.* 2001]. The use of nefazodone is, however, curtailed by its hepatotoxicity [Stewart, 2002].

Antipsychotics. The association of antipsychotic medication with the development of sexual dysfunction has been reported in several studies. A cross-sectional survey of people with established schizophrenia or schizoaffective disorder, in southeast England, showed that the vast majority of the patients (96.4%) were receiving at least one antipsychotic medication in the previous 6 months. The prevalence of orgasmic disorder among men was 31% compared with 17% in the general population [Harley *et al.* 2010]. The prevalence of sexual dysfunction in patients with schizophrenia under antipsychotic therapy showed that ejaculation problems were seen in 64.2% and retarded ejaculation occurred in 63.6% [Uçok *et al.* 2007].

Another study of sexual dysfunction in young adults with schizophrenia treated with neuroleptics showed that patients had significantly more DE (21.7%) and anejaculation (26.1%) *versus* normal controls (0.0% and 3.8%, respectively) [Fortier *et al.* 2003]. Thioridazine treatment was associated with 60% incidence of difficulties in sexual function [Kotin *et al.* 1976]. Ejaculatory problems were the most frequent dysfunction; a third of these patients experienced retrograde ejaculation. Treatment with other major tranquilizers was not associated with retrograde ejaculation [Kotin *et al.* 1976].

Certain antipsychotics may have less of a deleterious effect on sexual function. Clozapine treatment in schizophrenic male patients was associated with better sexual function scores in the domains of orgasm compared with classical antipsychotics [Aizenberg *et al.* 2001]. A study addressed the question of whether schizophrenia itself or its treatment affected sexual function. The authors reported that while schizophrenia affected desire, it was the neuroleptic treatment that was associated with erectile, orgasmic and sexual satisfaction problems [Aizenberg *et al.* 1995].

The underlying mechanism by which antipsychotics induce sexual dysfunction was studied. Several studies incriminated elevated prolactin level in the development of sexual dysfunction in men. Increase in serum prolactin level in patients with schizophrenia during antipsychotic treatment correlated with orgasmic dysfunction [Rettenbacher *et al.* 2010]. In patients treated with prolactin-raising and prolactin-sparing antipsychotics, EjD was associated with the prolactin raising medications [Knegtering *et al.* 2008].

Aripiprazole is an antipsychotic associated with a reduction in prolactin level in antipsychotic-induced hyperprolactinemia [Mir *et al.* 2008]. In males, after switching treatment to aripiprazole, ejaculatory difficulty was significantly reduced [Mir *et al.* 2008]. A descending view in one study did not find such correlation between elevated prolactin level and antipsychotic-induced sexual dysfunction [Westheide *et al.* 2008].

Narcotics. Addiction to narcotics or alcohol is associated with sexual dysfunction affecting ejaculation and the effect might be reversible. A telephone survey of Australians aged 16–64 years on cannabis use and its effect on sexual function was reported [Smith *et al.* 2010a]. Frequency of cannabis daily use *versus* no use was associated with significant increased reporting among men of an inability to reach orgasm, reaching orgasm too quickly, and too slowly [Smith *et al.* 2010a]. In male heroin addicts 22–50 years old treated with methadone for at least 3 months, inhibited ejaculation improved from 24.5% to 6.9% [Zhang *et al.* 2011]. Treatment of addiction itself might be associated with specific adverse effect on sexual function. Methadone treatment of men with opioid dependence is associated with orgasmic dysfunction that is dose dependent [Brown *et al.* 2005]. Interestingly, internal opioids may have a role in inhibiting orgasm. In healthy volunteers, orgasm was more intense and more frequent in the group treated with naltrexone compared with placebo [Sathe *et al.* 2001].

Likewise, alcohol addiction was 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 [Mandell and Miller, 1983]. During heavy drinking, 59% of patients experienced erection dysfunction, 48% reported ejaculation incompetence and 84.4% had experienced at least one kind of sexual dysfunction [Mandell and Miller, 1983].

Miscellaneous drugs. Other substances that showed increased risk for developing EjD include

antihypertensives, medications for epilepsy, industrial chemicals and hormones.

Several antihypertensive agents were prospectively evaluated for sexual adverse effects and the underlying possible hormonal disturbance [Suzuki *et al.* 1988]. In short-term treatment (1–4 weeks), trichlormethiazide, atenolol and slow-release nifedipine but not captopril caused sexual dysfunction including problems in ejaculation. Serum levels of both testosterone and follicular stimulating hormone were decreased significantly while there was mild elevation of estradiol in patients on atenolol. After 1 year of treatment, only patients taking atenolol experienced sexual dysfunction and mild reduction of serum levels of testosterone [Suzuki *et al.* 1988].Thiazide diuretics treatment in mildly hypertensive men between the ages of 35 and 70 years was associated with significantly greater difficulty with ejaculation [Chang *et al.* 1991]. Labetalol, an antihypertensive drug with α-1 and β-adrenergic blocking properties, was reported to cause ejaculatory failure in some patients after treatment for moderate to severe essential hypertension [O'Meara and White, 1988]. A mild PEVR was associated with the use of α-blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers [Corona *et al.* 2011].

The antiepileptic gabapentin used for treatment of neuropathic pain, seizures and bipolar disease is associated with orgasmic inhibition in older male patients that is dose dependent [Perloff *et al.* 2011].

Certain chemicals have been associated with EjD. Bisphenol-A, a widely available chemical ingredient in consumer goods has been associated in workers having high exposure with sexual dysfunction including decrease in ejaculatory force [Li *et al.* 2010a]. Compared with controls, exposed workers had a significantly increased risk of ejaculation difficulty [Li *et al.* 2010b].

Androgen deprivation therapy for prostatic cancer is associated more often with a complete absence of ejaculate [Corona *et al.* 2011].

In patients with ED or hormonal disturbances

The association of sexual dysfunction with hormonal disturbances was recognized early on. The hormones implicated include testosterone, prolactin and thyroid hormone. In a series, heterosexual male patients attending an andrology and sexual medicine outpatient clinic for ED for the first time, hypogonadism, diabetes mellitus, severe ED and patient's and partner's hypoactive sexual desire (HSD) were all independently associated with PEVR [Corona *et al.* 2011]. A progressive increase in severity of PEVR was associated with higher glucose and lower testosterone plasma levels [Corona *et al.* 2011]. The use of androgen deprivation therapy was associated more often with a complete absence of ejaculate (anejaculation) [Corona *et al.* 2011]. Testosterone level was found to play an important role affecting the timing of ejaculation and orgasm. In healthy volunteers, pharmacologically induced hypogonadism was associated with diminished orgasmic function which was corrected to normal after androgen replacement [Schmidt *et al.* 2009]. Free testosterone and sex hormone binding globulin (SHBG) levels are significantly correlated with the orgasmic dysfunction domain of the IIEF after correction for age [Ahn *et al.* 2002]. In a consecutive series of male patients with sexual dysfunction, the prevalence of reported PE and DE was 25.9% and 4.4%, respectively. In older men, lower total testosterone and free testosterone levels were observed in DE subjects. Patients with PE showed the lowest (12%) and subjects with DE the highest (26%) prevalence of hypogonadism [Corona *et al.* 2008]. Treatment of hypogonadal men with testosterone gel improved EjD score (difficulty and volume) [Khera *et al.* 2011].

The association of metabolic syndrome and EjD was explored. In a prevalence study from Denmark evaluating the association of obesity with sexual dysfunction, obese men and those with substantially increased waist circumference are most likely to report anorgasmia [Christensen *et al.* 2011c]. Morbidly obese men undergoing gastric bypass reported lower than normal scores in all domains of the Brief Male Sexual Function Inventory. At a mean postoperative follow up of 19 months, mean ejaculatory function score improved. The amount of weight loss independently predicted the degree of improvement in all BSFI domains. After an average 67% excess weight loss, BSFI scores approached those of the reference controls [Dallal *et al.* 2008]. Vardenafil for the treatment of ED in men with metabolic syndrome was associated with improved ejaculation success rate of 71.3% *versus* 44% in the placebo group [Schneider *et al.* 2011].

Male hyperprolactinemia is known to induce different types of sexual dysfunctions. A total of 136

men, who presented at the Masters & Johnson Institute for the treatment of impotence, ejaculatory incompetence and inhibited sexual desire, underwent endocrine screening. Eleven men (8.1%) were found to be hyperprolactinemic [Schwartz *et al.* 1982]. Serum prolactin was assayed in patients with clinically idiopathic sexual dysfunction. Hyperprolactinemia was found in 3%. Mild hyperprolactinemia was found in 10% of cases with PE, however, serum prolactin was normal in cases complaining of an ejaculation without orgasm [Buvat *et al.* 1985]. A high prolactin level might be involved in sexual dysfunction associated with SSRI treatment. In a series of patients with sexual dysfunction, higher prolactin was observed only in patients using SSRIs [Corona *et al.* 2009].

Thyroid hormone is another factor affecting sexual function. A prospective study evaluated the prevalence of sexual dysfunctions in patients with hyperthyroidism and hypothyroidism and their resolution after normalization of thyroid hormone levels [Carani *et al.* 2005]. In hyperthyroid men, DE prevalence was 2.9%, whereas in hypothyroid men, the prevalence of HSD, DE and ED was 64.3%. DE in hypothyroid men was associated with either HSD or ED. After thyroid hormone normalization in hypothyroid subjects, DE was improved in half of the treated men [Carani *et al.* 2005].

