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Psychobiological Correlates of Delayed Ejaculation in Male Patients With Sexual Dysfunctions

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ABSTRACT: The pathogenesis of delayed ejaculation (DE) is rather unknown, though the contribution of various psychological, marital, hormonal, and neurological factors has been advocated. In this study we systematically investigated the relative relevance of the aforementioned factors in 1632 men who were seeking medical help for sexual dysfunction. The severity of DE was classified according to Kaplan criteria. Mild and moderate forms of DE (MMDE) recognized different risk factors than the most severe ones (anejaculation or severe DE [ASDE]). ASDE was essentially coupled with the presence of neurological diseases or with the use of serotoninergic drugs. Serotoninergic drugs also significantly increase (by at least 10-fold) the risk for MMDE, which, however, was also coupled with other relational factors (eg, partner's impaired climax, patient's hypoactive sexual desire [HSD]) or intrapsychic factors (eg, stress at work). At multiple regression analysis, some organic pathological conditions (such as psychiatric disorders and hypogonadism) were also associated with MMDE. In particular, hypogonadism retained significance for DE even after adjustment for HSD (adjusted odds ratio = 2.08 [1.11–3.89]; $P < .05$), suggesting other effects of testosterone deficiency on the ejaculatory reflex besides reduced libido. In conclusion, the present study demonstrates that multiple psychobiological determinants are associated with DE, a still obscure condition that substantially impairs psychosexual equilibrium of the couple.

Key words: SIEDY, structured interview, testosterone.
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The ejaculatory reflex consists of a set of neuromuscular events coordinated by serotoninergic (inhibitory) and dopaminergic (facilitatory) neurons in hypothalamic nuclei; peripherally, it consists of 2 separate phases: emission and expulsion (or true ejaculation) (see Jannini and Lenzi, 2005, and Ralph and Wylie, 2005, for reviews). Emission involves the entire male genital tract (MGT) essentially under sympathetic control and allows seminal fluid to reach posterior urethra and closure of the bladder neck. Other purinergic (adenosine triphosphate; Mulryan et al, 2000), peptidergic (oxytocin, endothelin-1; Filippi et al, 2002, 2005), or gaseous (nitric oxide, carbon monoxide; Burnett et al, 1998; Mancina et al, 2005) neuromediators participate in the semen emission process. Emission is not accompanied by any intense sensation; rather, it is just a warning of the growing approach to climax. The second phase, expulsion, consists of the passage of the ejaculate through the urethra and its outer propulsion. The expulsion phase is under parasympathetic and somatic control and requires the contraction of the perineal muscles. It is responsible for the final, vigorous semen-propelling activity and the pleasant sensation that the orgasm reaction can bring.

In andrology practice, concern about ejaculation—and, in particular, about an inappropriately rapid or premature ejaculation (PE)—is quite common. Retarded, inhibited, or delayed ejaculation (DE) is another ejaculatory dysfunction, though less frequently referred than PE. Therefore, until now, only few systematic studies targeted biological and psychological correlates of DE (Rowland et al, 2004; Rowland, 2005). Even the definition of DE is not completely clarified. The *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2000) includes DE (and anorgasmia) under male orgasmic disorders, saying that "after a normal phase of sexual excitement, the man's orgasm is persistently or repeatedly delayed or

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absent.'' DE refers essentially to an overcontrol of the ejaculatory reflex despite a normal genital arousal. Hence, affected men have normal erections but are often unable to ejaculate during intercourse or, in some cases, during manual stimulation. Kaplan (1974) identified different degrees of DE. In the milder form, men are able to ejaculate but only with great effort and after prolonged intercourse. In the intermediate form, men could reach orgasm during sexual intercourse but only with vigorous manual stimulation, though in the presence of the partner. In the most severe form, orgasm can be obtained only with autoerotism, in the absence of the partner, or it cannot be obtained at all (anejaculation). DE should not be confused with the more common condition known as retrograde (or dry) ejaculation (RE). In the latter case, ejaculatory bolus goes back into the bladder instead of out the urethra, owing to incompetence of the bladder neck. Remarkably, in RE, though anterograde ejaculate is absent, the orgasm is still present. Both DE and RE impair couple fertility because of no semen deposition in vagina. However, only DE severely affects a couple's sexual enjoyment because male orgasm is not timely reached or is not reached at all.