Few studies reported the prevalence of EjD in patients presenting for the management of sexual dysfunction. A consecutive series of male patients with sexual dysfunction was studied. The prevalence of DE was 6.8%, which was mild–moderate in 5% and severe or anejaculation in 1.8% [Corona *et al.* 2009]. A high risk for DE was observed in SSRI users and in subjects using non-SSRI antidepressants [Corona *et al.* 2009]. A meta-analysis of 28 ED tadalafil trials showed that only 42.2% of patients reported normal ejaculatory function, and 35.6% normal orgasm, regardless of ED severity [Paduch *et al.* 2012]. Frequencies of EjD and orgasmic dysfunction increased with increasing ED severity. There was an observed dissociation between ejaculation and orgasm in some patients. Poor sensation of orgasm occurred in 15.6% of patients with normal ejaculatory function, while 5.2% of subjects with normal orgasm had poor ejaculatory function. Risk factors of EjD and orgasmic dysfunction included cardiomyopathy, cardiac failure and use of antipsychotics, SSRIs and tricyclic antidepressants [Paduch *et al.* 2012]. In a survey of randomly selected members of the American Association of Sexuality Educators, Counselors and Therapists, ejaculatory inhibition accounted for 5% of the case load [Kilmann *et al.* 1986]. In male patients consulting for sexual dysfunction, relational factors including menopausal symptoms, partner's medical illness interfering with sexual activity and reduced partner desire and climax were significantly and independently associated with DE [Corona *et al.* 2006b].

Psychophysiological factors in men with idiopathic EjD

In the absence of a clear organic cause of EjD, certain psychological, behavioral and social conditions may be identified. The effect of having a partner during sexual activity was reported [Corty, 2008]. The perceived ejaculatory latency was studied in volunteers in different partnered and masturbatory sexual activities. There was no difference in time to ejaculation among any of the partnered outlets, however ejaculation occurred more quickly with masturbation [Corty, 2008]. Men with inhibited ejaculation and having no apparent somatic etiology may commonly have inhibited arousal. During psychosexual stimulation in the lab, men with inhibited ejaculation were found to have the lowest levels of sexual arousal compared with control subjects [Rowland *et al.* 2004]. Men with lifelong DE exhibited significantly higher masturbatory activity during marital period, lower night emissions, longer IELT, lower orgasmic and intercourse satisfaction domains of IIEF and higher anxiety and depression scores compared with the controls [Abdel-Hamid and El Saleh, 2011].

Other psychosocial factors more commonly identified in men with inhibited ejaculation included lower level of relationship satisfaction, greater level of distress, higher level of health-related problems and lower levels of self-reported subjective sexual arousal, despite having high-quality erections across a variety of situations [Rowland *et al.* 2005]. Functional disorders of the brain and their treatment might be associated with ejaculatory and orgasmic dysfunction (see below). Untreated depression in itself has been shown to cause sexual dysfunction. Untreated men with major depressive disorder reported high rates sexual dysfunction including orgasm. Multiple linear regression analyses revealed that depression status and not androgen hormonal level was the main factor

influencing sexual function [Rizvi *et al.* 2010]. In community-dwelling men, chronic anxiety or depression was strongly associated with anorgasmia [Christensen *et al.* 2011a]. Community or institutionalized men with schizophrenia report orgasmic impairment [Acuña *et al.* 2010].

In patients with UTI/inflammation

EjD was reported in association with urinary tract inflammation due to different causes.

A strong association was often found between CP/CPPS, ejaculatory pain and UTI, particularly recurrent infection [Daniels *et al.* 2007]. Patients with evidence of prostatic inflammation but no infection had ejaculation disorder in 67.7% even more common than ED (30.2%). Hemospermia occurred in 20.8% [Tuncel *et al.* 2006]. Chronic bacterial prostatitis may cause ejaculatory pain and hematospermia which were significantly attenuated by antibiotic treatment [Magri *et al.* 2011]. In a group of patients presenting to infertility clinic and diagnosed clinically as having male accessory gland infections with or without TRUS abnormal findings, painful ejaculation occurred in 36%. Painful ejaculation was more prevalent in ultrasound-positive patients (57%) compared with ultrasound-negative patients (30%) and healthy controls (5%) [La Vignera *et al.* 2012]. Specific infections may cause EjD in endemic areas. *Schistosoma hematobium* infection was associated with sexually transmitted disease in a group of men in an endemic region. Painful ejaculation occurred in 15% of men, and decreased after 1 month following sexually transmitted disease treatment and disappeared 6 months after schistosoma treatment [Leutscher *et al.* 2008].

In patients with neurologic disease

Diseases, functional or organic, affecting the brain and spinal cord may cause EjD depending on the level and extent of pathology. After stroke, 45.9–64.5% of men in a stable condition and mild or no disability, reported diminished or absent ejaculation [Cheung, 2002; Tamam *et al.* 2008]. The side of hemispheric lesions did not affect ejaculation [Tamam *et al.* 2008]. Focal epilepsy was associated with orgasmic dysfunction in 15% of affected men [Kuba *et al.* 2006]. Treatment with carbamazepine and significant decrease of dehydroepiandrosterone sulfate were found in these patients.

Multiple sclerosis is associated with ED (63.2%), EjD and/or orgasmic dysfunction (50%) and reduced libido (39.5%) [Zorzon *et al.* 1999]. In a community-based study, men with multiple sclerosis reported masturbation difficulties, difficulty with achieving vaginal orgasms, retarded ejaculation and PE [Redelman, 2009].

In patients with spinal cord injury (SCI), post-shock phase, ejaculation was preserved in all men with a lesion level below T12 and with positive perineal sympathetic skin responses [Tas *et al.* 2007]. The ability to achieve orgasm was tested in the lab in men with SCI but capable of self-stimulation and compared with able-bodied men. In response to visual erotic stimulation, 50% of SCI men achieved orgasm compared with 100% of controls. Men with incomplete SCIs were more likely to achieve orgasm than those with complete SCIs or with complete lower motor neuron dysfunction affecting their sacral segments. A disconnect was noted between the presence of orgasm and the presence of ejaculation [Sipski *et al.* 2006]. Congenital anomalies affecting the lower segment of the spinal cord are associated with a lesser degree of EjD. In young male patients with spina bifida, the positive rates of ejaculation and orgasm were 88% and 65%, respectively. Orgasm correlated with touch sensation on the penis [Shiomi *et al.* 2006]. Peripheral nerve damage may impair ejaculation and orgasm. In a study of a cohort of men with type 1 diabetes mellitus 20% reported abnormal ejaculatory function [Penson *et al.* 2009]. An absent bulbocavernosus reflex was found in 22% of men with primary complete anorgasmia [Brindley and Gillan, 1982]. Interestingly, one neurological disease had a positive effect on sexual function. Compared with normal controls, a group of men with Parkinson's disease demonstrated easier ability to reach orgasm [Celikel *et al.* 2008].

Prevalence of non-PE EjD in patients after surgery

Prostatic surgery for LUTS

Different surgical modalities for the treatment of LUTS due to BPH are associated with variable adverse effects on ejaculatory function. Transurethral resection of the prostate (TURP) is the gold standard treatment with which all other surgeries are compared. Less invasive surgeries include transurethral incision of the prostate/bladder neck (TUIP), laser prostatectomy, transurethral needle ablation

(TUNA) and transurethral microwave thermotherapy. The lasers commonly used in prostatic surgery are potassium-titanyl-phosphate (KTP), holmium:YAG and neodymium:YAG (Nd:YAG).

EjD is a significant problem after prostatic surgery. A prospective study to determine the impact of four different interventional therapies on the quality of life and sexual function of men with BPH was reported [Arai *et al.* 2000]. The most significant impact on deterioration of sexual quality of life was due to EjD. Ejaculation loss or severe decrease in ejaculate volume was reported by 48.6%, 28.1%, 21.6% and 24.3% of the TURP, microwave thermotherapy, laser coagulation and TUNA groups, respectively [Arai *et al.* 2000].

A systematic review reported pooled mean deterioration of ejaculatory function in 74.7% and 69.3% of patients undergoing holmium laser prostatectomy *versus* TURP, respectively (5 studies); 33.6% and 32.9% for KTP prostatectomy *versus* TURP, respectively (two studies); 15.3% and 48.3% for Nd:YAG laser prostatectomy *versus* TURP, respectively (three studies); 17.8% and 42.7% for transurethral microwave thermotherapy *versus* TURP, respectively (three studies); and, finally, 5.6% and 34.7% for TUNA *versus* TURP, respectively (four studies) [Frieben *et al.* 2010]. Although the less-invasive procedures had a lower complication rate on ejaculation, a comparison of the efficacy of the treatments on relieving outflow obstruction was not included in the analysis [Frieben *et al.* 2010].

Open prostatectomy was associated with more sexual complications than TURP. In a randomized study, 70% of transvesical prostatectomy patients and 57% of TURP patients reported retrograde ejaculation at follow up [Meyhoff *et al.* 1984]. The prevalence of reported ejaculate volume reduction after prostatectomy for BPH (open or TURP) was mild in 2.5%, moderate in 9.4%, and severe (anejaculation) in 56.3% [Corona *et al.* 2011]. A prospective study involving a large number of patients from multiple centers in the United Kingdom, undergoing prostatectomy by urologists and nonurologists, showed that the procedure was effective in reducing both symptoms and symptom bother with good improvement reported by 63.5% of patients. Retrograde ejaculation occurred in two thirds of patients assessed 3 months after surgery [Emberton *et al.* 1996]. Orgasmic function, however, was not affected by open prostatectomy for BPH [Gacci *et al.* 2003].

Multiple prospective studies have looked at the effect of TURP on sexual function. A study from 11 hospitals in Switzerland reported that 73.1% of patients were sexually active before TURP and 73.8% of the patients were sexually active 4 months postoperatively. The mean ejaculatory function score, however, worsened from 1.27 to 2.34 [Muntener *et al.* 2007]. In a study comparing the effect of TURP and transurethral resection of a bladder tumor on sexual function, 70% of the prostatectomy patients developed new onset ejaculatory disturbance at 6 months [Jaidane *et al.* 2009]. Another study revealed that 84% of patients had retrograde ejaculation at 12 months following TURP [Kunelius *et al.* 1998].

Variations of TURP were introduced to decrease complications. These techniques included electrovaporization of the prostate, minimal resection and TUIP. Several prospective studies compared electrovaporization of the prostate with TURP and proved similar efficacy. Retrograde ejaculation after electrovaporization was reported in a wide range of patients from 12.5% to 72% at follow up to 3 years [Erdağı *et al.* 1999; Küpeli *et al.* 1998; Kaplan *et al.* 1998; Hammadeh *et al.* 2003; Kaya *et al.* 2007]. In these studies TURP was more commonly associated with retrograde ejaculation in a range of 34–89%.

Using another technique minimizing resection, several reports showed variable results on efficacy and complications. A comparison between 'minimal' and 'total' TURP concerning the effect on sexual activity and the occurrence of retrograde ejaculation revealed no significant difference [Møller-Nielsen *et al.* 1985]. Several other studies however report different findings. In a group of patients with LUTS and prostates less than 25 ml, minimal resection and bladder neck incision were associated with significantly lower retrograde ejaculation compared with TURP. Both groups had comparable results in symptom score and uroflow improvements [Yeni *et al.* 2002].

In a prospective comparison between TURP and TUIP in small prostates <20 ml, TURP was associated with better patient improvement in symptoms and flow rates. Retrograde ejaculation was, however, seen in more than half of the patients in the TURP group and only one patient in the TUIP group [Dørflinger *et al.* 1992]. A

similarly designed study showed that efficacy was comparable but retrograde ejaculation developed more commonly after TURP affecting 68% of patients and only 35% after TUIP [Riehmann *et al.* 1995]. Another randomized study confirmed equal efficacy of TURP and TUIP for prostates 20 g or less. However, retrograde ejaculation was reported in 100% and 28%, respectively [Larsen *et al.* 1987].

Laser prostatectomy was introduced adding safety to the procedure in terms of lower risk of bleeding and less irrigation-induced dilutional hyponatremia. Following photoselective KTP laser vaporization of the prostate for LUTS, up to 26% of the sexually active men experienced retrograde ejaculation [Malek *et al.* 2005]. With the 80 W KTP laser, retrograde ejaculation was reported in 67% at 12 months [De Nunzio *et al.* 2010]. Prostatectomy using 120 W KTP laser for prostates with a median volume of 62 ml was associated with new onset retrograde ejaculation of 30% after 1-year follow up [Spaliviero *et al.* 2010]. Other types of lasers used for vaporization of the prostate had similar results. Photoselective vaporization of the prostate using the 120 W lithium triborate laser was associated with loss of emission on orgasm in 65% of patients [Hossack and Woo, 2012]. Prostate vaporization with the high-power diode laser caused retrograde ejaculation in 31.7% patients at 3 months postoperatively [Erol *et al.* 2009].

Another form of laser ablation of the prostate was associated with less common adverse effect on ejaculation. Retrograde ejaculation was reported in 12% of sexually active men following Nd:YAG visual laser ablation of the prostate [Sengör *et al.* 2002]. In a prospective study comparing Nd:YAG laser prostatectomy with transurethral electrovaporization of the prostate, retrograde ejaculation was more common following electrovaporization (63%) than with laser therapy (18%). However, the efficacy of laser treatment was significantly lower in relieving symptoms and improving urine flow and reducing residual urine [Abdel-Khalek *et al.* 2003].

A holmium:YAG laser has been used to incise, vaporize or enucleate the prostate. In a prospective randomized trial, holmium:YAG laser vaporization and TURP for BPH were equally effective and had comparable adverse effect on ejaculation [Mottet *et al.* 1999]. Similarly, laser enucleation of the prostate was associated with retrograde ejaculation in 70% of the sexually active patients 6 months postoperatively [Meng *et al.* 2007]. In a prospective, randomized study of the effect of holmium laser enucleation *versus* TURP, 78.3% of sexually active men in both arms had complete retrograde ejaculation at 24-month follow up [Briganti *et al.* 2006]. An additional 18.3% and 16.7% of patients respectively, had diminished ejaculatory volume [Briganti *et al.* 2006]. On the other hand, transurethral incision of the prostate using holmium:YAG laser had the least impact on ejaculation leading to EjD in eight out of 77 potent men at 2-year follow up [Cornford *et al.* 1998].

Interestingly, prostatectomy might improve ejaculatory pain in some patients presenting with LUTS. In a group of men presenting with LUTS, a prospective study evaluated the impact of TURP and noncontact laser therapy, using side firing neodymium:YAG probe or observation on sexual function [Brookes *et al.* 2002]. At baseline, 70% of men had EjD and 18% had discomfort or pain during ejaculation. These patients were significantly bothered by these symptoms in 41% and 74%, respectively. After treatment, there was a significant decrease in pain during ejaculation in the TURP group compared with baseline. EjD increased in all groups by average 11% [Brookes *et al.* 2002]. Laser prostatectomy may improve painful ejaculation in LUTS patients with urodynamically confirmed bladder outlet obstruction. Before TURP or laser prostatectomy, a group of patients with LUTS had a high prevalence of ED (86%), ejaculatory volume change (83%) and pain or discomfort on ejaculation (26%) which was considered problematic by most of them. TURP significantly decreased or totally eradicated the amount of ejaculate while both laser and TURP treatments improved pain or discomfort on ejaculation [Tuhkanen *et al.* 2004].

Much less-invasive surgical treatments for LUTS due to BPH have been developed with the aim of avoiding anesthesia. TUNA of the prostate was compared with TURP in a prospective, randomized clinical trial of men 50 years old or older at seven medical centers across the United States [Bruskewitz *et al.* 1998]. At 1-year follow up, both procedures were equally effective in enhancing quality of life, but resection was associated with better improvement of symptom score and uroflow. TURP was associated with 38.2% retrograde ejaculation compared with 0% in the TUNA group [Bruskewitz *et al.* 1998]. A 5-year follow-up report showed that 41% of TURP patients had

retrograde ejaculation, while the TUNA group reported none [Hill *et al.* 2004].

Another minimally invasive treatment for LUTS due to BPH is high-energy transurethral microwave thermotherapy. In a prospective, randomized study, thermotherapy was associated with persistent ability to ejaculate in 74% compared with 27% in the TURP group at 3-month follow up [Francisca *et al.* 1999].

Prostatic surgery for cancer

Radical prostatectomy for prostatic cancer 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. In a retrospective study, following radical prostatectomy 74% of men reported decreased or complete absence of orgasm, 22% no change and 4% improved orgasm [Barnas *et al.* 2004]. Pain during orgasm occurred in 14% [Barnas *et al.* 2004]. Better preservation of orgasm was reported by another study. A comparison between preoperative and postoperative sexual function in a large cohort of patients undergoing radical prostatectomy for prostate cancer showed that normal orgasmic function decreased from 90% of men preoperatively to 66.8% [Dubbelman *et al.* 2010]. The effect on orgasm is influenced by patients' age and the attempt to preserve nerves during surgery. Patients younger than 58 reported at least fair ability to achieve orgasm after radical prostatectomy with bilateral nerve preservation, unilateral nerve preservation or no nerve preservation in 84%, 68% and 67%, respectively, compared with 94% in age-matched controls [Hollenbeck *et al.* 2003]. For older patients, the corresponding percentage achieving orgasm was 10–15% less. Another study showed that at least unilateral nerve sparing is associated with a less adverse effect on orgasm. Orgasmic function was preserved in 73.4% of men after a bilateral nerve-sparing procedure, in 70.9% after a unilateral nerve-sparing procedure and in 54.0% after non-nerve-sparing technique [Dubbelman *et al.* 2010]. Orgasmic function was significantly affected by age ≥60 years [Dubbelman *et al.* 2010]. Robotic radical prostatectomy had similar results compared with the open procedure. Of patients who received bilateral nerve sparing robotic radical prostatectomy 90.7% were able to achieve orgasm postoperatively compared with 82.1% patients who received unilateral nerve sparing and 60.8% men who received non-nerve-sparing surgery [Tewari *et al.* 2011].