The aim of the present study is to investigate the psychobiological factors associated with DE in a large sample of patients referring to an andrology clinic for sexual dysfunction.

Materials and Methods

A consecutive series of 1632 male patients presented for the first time at the Outpatient Clinic for sexual dysfunction of the Andrology Unit of the University of Florence at Careggi Hospital. Patients with mental retardation or who were not fluent in Italian were excluded. In particular, the exclusion of foreign men was because the national version of the Structured Interview on Erectile Dysfunction (SIEDY) has not been completely validated for foreign subjects. Patients with a history of radical prostatectomy, retroperitoneal surgery, or other causes of RE were also excluded from the analysis because RE might overlap with DE and mask its true psychobiological determinants.

The enrolled patients underwent the usual diagnostic protocol applied to newly referred subjects at the andrology Outpatient Clinic. All the data provided were collected as part of the routine clinical procedure. Patients were interviewed before the beginning of any treatment and before any specific diagnostic procedures by using the SIEDY (Petrone et al, 2003), which is a 13-item interview composed of 3 scales that identify and quantify components concurring to sexual dysfunctions. Scale 1 deals with organic disorders, scale 2 deals with disturbances in relationship with partner, and scale 3 deals with psychological traits. DE was defined as ''slowness to ejaculate'' (as reported by the patient by using a stop watch method) according to previously described criteria (Kaplan, 1974; Apfelbaum, 2005). In particular, severity of DE was categorized on a 3-point scale with a standard question (''In the last 3 months is it difficult to ejaculate during sexual intercourse?'') and rating: 0 = no DE, 1 = mild or moderate DE (MMDE), and 2 = anejaculation or severe DE (ASDE). MMDE was diagnosed if ejaculation and climax were still possible but only with great effort and after prolonged intercourse (mild DE) or possible only with autoerotism, though in the presence of the partner but not during coitus (moderate DE). ASDE was diagnosed if orgasm and ejaculation could not be obtained at all (anejaculation) or could be obtained but only with autoerotism conducted in the absence of the partner (severe DE). Stress at work was assessed with question 3 of the SIEDY (''Do you ever think of your job out of the working hours?''), the patient's partner's libido was assessed with question 8 (''Does your partner have more or less desire to make love than in the past?''), the partner's climax was assessed with question 9 (''Does your partner reach climax?''), and the patient's hypoactive sexual desire (HSD) was assessed with question 14 (''Did you have more or less desire to make love in the last 3 months?''). Ratings were 0 = no, 1 = mild, 2 = moderate, and 3 = severe problem. The presence of neurological diseases was assessed with question 4B of SIEDY.

Patients were asked to specify any current pharmacological treatment in the past 3 months. Serotoninergic drugs included citalopram, paroxetine, sertraline, fluoxetine, fluvoxamine, escitalopram, venlafaxine, and chlorimipramine. Antidopaminergic drugs included domperidone, fluphenazine, perphenazine, promazine, risperidone, haloperidol, L-sulpiride, metoclopramide, clopixol, cisapride, and clebopride.