Another ejaculatory problem associated with radical prostatectomy for prostate cancer is the loss of urine during orgasm (climacturia), reported in 20–45% [Tsivian *et al.* 2009; Nilsson *et al.* 2011; Choi *et al.* 2007; Lee *et al.* 2006]. The majority of patients were bothered by the problem [Tsivian *et al.* 2009]. Nearly 2 years following radical prostatectomy, 21% of patients reported that climacturia occurred most of the time or always, 48% reported that it caused significant bother and 21% thought that it was of significant bother to their partners [Lee *et al.* 2006]. Among sexually active patients who reported urine leak during orgasm, 86% were daytime continent [Nilsson *et al.* 2011]. Men who reported orgasm associated incontinence had higher prevalence ratios of not being able to satisfy the partner, avoiding sexual activity because of fear of failing, low orgasmic satisfaction and having sexual intercourse infrequently [Nilsson *et al.* 2011]. Orgasm-associated incontinence is unrelated to whether prostatectomy is open or laparoscopic [Choi *et al.* 2007]. The problem usually occurs within 1 year following surgery and is more prevalent in men who complain of orgasmic pain and/or penile shortening [Choi *et al.* 2007].

Radiation therapy is an alternative treatment option for localized prostate cancer, and similar to surgery is associated with ejaculatory adverse effects. Men treated with radiotherapy and retaining orgasm reported a decreased orgasmic pleasure in 47% and a reduced ejaculation volume in 91% [Helgason *et al.* 1995]. Following permanent iodine-129 prostate brachytherapy for localized prostate cancer, 81.3% of men had conserved ejaculatory function with 84.9% reporting reduced ejaculatory volume, 18.7% dry ejaculation, 30.3% painful ejaculation and 10% no orgasm [Huyghe *et al.* 2009]. Other forms of EjD may follow brachytherapy. Hematospermia, pain at the time of orgasm and alteration in intensity of orgasm were reported in 26%, 15% and 38% of patients, mostly for a limited duration [Merrick *et al.* 2001]. Another study reported pain on orgasm and hematospermia in 40% and 17% after brachytherapy [Finney *et al.* 2005].

Pelvic surgery for nonurological diseases

Surgery for rectal cancer is associated with EjD. Total mesorectal excision with intention to treat

low rectal cancers was associated with inability to ejaculate in 67% of sexually active men after 1 year [Nishizawa *et al.* 2011]. Another study reported similarly high rate of EjD affecting orgasm in 41% and ejaculation in 43% [Hendren *et al.* 2005]. Others reported lower rates of EjD. 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 preoperative state [Zugor *et al.* 2010]. Following rectal cancer surgery EjD was related to injury of the superior hypogastric plexus [Maas *et al.* 2000]. 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, among patients who maintained sexual activity, 70% of patients without lateral node dissection and 10% of those with lateral node dissection maintained ejaculation [Kyo *et al.* 2006]. In prospective studies in patients undergoing mesorectal excision for rectal cancer, as little as 8–13.2% developed retrograde ejaculation [Nesbakken *et al.* 2000; Kim *et al.* 2002]. Pelvic autonomic nerve preservation contributed to this low prevalence [Kim *et al.* 2002]. However, orgasmic function score of the IIEF significantly decreased after surgery [Kim *et al.* 2002].

Laparoscopic surgery for rectal cancer was similarly associated with EjD, however, with a variable range of reported prevalence. One retrospective study reported no difference in sexual complication between laparoscopic and open surgical treatment for rectal and rectosigmoid cancer [Nitori *et al.* 2008].

After laparoscopic total mesorectal excision, 70% were able to penetrate and have normal ejaculation and orgasm [Sartori *et al.* 2011]. Another retrospective study showed that after laparoscopic total mesorectal excision with autonomic nerve preservation the ability to achieve orgasm and ejaculation was maintained by 37.8% of the patients [Morino *et al.* 2009]. The frequency of performing surgery affects outcome. In a high-volume single unit performing laparoscopic colorectal surgery, a retrospective analysis showed a very low rate of retrograde ejaculation of less than 4% [Jones *et al.* 2009]. Prospective studies compared open with laparoscopic surgery and nerve to non-nerve preservation. In a group of patients with rectal cancer randomized to open or laparoscopic mesorectal resection, impotence or impaired ejaculation was significantly more common in the laparoscopy group [Quah *et al.* 2002]. An opposite view was reported by another prospective study evaluating laparoscopic pelvic autonomic nerve preservation during standard anterior resection of sigmoid colon cancer on sexual function [Liang *et al.* 2008]. At follow up (mean 18 months) ejaculation was ranked as good by 90.9%, fair (decrease in ejaculatory amounts) by 6.8% and poor (retrograde ejaculation, failure of ejaculation) by 2.3% [Liang *et al.* 2008].

The addition of chemotherapy or radiotherapy to the surgical treatment increased the prevalence of sexual adverse effects. In patients with resectable rectal cancer, preoperative radiotherapy was associated with more frequent ejaculation disorders than in patients with total mesorectal excision alone [Marijnen *et al.* 2005]. Ejaculatory problems developed or worsened postoperatively in 72.2% of the patients, of whom 67.4% had a severe problem [Lange *et al.* 2009]. The problem was significantly associated with pre-operative radiotherapy, autonomic nerve damage and anastomotic leakage [Lange *et al.* 2009]. Short-term preoperative radiotherapy and laparoscopic total mesorectal excision, reported better results with 89% of men maintaining ejaculation at 15 months follow up [Breukink *et al.* 2008]. Preoperative combined chemotherapy and radiotherapy and laparoscopic pelvic autonomic nerve-preserving surgery for patients with lower rectal cancer resulted in 25% of sexually active men having retrograde ejaculation or failure to ejaculate after 6 months [Liang *et al.* 2007].

Postoperative adjuvant radiotherapy compared to no radiotherapy was associated with higher orgasmic dysfunction developing 8 months after surgery [Heriot *et al.* 2005]. Adjuvant radiochemotherapy in the management of patients with low rectal cancer resulted in 78.4% prevalence of retrograde ejaculation postoperatively [Han *et al.* 2010].

Surgery for ulcerative colitis is associated with EjD. In a consecutive group of patients who underwent hand-sewn ileal J pouch anal restorative proctocolectomy for ulcerative colitis, no males developed impotence, but 19% had retrograde ejaculation [Michelassi *et al.* 1993]. Another retrospective analysis of a similar procedure reported only 2.3% retrograde ejaculation [Tiainen *et al.* 1999]. A prospective study in patients with ulcerative colitis followed for 1 year

after an ileal-pouch anal anastomosis reported comparable results. Only 12% of men with normal pre-operative sexual function developed loss of ejaculation [Berndtsson *et al.* 2004]. Compared with adult ulcerative colitis, patients with surgical treatment in childhood or adolescence only rarely reported ejaculatory disturbance in adulthood [Koivusalo *et al.* 2009]. Surgical treatment at a young age does not seem to affect sexual function in adulthood. Fecal incontinency, however, disturbed sexual function in all patients [Koivusalo *et al.* 2009].

Other surgical procedures for colorectal disease were associated with EjD. Laparoscopic sigmoid colectomy for diverticular disease had a low prevalence of retrograde ejaculation affecting 4.1% of men [Trebuchet *et al.* 2002]. Posterior rectopexy for treatment of rectal prolapse is associated with extensive pelvic dissection. Postoperative retrograde ejaculation and impotence were reported in 17.2% of male patients [Yakut *et al.* 1998]. In men who underwent surgery for high- or intermediate-type anorectal malformation, ejaculatory incompetence was found in 29.4% and retrograde ejaculation in 11.8% [Konuma *et al.* 2006].

Retroperitoneal surgery

Retroperitoneal surgery might affect the sympathetic nerve plexus and impair ejaculation. EjD has been reported with RPLND for testicular tumors, after reconstruction of the great vessels for aneurysm and after surgery of the spine.

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%) [Fegg *et al.* 2003]. In a study involving Norwegian men, testicular cancer survivors had significantly worse scores on ejaculatory and sexual problems compared with the general population in both young (20–39 years old) and middle-aged (40–59 years old) males. EjD had a prevalence of 18–19% in cancer survivors whereas it was 6–9% in controls [Dahl *et al.* 2007]. A long-term follow-up assessment of testicular cancer survivors in Denmark showed that 7% had ejaculatory problems and 3% increased sexual discomfort [Rossen *et al.* 2012]. Changes in body image were significantly associated with sexual dysfunction. When comparing treatments, only the RPLND procedure was associated with sexual dysfunction in the form of EjD [Rossen *et al.* 2012].

Several factors affect the impact of RPLND on ejaculation, namely the stage of the tumor, associated chemotherapy and the attempt of nerve preservation. In a retrospective study of primary RPLND for early stage testicular cancer, antegrade ejaculation was preserved in 98% of patients who underwent nerve-sparing surgery [Baniel *et al.* 1994]. In another report, primary unilateral or bilateral nerve sparing RPLND for testicular clinical stage I nonseminomatous germ cell tumor (NSGCT) was associated with retrograde ejaculation of 6.7% [Heidenreich *et al.* 2003]. A prospective study comparing modified (ipsilateral) and radical RPLND in testicular stage I NSGCT, reported postoperative preserved antegrade ejaculation in 74% and 34%, respectively [Weissbach *et al.* 1990].

A report of a contemporary series of primary RPLND of testicular cancer patients emphasized the importance of the nerve-sparing approach. The overall retrograde ejaculation rate was only 3%. A total of 99% of patients who had a nerve-sparing procedure could ejaculate compared to only 89% in the non-nerve-sparing group [Beck *et al.* 2010]. The reported rate of retrograde ejaculation with nerve preservation varies according to the extent of dissection. In patients with RPLND for testicular cancer, antegrade ejaculation was preserved in 94.1% of patients with modified template dissection, whereas no patients with additional dissection below the level of the inferior mesenteric artery had the function been preserved [Tanaka *et al.* 2006].

RPLND after chemotherapy is associated with more adverse effects on sexual function. Post-chemotherapy RPLND with no nerve preservation for testicular NSGCT was associated with permanent loss of ejaculation in 29% of patients [Bell and Sibley, 1999]. After nerve-sparing post-chemotherapy RPLND for NSGCT, antegrade ejaculation was reported by 79% of patients [Pettus *et al.* 2009]. A right-sided primary testicular tumor and residual masses ≥5 cm were associated with retrograde ejaculation [Pettus *et al.* 2009]. In another group of patients with a NSGCT stage II or III, 2 years after treatment with surgery and combination chemotherapy, 54% experienced sexual functional disorders [Nijman *et al.* 1988]. Interestingly, some of these patients were only treated by chemotherapy and demonstrated greatly reduced or absent antegrade ejaculation. The results indicate that chemotherapy alone might be responsible for

ejaculatory disorders in 30% of the patients [Nijman *et al.* 1988].

Nerve sparing has decreased ejaculatory side effects related to post-chemotherapy RPLND. Removal of residual masses after chemotherapy for metastatic NSGCT has been associated with significantly less postoperative EjD (16%) since 1984 when a nerve sparing dissection was introduced *versus* 36% before 1984 [Jones *et al.* 1993]. Nerve-sparing RPLND at least on one side in advanced testicular cancer following chemotherapy, was associated with 84.6% antegrade ejaculation [Nonomura *et al.* 2002]. More recently, laparoscopic RPLND using a modified template dissection and adjuvant chemotherapy for NSGCT stage II was associated with minimal retrograde ejaculation rate affecting 3.4% of patients [Cresswell *et al.* 2008].

Spine surgery has opposing effects on sex life depending on the technique and the extent of possible retroperitoneal nerve damage. Anterior lumbar fusion surgery was significantly associated with improved sex life due to reduced back pain but with a significant disturbance of ejaculation and genital sensation in men compared with conservative treatment [Hägg *et al.* 2006]. Anterior fusion had significantly more men reporting disturbed ejaculation (41%) and retrograde ejaculation (13%) compared to posterior fusion (11% and 5%) [Hägg *et al.* 2006]. The transperitoneal approach of anterior lumbar interbody fusion had significantly a greater chance of causing retrograde ejaculation in men than a retroperitoneal approach [Sasso *et al.* 2003]. Total disc replacement via an anterior retroperitoneal approach was compared with posterior lumbar spine interbody fusion. Despite a reduction of lower back pain, 26% of all men in the fusion group, compared with 3% in the total disc replacement group, reported postoperative deterioration in the ability to achieve orgasm [Berg *et al.* 2009]. The midline anterior retroperitoneal approach from the right side for interbody fusion and total disc replacement has a better outcome on ejaculation compared with the classical approach from the left side. The absence of retrograde ejaculation confirms the importance of preserving the integrity of the superior hypogastric plexus on the left side [Edgard-Rosa *et al.* 2012]. This observation was confirmed in another study using a different approach. Laparoscopic exposure for anterior lumbar interbody fusion involving L4–L5 affects ejaculation depending on vascular variation. Avoiding the left side of the aorta or the left iliac artery may minimize the risk of EjD [Kleeman *et al.* 2002].

The damage to the nerve plexus can be also induced by nonsurgical trauma. Anterior lumbar spine interbody fusion using growth factor recombinant bone morphogenic protein-2 (rhBMP-2) was associated with increased risk of retrograde ejaculation compared to conventional surgery. A total of 7% of patients had postoperative retrograde ejaculation, which resolved in half the affected men after 1 year [Carragee *et al.* 2011]. Utilization of minimal surgical dissection is associated with less ejaculatory adverse effects. Reports on men undergoing mini laparotomy retroperitoneal anterior lumbar surgery for the treatment of a variety of lumbosacral disease showed no effect on ejaculation or a very low rate of postoperative retrograde ejaculation of 0.01% [Kang *et al.* 2009; Brau, 2002].

Other retroperitoneal procedures that may affect ejaculation include aorto-iliac surgery and lumbar sympathectomy. Retroperitoneal abdominal aortic aneurysm surgical repair is associated with 9% retrograde ejaculation postoperatively in sexually active men [Ballard *et al.* 2006]. In a retrospective comparison, conventional open surgery for prosthetic replacement of the aneurysmatic tract, was associated with 17.6% retrograde ejaculation whereas none was reported with endovascular exclusion or observation [Gabrielli *et al.* 2007]. A prospective comparison between elective endovascular aneurysm repair and hand-assisted laparoscopic surgery for abdominal aortic aneurysm showed that only 6% of patients in the laparoscopy group and none in the endovascular group suffered from retrograde ejaculation at 1-year follow up [Veroux *et al.* 2010]. Another prospective follow up of sexual function after elective repair of abdominal aortic aneurysms using open and endovascular techniques gave a different opinion. Patients treated with endovascular but not the open techniques reported a significant impairment in the quality of erection and their ability to achieve ejaculation 1 year after the operation [Pettersson *et al.* 2009]. In a study of sexual function in patients undergoing aorto-iliac operations, retrograde ejaculation occurred in 30% of patients. All men with retrograde ejaculation had extensive dissection of the anterior wall of the abdominal aorta and common iliac vessels [Weinstein and Machleder, 1975]. Resection of the lower sympathetic lumbar trunk is not associated with retrograde ejaculation. A low incidence

of retrograde ejaculation was reported following laparoscopic lumbar sympathectomy for the treatment of planter hyperhidrosis. Only one patient out of 59 men developed retrograde ejaculation [Rieger *et al.* 2009].

Circumcision

Considering the controversy on the pros and cons of circumcision, few studies looked at the impact of circumcision on ejaculation. Circumcision performed by plastic clamp technique in adult males did not adversely affect ejaculation based on the brief male sexual function inventory scores [Senel *et al.* 2012].

In a prospective, randomized trial to assess adult male circumcision's effect on men's sexual function and pleasure, circumcision was not associated with sexual dysfunction. Circumcised men reported increased penile sensitivity and enhanced ease of reaching orgasm [Krieger *et al.* 2008]. In another study, no effect of male circumcision was found on ejaculatory function [Kim and Pang, 2007].

Urethral surgery

Pelvic trauma might affect the nerves and vessels contributing to sexual function, whereas establishing urethral patency might have a positive impact on ejaculation. The effect on sexual function of pelvic fracture–urethral distraction defect injuries in patients who had a posterior urethroplasty was reported [Anger *et al.* 2009]. Although erectile function was compromised in 54%, orgasmic function and ejaculation were maintained in all patients [Anger *et al.* 2009]. Bulbar end-to-end anastomosis, however, was associated with 23.3% EjD at long-term follow up [Barbagli *et al.* 2007]. Anterior urethroplasty was not associated with significant difference between preoperative and postoperative score of the ejaculatory function [Erickson *et al.* 2010]. Another group reported even improved ejaculation following reconstructive procedures for anterior urethral stricture disease [Erickson *et al.* 2007].

Surgeries for congenital anomalies affecting the urethra were sometimes linked to EjD. In men treated in infancy for posterior urethral valves, erections and orgasm were normal in 20 men and one man had lifelong impotence. Nine men had slow or dry ejaculation [Woodhouse *et al.* 1989]. In another group of adult males surgically treated for exstrophy–epispadias complex, long-term follow up showed that only three out of 21 suffered retrograde ejaculation [Ebert *et al.* 2008]. Following two-stage hypospadias repair for severe hypospadias and chordae, 74% were able to ejaculate and 33% had to milk the ejaculate [Lam *et al.* 2005].

Other surgeries

Ejaculatory pain is sometimes a complication of groin hernia surgery. In a large group of patients followed for 1 year after inguinal hernia repair, sexual dysfunction was assessed. Genital or ejaculatory pain was found in 12.3% of patients and 2.8% of patients reported that the pain impaired their sexual activity [Aasvang *et al.* 2006]. Sensory testing showed abnormal sensory thresholds with a maximum pain felt in the area of the external inguinal ring of the surgery side in affected patients [Aasvang *et al.* 2007]. Less ejaculatory pain was reported after laparoscopic herniorrhaphy. Only 3.1% of men registered in the Danish Hernia Database reported ejaculatory pain [Bischoff *et al.* 2012]. Vasectomy has been reported to cause ejaculatory pain. In a small retrospective study involving 13 patients developing long-term pain following vasectomy, four patients had pain during ejaculation. Most of the patients had complete resolution of their pain after vasectomy reversal [Nangia *et al.* 2000]. Vasectomy however did not affect orgasm as reported in a population-based study of Australian men [Smith *et al.* 2010b].