All patients underwent a complete general and andrological physical examination with measurement of blood pressure (mean of 3 measurements 5 minutes apart in sitting position with a standard sphygmomanometer), height, weight, and testis volume (Prader orchidometer); penis evaluation; and digital rectal examination. Blood samples were drawn in the morning after an overnight fast for determination of blood glucose by the glucose oxidase method (Aeroset Abbott, Rome, Italy), total cholesterol, high-density lipoprotein cholesterol and triglyceride by the automated enzymatic colorimetric method (Aeroset Abbott), glycated hemoglobin (HbA1c) by the high-pressure liquid chromatography method (Menarini Diagnostics, Florence, Italy) with upper limit of the normal range of 5.9%, total testosterone, prolactin (PRL), follicle-stimulating hormone, luteinizing hormone, thyrotropin, and prostate-specific antigen by the electrochemiluminescent method (Modular Roche, Milan, Italy). Hypogonadism was defined when circulating total testosterone (T) was below 10.4 nmol/L (300 ng/dL; lower limit of our laboratory normal range), and hyperprolactinemia was defined when prolactin was higher than 288 mU/L (14 ng/dL; upper limit of our laboratory normal range).

Data were expressed as mean ± SD when normally distributed and as median (quartiles) for parameters with nonnormal distribution unless otherwise specified. Differences

*Sociodemographic characteristics of the sample**

	No DE	MMDE	ASDE	*P*
Age, y (mean ± SD)	51.5 ± 13	50 ± 12.5	48.7 ± 13	NS
Marital status, %				
Stable relationship	88.5	87.1	89.5	NS
No stable relationship	11.5	12.9	10.5	NS
Education, %				
Not graduated	44.4	40	22.2	NS
Graduated (high school or university)	55.6	60	77.8	NS
Employment, %				
Retired or unemployed	39.4	39.2	42.1	NS
Employed	59.6	60.8	57.9	NS

* DE indicates delayed ejaculation; MMDE, mild or moderate DE; ASDE, anejaculation or severe DE; and NS, not significant.

between more than 2 groups were assessed with 1-way analysis of variance or Kruskal-Wallis test whenever appropriate. Relative risk (RR) and 95% confidence interval for DE were derived from cross-tab analysis. Chi-square test was used for comparison of categorical parameters. Stepwise multiple logistic regressions were applied for multivariate analysis whenever appropriate.

All statistical analysis was performed on SPSS for Windows version 12.1 (SPSS Inc, Chicago, Ill).

Results

Among the 1632 patients studied, 82 (5.0%) reported DE; of those, 62 reported MMDE and 20 reported ASDE. Patients with any type of DE did not show any significant difference in sociodemographic characteristics, including age, when compared with the rest of the sample (Table).

Patients with any type of DE have a higher score of erectile function (as assessed by question 1A of the SIEDY appendix A) than do the rest of the sample (1.29 ± 0.16 vs 0.97 ± 0.03; $P < .05$).

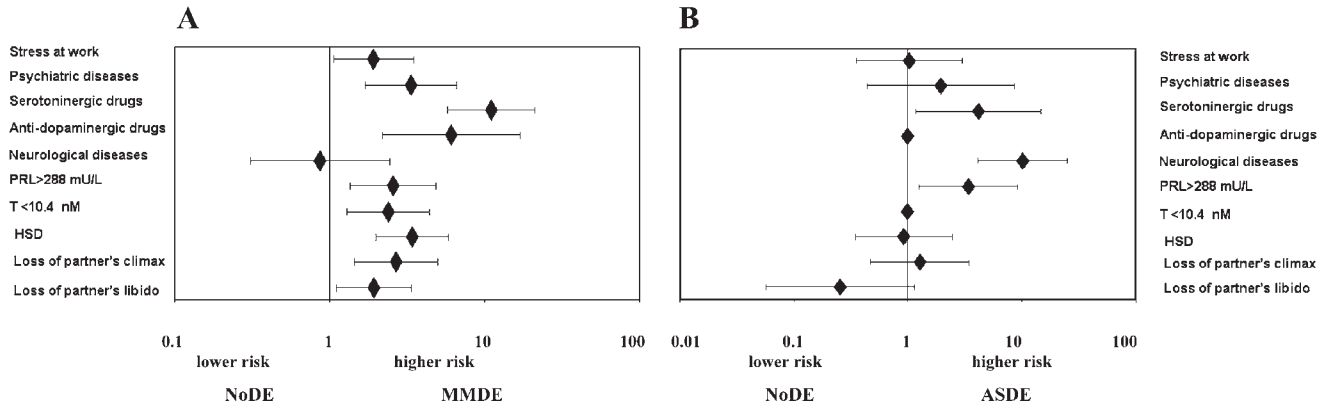
The Figure reports RR for MMDE and ASDE associated with different psychological, relational, and physiological parameters. The presence of stress at work (as explored by question 3 of the SIEDY) and serious psychiatric diseases at anamnesis, such as major depression, delusional disorders, or schizophrenia, were significantly related to MMDE but not to ASDE. At logistic regression analysis, considering stress at work and psychiatric diseases as putative predictor of MMDE, both factors resulted independent contributors to MMDE (adjusted odds ratio [OR] = 2.11 [1.16–3.84]; $P < .05$; and adjusted OR = 4.52 [2.02–9.27]; $P < .0001$; respectively).