One study evaluated ejaculatory and orgasmic function following penile prosthesis implantation. Prior to surgery, 71% were able to experience ejaculation and 80% experienced orgasm even with impaired erection. Penile prosthesis implantation did not interfere with ejaculation or orgasm. Even 14.3% of previously non-orgasmic men reported having orgasm after surgery [Coleman *et al.* 1985].

Another study reported EjD associated with liver transplantation. After orthotopic liver transplantation, 33% of men reported having difficulty reaching orgasm with intercourse [Ho *et al.* 2006].

Orgasmic headache and post-orgasmic illness

Many single case reports and few case series described the condition of sudden onset of a throbbing or a constant headache during sexual activity and at or around the time of orgasm. The

condition was described as benign sexual headache because no obvious clinical evidence could link it to an intracranial pathology.

In a series of 21 patients, two variants of sexual headache were noted [Lance, 1976]. The first developed with sexual excitement mount and had the characteristics of muscle contraction headache. The second was a severe throbbing headache occurring at the time of orgasm, presumably of vascular origin. No structural lesions were found in the majority of patients; however, the possibility of intracranial vascular or other lesions must be considered [Lance, 1976]. In another series of 38 men with benign vascular sexual headache, 63% experienced benign vascular sexual headache alone, while 37% had experienced both benign vascular sexual headache and benign exertional headache on at least one occasion [Silbert *et al.* 1991]. Risk factors included history of migraine, stress and fatigue. The finding of negative angiography outline a benign form of coital cephalalgia, possibly resulting from ischemic disturbances triggered by hemodynamic changes occurring in orgasm [Martinez *et al.* 1988].

Another interesting condition of post orgasmic illness syndrome was reported in single cases. A recent study looked into the possible cause of post orgasmic illness syndrome, which is characterized by a combination of local allergic symptoms and transient flu-like illness following ejaculation [Waldinger *et al.* 2011]. A total of 45 men with the condition were evaluated. Findings from a positive skin prick test to own diluted semen suggested an immunogenic etiology underlying this condition [Waldinger *et al.* 2011].

Conditions of the prostate and seminal vesicles causing hematospermia

Hematospermia was reported because of prostatic disease, seminal vesicular disease, ejaculatory duct obstruction, TRUS biopsy and brachytherapy [Abdelkhalek *et al.* 2012; Trinchieri *et al.* 2007; Weintraub *et al.* 1993; Schnall *et al.* 1992]. Commonly, however, no definite pathology could be associated with the condition [Badawy *et al.* 2012; Schnall *et al.* 1992]. Idiopathic refractory hematospermia was reported in 34.3% in patients evaluated for the condition [Badawy *et al.* 2012]. In another study using MRI for diagnosis, it was not possible to find any pathological etiology in 57.7% of patients with EjD and hematospermia [Schnall *et al.* 1992].

Hematospermia may indicate an underlying pathology of the prostate and seminal vesicles detected by MRI such as Müllerian cysts, Wolffian cysts, anaplastic prostatic carcinoma, ejaculatory duct obstruction and seminal vesiculitis [Schnall *et al.* 1992]. Other reports confirm that ejaculatory duct obstruction may cause hematospermia [Weintraub *et al.* 1993]. Calculi in the seminal vesicles or ejaculatory ducts were significantly associated with hematospermia and ejaculatory pain [Littrup *et al.* 1988; Song *et al.* 2012]. Prostatic cysts may be found in patients with hematospermia. The presence of a medial prostatic cyst in patients with prostatitis-like symptoms was associated with 24% of patients complaining of hematospermia [Dik *et al.* 1996]. The diagnosis of enlarged prostatic utricle by TRUS was associated with hematospermia in 40% of patients [Coppens *et al.* 2002]. In patients with symptoms suggesting prostatitis without urethral discharge, TRUS showed that hematospermia was significantly associated to asymmetry or inflammatory changes of the seminal vesicles [Trinchieri *et al.* 2007]. A more invasive diagnostic approach may reveal the underlying etiology in the majority of patients with hematospermia. Using vesiculoscopy a definite diagnosis of the cause of hemospermia was made for 93.1% patients. The findings included seminal vesicular inflammatory mucosal edema, congestion and hemorrhages affecting a single vesicle in 58.3% and both vesicles in 34.7% of patients. In addition, ejaculatory duct obstruction and calculi in one or both seminal vesicles and in the verumontanum lumen were found in a significant number of patients [Liu *et al.* 2009].

Interventions for the management of prostatic cancer are commonly associated with hematospermia. TRUS biopsy or brachytherapy are associated with short-term hematospermia. Of patients undergoing TRUS-guided prostatic biopsy for suspected prostate cancer, 45% experienced hematospermia, for a mean duration of 4 weeks [Abdelkhalek *et al.* 2012]. Hematospermia was reported in 17–26% of patients after prostate brachytherapy for low-risk cancer mostly for a limited duration [Merrick *et al.* 2001; Finney *et al.* 2005].

Treatment of non-PE EjD

Retrograde ejaculation and anejaculation

Imipramine and sympathomimetic medications showed variable success rates in the treatment of

retrograde ejaculation of different etiologies. In a systematic review of medical treatments for EjD, 36 studies dealing with patients with retrograde ejaculation and 40 with anejaculation were included [Kamischke and Nieschlag, 2002]. Imipramine and chlorpheniramine + phenylpropanalamine showed significantly higher reversal rates of retrograde ejaculation compared with ephedrine. Midodrine showed significantly better rates than imipramine, pseudoephedrine and ephedrine for the reversal of anejaculation [Kamischke and Nieschlag, 2002]. Several studies reported a variable success rate in drug treatment of retrograde ejaculation. Ephedrine sulfate or imipramine hydrochloride, 4-week treatment gave positive results in 29.3% of patients with retrograde ejaculation or lack of emission [Gilja *et al.* 1994]. In cases with diabetes mellitus and complete retrograde ejaculation, imipramine was successful in producing antegrade ejaculate in 38.5% while pseudoephedrine was successful in 47.8%, and both drugs given together were successful in 61.5%. In cases with partial retrograde ejaculation, there was significant increase in the antegrade semen sample volume with imipramine alone, pseudoephedrine alone, and both drugs [Arafa and El Tabie, 2008]. Amezinium, a sympathomimetic agent in a daily dose of 10 mg, achieved antegrade ejaculation in all patients with retrograde ejaculation [Ichiyanagi *et al.* 2003]. Patients suffering from organic anejaculation not due to SCI were treated with oral midodrine 7.5–15 mg per day in a stepwise approach or placebo. Antegrade, retrograde and antegrade + retrograde ejaculation occurred in 29.5%, 13.1% and 14.8% patients in midodrine group, respectively. No change of EjD was observed in the placebo group [Safarinejad, 2009]. Intravenous midodrine 5–15 mg given 30 min before ejaculation resulted in improvement of sperm concentration or total sperm count in 23/140 patients suffering from severe oligozoospermia or retrograde ejaculation [Kohn and Schill, 1994].

Similarly, imipramine and sympathomimetics were useful in the management of EjD associated with retroperitoneal sympathetic nerve damage. In patients with retrograde ejaculation following RPLND, imipramine treatment for 7 days resulted in antegrade ejaculation for sperm retrieval [Ochsenkühn *et al.* 1999]. With daily oral doses of 25–50 mg imipramine, the majority of patients regained antegrade ejaculation [Nijman *et al.* 1982]. Midodrine was successful in management of RPLND induced retrograde ejaculation. Midodrine, administered orally, led to improvements in the intensity of orgasm and the degree of erection. Normal ejaculation was induced in seven out of 12 patients and emission of spermatozoa into the posterior urethra was restored in three out of 12 patients by a single intravenous injection of 25–30 mg midodrine [Jonas *et al.* 1979].

SCI patients suffer from ejaculatory failure and several studies addressed techniques to increase sperm retrieval for assisted reproduction. In a meta-analysis of published articles on fertility of persons with SCI until 2003, pooled results of semen harvesting, including vibration or electroejaculation, yielded an overall ejaculation response rate of 86%. Within the last decade, the success rate of these case series approached 100% [DeForge *et al.* 2005]. Usually patients attempt to produce semen by masturbation for in vitro fertilization but the success rate is affected by anxiety and becomes even lower with SCI. During evaluation for infertility, 11% of men having no prior sexual problems, failed to collect semen by masturbation after repeated attempts. Using a vibratory stimulation, 20% of these patients were able to collect semen [Saleh *et al.* 2003]. While among patients with SCI subjected to semen retrieval procedures for fertilization, only 9% could produce semen by masturbation while penile vibratory stimulation was successful in 86% [Brackett *et al.* 2010]. The amplitude of stimulation and the level of SCI affect the results of sperm retrieval. Ejaculatory response to penile vibratory stimulation was evaluated in men with SCI and anejaculation. High-amplitude stimulation caused 54.5% patients to ejaculate.

The ejaculatory success rate was highest in men with injuries at C3 to C7, followed by T1 to T5, T6 to T10 and T11 to L3 [Brackett *et al.* 1998]. Electroejaculation is another method used in the infertility patients to retrieve sperms. Psychogenic anejaculation and SCI patients in infertility *in vitro* fertilization clinic were subjected to electroejaculation to obtain semen, which resulted in fertilization rate of 47.0–57.0% [Gat *et al.* 2012].

SCI patients with anejaculation during sexual intercourse and who failed to respond to penile vibratory stimulation were treated with midodrine 30–120 minutes before a new stimulation [Soler *et al.* 2007]. Antegrade or retrograde ejaculation was achieved in 64.6%. A significant but moderate increase occurred in the mean arterial

pressure in all patients. The average dose of midodrine required for ejaculation was 18.7 mg [Soler *et al.* 2007]. Orgasm without ejaculation was reported by 9% of patients on baseline penile vibratory stimulation, and 59% experienced orgasm during penile vibratory stimulation on midodrine [Soler *et al.* 2008]. Of patients with a complete spinal cord section and suffering from loss of ejaculation, physostigmine allowed 55.6% to ejaculate [Chapelle *et al.* 1988]. The effect depended on the integrity of the T12–L2 metamers.

Drug-induced retrograde ejaculation may be reversed by intermittent treatment or using a lower dose. Retrograde ejaculation associated with tamsulosin 0.4 mg daily treatment for LUTS was reversed by intermittent tamsulosin treatment in 63.3% of affected men [Goktas *et al.* 2006]. Lowering the dose to tamsulosin 0.2 mg daily treatment for LUTS had less adverse effects on ejaculation [Song *et al.* 2011; Yokoyama *et al.* 2011]. Other α-blockers for the treatment of LUTS were not associated with significant EjD [Roehrborn *et al.* 2003].

Surgical reconstruction of the bladder neck was sometimes reported to treat retrograde ejaculation when medical treatment fails. The Young–Dees type of bladder neck reconstruction to convert retrograde ejaculation into normal or antegrade ejaculation was successful in four of five patients [Middleton and Urry, 1986]. In a group of patients who had Bilharziasis and bladder neck obstruction, retrograde ejaculation developed following surgery to relieve the obstruction. Lengthening of the premontanal urethra was carried out by reconstruction using the trigonal urothelium and the trigonal muscles. Antegrade ejaculation was restored in four of five patients [Ramadan *et al.* 1985].

Decreased intensity and force of ejaculation are sometimes reported in infertile men. The problem may be due to ejaculatory duct obstruction and might be relieved by transurethral resection of the ejaculatory ducts (TURED) [Pace *et al.* 2008]. TURED not only improves volume of ejaculation but also has other beneficial effects in alleviating EjD associated with ejaculatory duct obstruction. In infertile men with ejaculatory duct obstruction symptoms included nonprojectile ejaculation (93.3%), a decrease in sensation of orgasm, pain with ejaculation (26.7%) and/or 13.3% hematospermia [Johnson *et al.* 2005]. After TURED, 93.3% of men reported return of projectile ejaculation, an increase in the volume of their ejaculate and resolution of their hematospermia and pain with ejaculation. The sensation of orgasm markedly improved in 53.3% of patients [Johnson *et al.* 2005].

Ejaculatory pain

Alpha-blockers and 5α-reductase inhibitors have been used successfully to treat ejaculatory pain in some clinical conditions. In a prospective study to evaluate dutasteride in prevention of cancer prostate, 7.9% of enrolled men had pelvic or ejaculatory pain at baseline. The symptoms were significantly reduced in the dutasteride group (46%) compared with placebo (35%) [Nickel *et al.* 2011]. With tamsulosin 0.4 mg daily treatment, 77% patients reported significant improvement in orgasmic pain and 12% noted complete resolution of their pain [Barnas *et al.* 2005]. Another study showed that tamsulosin treatment of ejaculatory pain produced a significant relief in 16% of patients compared to 13% in the placebo group [Safarinejad, 2006]. Alfuzosin treatment showed similar effect on painful ejaculation. In a large sample of sexually active men with LUTS, 20.5% had pain/discomfort on ejaculation and 89.2% considered it a problem.

Under alfuzosin 10 mg once-daily treatment for 6 months there was a significant improvement in the score for painful ejaculation [Nickel *et al.* 2006]. Painful ejaculation may occur because of ejaculatory duct obstruction, which can be relieved by TURED. Ejaculatory duct manometry demonstrated that men with clinically suspected ejaculatory duct obstruction had higher ejaculatory duct opening pressure than controls and ejaculatory duct pressure decreased after TURED [Eisenberg *et al.* 2008]. In infertility patients with obstructive azoospermia, TURED resulted in disappearance of associated painful ejaculation and hemospermia in all cases [Popken *et al.* 1998]. In radiologically proven ejaculatory duct obstruction, TURED resolved the symptoms of painful ejaculation, hematospermia, and perineal and/or testicular pain in most patients [Weintraub *et al.* 1993].

Seminal vesicular cysts may cause ejaculatory pain and can be treated by TURED. In a pooled analysis of cases with seminal vesicle cysts associated with ipsilateral renal agenesis, ejaculatory pain was present in 21% of patients. Open

surgery or transurethral deroofing resulted in cure of symptoms in 75–100% of cases [van den Ouden *et al.* 1998].

Other techniques or medications may be useful in the treatment of ejaculatory pain. Men who had refractory chronic pelvic pain syndrome were treated with trigger point release/paradoxical relaxation training to release trigger points in the pelvic floor musculature. Ejaculatory pain was present in 56% and EjD in 31%. After treatment, symptomatic improvement was greater than 50% [Anderson *et al.* 2006]. When infection is the cause of ejaculatory pain, antibiotic treatment is indicated. In chronic bacterial prostatitis patients treated by fluoroquinolone–macrolide combination, ejaculatory pain and hematospermia were significantly attenuated [Magri *et al.* 2011].

Orgasmic headache

Treatment with a medication of migraine headache was effective in some patients with benign orgasmic headache. Four patients with orgasmic headache were treated with triptan [Frese *et al.* 2006]. Two out of four patients with severe headache continuing for >2 hours had a positive response to acute triptan therapy. Two out of three patients using triptans as short-term prophylaxis 30 min before sexual activity reported a reliable response on several occasions.

Delayed ejaculation

Several medications that act on the adrenergic or serotoninergic receptors had some effect in the treatment of DE. Bupropion, an atypical antidepressant, was shown to decrease orgasmic delay. Bupropion therapy for lifelong DE resulted in an increase of men rating control over ejaculation from 0 to 21.1%. Mean IELT decreased 0.74-folds after treatment. There was a significant improvement in the intercourse satisfaction and the orgasmic domains of IIEF and depression score from baseline [Abdel-Hamid and El Saleh, 2010]. In men with non-depression-associated orgasmic delay, bupropion treatment caused a significant improvement on orgasm and sexual satisfaction [Modell *et al.* 2000]. Gepirone-ER in the treatment of depressed men resulted in significant improvement of orgasmic function irrespective of its antidepressant and anxiolytic effect. Fluoxetine-treated subjects had lower orgasmic function scores less than placebo and gepirone-ER [Fabre *et al.* 2012]. After yohimbine treatment of patients with orgasmic dysfunction, 55.2% managed to reach orgasm and were able to ejaculate during either masturbation or sexual intercourse [Adeniyi *et al.* 2007].

Several reports showed that in certain clinical conditions, PDE5i could successfully treat ejaculatory and orgasmic dysfunction. In a prospective, placebo-controlled trial, sildenafil significantly improved ejaculation and orgasm in male outpatients with major depression and antidepressant treatment associated sexual dysfunction [Nurnberg *et al.* 2003]. In patients with ED, a pooled analysis of 17 placebo-controlled 12-week trials, treatment with tadalafil 10 or 20 mg was associated with significant improvement in ejaculatory and orgasmic function. In the tadalafil group, 66% of subjects with severe EjD or severe orgasmic dysfunction reported improvement compared with 35–36% in the placebo group [Paduch *et al.* 2013]. A randomized, double-blind, placebo-controlled study of tadalafil 5 mg once daily for 12 weeks in men with LUTS/BPH, tadalafil treatment significantly improved ejaculation and orgasm compared with placebo or tamsulosin treatment [Giuliano *et al.* 2013].

Treatment of hemospermia

In patients having refractory hemospermia of idiopathic nature and treated by finasteride 5 mg daily for 3 months, 66.7% demonstrated a remission of their symptom within 2–5 weeks and confirmed by repeated semen analysis. On the other hand, only 25% had symptomatic improvement but with persistent hematospermia in semen analysis [Badawy *et al.* 2012].

Vesiculoscopy and removal of seminal vesicular stones were successful in treating patients with intractable hematospermia [Song *et al.* 2012]. In another study, symptoms of hematospermia disappeared in 97.2% [Liu *et al.* 2009].

Transurethral marsupialization of prostatic cyst resulted in complete resolution of symptoms of small volume ejaculation, painful ejaculation, hemospermia and infertility in 78% or improvement in 94% [Dik *et al.* 1996].

The level of evidence of the cited treatments is provided in Table 3.

Table 3. Level of evidence: treatment of ejaculatory dysfunction.