The use of serotoninergic drugs significantly contributed to both ASDE and MMDE. The latter association retained significance even after adjustment for psychiatric diseases (adjusted OR = 10.66 [4.70–24.18]; $P < .0001$). The use of antidopaminergic medicaments was associated with MMDE only, but such a relationship was lost at logistic regression analysis after adjustment for psychiatric diseases (data not shown).

Considering other organic factors, the presence of neurological diseases (as explored by question 4B of the SIEDY) significantly contributed to ASDE but not to MMDE. In particular, 9 of 20 patients with ASDE reported a neurological disease (4 multiple sclerosis, 3 traumatic spinal cord injury, 1 diabetic neuropathy, 1 idiopathic tremor). At logistic regression analysis, considering neurological diseases and use of serotoninergic drugs as putative factors of ASDE, both parameters were significantly related to ASDE (adjusted OR = 4.69 [1.27–17.40]; $P < .05$; and adjusted OR = 1.98 [1.45–2.70]; $P < .0001$; respectively).

Among hormonal parameters, the presence of hyperprolactinemia (PRL >288 mU/L) contributed to both MMDE and ASDE; however, these associations were lost after adjustment for confounding factors such as the use of antidopaminergic or serotoninergic drugs (data not shown). A reduced testosterone plasma level (T <10.4 nmol/L) was significantly associated with MMDE but not with ASDE. Furthermore, testis volume was lower ($P < .001$) in MMDE patients (17.9 ± 0.6 mL) but not in ASDE patients (19 ± 1.4 mL) than in the rest of the sample (20 ± 0.1 mL). No other biochemical and hormonal parameters significantly contributed to DE (data not shown).

Finally, considering psychorelational factors, a patient's HSD (question 14 of the SIEDY), a partner's impaired climax (question 9), and a partner's decreased libido (question 8) all significantly contributed to MMDE but not to ASDE. At logistic regression analysis, considering HSD, loss of partner's climax, and loss of partner's libido as putative factors of MMDE, only HSD and partner's impaired climax retained significance (adjusted OR = 2.93 [1.62–5.31] and adjusted OR = 2.49 [1.26–4.91], respectively; both $P < .01$). Furthermore, at multiple regression analysis both HSD and hypogonadism resulted in independent



Relative risk for mild or moderated delayed ejaculation **(A)** and anejaculation or severe delayed ejaculation **(B)** associated with different psychological, relational, and physiological parameters.

determinants of MMDE (adjusted OR = 3.00 [1.67–5.39] and adjusted OR = 2.08 [1.11–3.89]; both $P < .05$).

Patients with MMDE showed higher SIEDY scale 2 and 3 scores when compared with the rest of the sample (2.8 ± 0.5 vs 1.9 ± 0.1 for scale 2 and 5.9 ± 0.3 vs 5.2 ± 0.1 for scale 3; both $P < .05$), whereas no difference was observed regarding scale 1 score (4.2 ± 0.4 vs 3.7 ± 0.1; P value not significant). On the other hand, patients with ASDE did not show any significant difference in SIEDY scores in comparison with the rest of the sample (data not shown).