Author/s	Study design	Patients	Drug/s or intervention	Level of evidence*
Nickel *et al.* [2006]	Open-label study, clinical trial	Sexually active men with LUTS and pain/discomfort on ejaculation	Alfuzosin 10 mg once daily treatment for 6 months	2
Ichiyanagi *et al.* [2003]	Case series	Patients with retrograde ejaculation	Amezinium 10 mg orally once a day	3
Magri *et al.* [2011]	Case series	Patients with category II chronic bacterial prostatitis	Azithromycin (500 mg, thrice weekly) combined with a once-daily 500 or 750 mg dose of ciprofloxacin for 4–6 weeks	3
Abdel-Hamid and El Saleh [2011]	Prospective open-label controlled clinical trial	Consecutive men with primary lifelong DE	Bupropion-SR 150 mg/day for 2 months	2
Modell *et al.* [2000]	Single-blind, sequential treatment placebo-controlled	Nondepressed men having nonphysiologic orgasmic delay or inhibition	Bupropion-SR 150 mg/ day, bupropion-SR 300 mg/ day, placebo; sequential treatment order of 3 weeks each	2
Nickel *et al.* [2011]	Prospective randomized placebo-controlled	Men at risk for prostate cancer	Dutasteride 0.5 mg	1
Gat *et al.* [2012]	Retrospective study	Couples with isolated psychogenic anejaculation or SCI	Electroejaculation and ICSI	3
Gilja *et al.* [1994]	Case series	Patients with retrograde ejaculation/loss of emission due to diabetes mellitus or RPLND	Ephedrine sulfate 50 mg once daily or second line imipramine hydrochloride 75 mg once daily for 4 weeks	3
Badawy *et al.* [2012]	Prospective randomized	Patients with refractory hemospermia of idiopathic nature	Finasteride 5 mg *per os* for 3 months	2
Fabre *et al.* [2012]	Prospective, controlled double blind study.	Men with MDD	Gepirone extended release *versus* fluoxetine or placebo	1
Nijman *et al.* [1982]	Case series	Patients with bilateral RPLND who developed absent ejaculation	Imipramine 25 mg twice daily by mouth	3
Arafa and El Tabie [2008]	Case series	Diabetic patients with retrograde ejaculation	Imipramine 25 mg twice/day, pseudoephedrine 120 mg twice/day, or combination of the two drugs; three sequential courses	3
Ochsenkühn *et al.* [1999]	Open, uncontrolled clinical trial	Infertility patients with retrograde ejaculation following RPLND	Imipramine treatment 25 to 50 mg *per os* once daily for 7 days prior to SA	2
Jonas *et al.* [1979]	Case series	Patients with retrograde ejaculation disorder following RPLND	Midodrine	3
Soler *et al.* [2008]	Dose–response Relationship, drug, case series	SCI men on midodrine as part of a treatment for anejaculation, after they failed a baseline PVS	Midodrine	2

(Continued)

Table 3. (Continued)

Author/s	Study design	Patients	Drug/s or intervention	Level of evidence*
Soler *et al.* [2007]	Dose–response Relationship, drug, case series	SCI patients with anejaculation during sexual intercourse and who failed to respond to penile vibratory stimulation	Midodrine 7.5–30 mg orally, 30–120 minutes before a new stimulation	2
Safarinejad [2009]	Prospective randomized placebo-controlled double-blind clinical study	Patients with organic anejaculation but not SCI	Midodrine 7.5–15 mg *per os* per day in a stepwise approach or placebo	1
Kohn and Schill [1994]	Case series	Patients with severe oligozoospermia, hypospermia or partial/ complete retrograde ejaculation	Midodrine intravenous injection of 5–15 mg 30 min before ejaculation	3
Brackett *et al.* [1998]	Meta-analysis	Men with spinal cord injury	Penile vibratory stimulation	2
Saleh *et al.* [2003]	A cohort observational study	Men undergoing infertility evaluation with no history of sexual dysfunction who failed to collect semen by masturbation	Penile vibratory stimulation	3
DeForge *et al.* [2005]	Meta-analysis	SCI men for semen harvesting	Penile vibratory stimulation or electroejaculation	2
Chapelle *et al.* [1988]	Case series	Men with a complete spinal cord section and loss of ejaculation	Physostigmine subcutaneous injection of 0–2 mg (with 40 mg *n*-butylhyoscine) followed by masturbation	3
Nurnberg *et al.* [2003]	Prospective, parallel-group, randomized, double-blind, placebo-controlled trial	Male outpatients with major depression in remission with sexual dysfunction associated with the use of selective and nonselective serotonin reuptake inhibitor antidepressants	Sildenafil or placebo at a flexible dose starting at 50 mg and adjustable to 100 mg before sexual activity for 6 weeks	1
van den Ouden *et al.* [1998]	Pooled analysis	Cases of seminal vesicle cysts combined with ipsilateral renal agenesis	Surgery: Open surgery, aspiration or transurethral deroofing of the cyst	2
Ramadan *et al.* [1985]	Case series	Men with retrograde ejaculation following bladder neck surgery for bilharzial bladder neck obstruction	Surgery: Reconstruction of the bladder neck	3
Song *et al.* [2012]	Case series	Patients with intractable hemospermia	Surgery: Transurethral seminal vesiculoscopy	3
Liu *et al.* [2009]	Case series	Patients with hemospermia	Surgery: Transurethral seminal vesiculoscopy	3
Pace *et al.* [2008]	Case series	Infertile men with ejaculatory duct obstruction	Surgery: TURED	3
Johnson *et al.* [2005]	Case series	Infertile men with symptomatic ejaculatory duct obstruction	Surgery: TURED	3
Eisenberg *et al.* [2008]	Prospective controlled trial	Patients with infertility or ejaculatory pain in whom ejaculatory duct obstruction was suspected and fertile men undergoing vasectomy reversal (controls)	Surgery: TURED	1

(Continued)

Table 3. (Continued)

Author/s	Study design	Patients	Drug/s or intervention	Level of evidence*
Popken *et al.* [1998]	Case series	Patients with azoospermia and ejaculatory duct obstructions	Surgery: TURED	3
Middleton and Urry [1986]	Case series	Infertile patients with retrograde ejaculation	Surgery: Young–Dees type of bladder neck reconstruction	3
Paduch *et al.* [2013]	Meta-analysis	Data from 17 placebo-controlled 12-week trials of tadalafil as needed in patients with ED	Tadalafil (5, 10, 20 mg)	1
Giuliano *et al.* [2013]	A randomized, double-blind, placebo-controlled study	Men with LUTS/BPH	Tadalafil 5 mg once daily for 12 weeks	1
Safarinejad [2006]	Randomized double-blind placebo-controlled trial	Patients with painful ejaculation	Tamsulosin 0.4 mg oral daily or placebo for 6 weeks	1
Barnas *et al.* [2005]	Prospective, non-placebo-controlled clinical trial	Patients with orgasmic pain	Tamsulosin 0.4 mg oral daily for at least 4 weeks	2
Goktas *et al.* [2006]	Prospective open-label noncontrolled study	Men above 50 with LUTS on daily 0.4 mg tamsulosin who developed abnormal ejaculation	Tamsulosin intermittent treatment 0.4 mg once daily every other day	2
Anderson *et al.* [2006]	Case series	Men who had refractory chronic pelvic pain syndrome	Trigger point release/ paradoxical relaxation training	3
Frese *et al.* [2006]	Case series	Patients with orgasmic headache	Triptan therapy	3
Adeniyi *et al.* [2007]	Case series	Men with anorgasmia or delayed ejaculation	Yohimbine flexible dosing	3

*See Abrams *et al.* [2010].
BPH, benign prostatic hyperplasia; DE, delayed ejaculation; ED, erectile dysfunction; ICSI, intracytoplasmic sperm injection; IV, intravenous; LUTS, lower urinary tract syndrome; MDD, major depressive disorder; PVS, penile vibratory stimulation; RPLND, retroperitoneal lymph node dissection; SCI, spinal cord injury; TURED, transurethral resection of the ejaculatory ducts.

Conclusion

Non-PE EjD is more common than previously appreciated. Underestimation of the problem is primarily due to less specific definition of the condition as compared to other sexual dysfunctions as ED or PE.

Consequently, there is little interest in developing effective treatments for this condition. Community-based studies, however, have shown that a significant portion of the male population have EjD. Age is a significant risk factor for EjD. This review of the literature has shown that non-PE EjD is commonly reported in association with certain disease conditions and in relation to medical or surgical therapy. An increased awareness of the large number of patients with LUTS and CP/CPPS brought attention to the commonly associated EjD. There is a significant bothersomeness in many patients because of EjD. Medical treatments of LUTS and of depression are commonly associated with EjD. Furthermore, many surgical procedures for prostatic disease and retroperitoneal and pelvic pathology are causing EjD. The knowledge of the risk factors that contribute to EjD is probably crucial in prevention. However, the treatment of non-PE EjD has been challenging and associated with modest success. As there is a need to improve the quality of life of aging men and for cancer survival patients, EjD is an area that requires more attention. More precise definitions, specific questionnaires, studies that better identify risk factors and

confounding variables and more effective treatment strategies are all needed to achieve this goal.

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Conflict of interest statement

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