Discussion

A neurobiological approach to DE is greatly warranted (Waldinger and Schweitzer, 2005), yet the most common cause of DE is still considered psychological, essentially because of an overcontrol of sexual enjoyment often coupled with fear of failure, which is associated with the belief that unresolved conflicts with conscious and unconscious worries (eg, religious, marital, or intrapsychic) might impair ejaculation. Recent studies indicate that psychogenic DE is essentially characterized by an uncoupling in sexual arousal between a decreased subjective reaction and a preserved genital reaction (Rowland et al, 2004; Rowland, 2005). The present study partially confirms these assumptions. In fact, several relational and intrapsychic factors resulted in an association with DE, at least in its milder form (MMDE). Also, a patient's HSD and partner's impaired climax significantly and independently contributed to MMDE, even after adjusting for confounding factors such as hypogonadism. This is interesting because a partner's adequate climax reaction during intercourse is reinforcing the patient's sexual competence and therefore the patient's sexual desire (Corona et al, 2005), transforming a merely vasocongestive event (the penile erection per se) into a complete sexual act. Hence, both the patient's reduced sexual drive and the lack of partner's orgasmic reaction might contribute to the hypoexcitability of MMDE subjects and to the previously described uncoupling between genital and subjective arousal (Rowland, 2005). In addition, we found that life stressors (eg, stress at work) also significantly contribute to MMDE, most probably by distracting the subject from pleasant emotions derived from attractiveness of the intercourse and by freezing sexual fantasies. Overall, the higher scores in the SIEDY's scale 2 and 3 (exploring the relational and intrapsychic domains, respectively) obtained in patients with MMDE further corroborate these notions. It should also be considered that DE is defined on the basis of the subjective perception of inadequately long duration of the sexual act, which, in its milder forms, can be influenced by relational factors. In fact, the perception of the partner's reaction to sexual intercourse (eg, partner's anorgasmia, or reduced sexual satisfaction) could affect the determination of a ''proper'' duration of the sexual act.

In this study, we found that in addition to distorted cognitive and behavioral aspects of sexual life there are also some organic factors associated with MMDE. Among these, the presence of psychiatric disturbances and the use of selective serotonin uptake inhibitors (SSRIs) and other serotoninergic drugs play an important role. SSRIs are antidepressant drugs, often with anxiolytic properties, used to treat several psychiatric disorders. Interestingly, both conditions (ie, the presence of a psychiatric disease and the use one of their more common treatment, serotoninergic drugs) are independently and significantly associated with MMDE, though to a different extent. A 10-fold increase in risk of MMDE is indeed associated with serotoninergic drug

treatment. It is well known that SSRIs and some tricyclic antidepressants quite often induce a variable delay in the ejaculatory reflex by increasing central serotoninergic transmission (Montgomery et al, 2005; Ralph and Wylie, 2005), therefore representing the most often used therapy for PE (Waldinger et al, 2004; Waldinger, 2005). Because PE and depression are very common—depression will soon become the second most disabling condition worldwide (Murray and Lopez, 1997)—the use of serotoninergic drugs will probably increase in the future. Hence, the frequency of DE will probably also increase, though general practitioners do not frequently recognize its link with serotoninergic drugs (Parelman, 2003). In the present study, we demonstrated that use of serotoninergic drugs is associated not only with the mildest forms of DE but also with the most severe forms, such as anejaculation. In addition, in a previous study we reported that serotoninergic drug treatment was also associated with a reduced sexual desire (Corona et al, 2005), which, in turn, as reported now, can contribute to DE. This study confirms previous evidence (see Rosen et al, 1999, and Montgomery et al, 2005, for reviews) that serotoninergic drugs may induce various degrees of impaired ejaculation and sexual desire, which should be promptly recognized to reassure the patient of the real nature of his sexual dysfunction and to tailor pharmacological treatment to the individual patient's needs. The present study also confirms that DE might also be caused by several neurological diseases that impair the peripheral ejaculatory reflex by disrupting the sympathetic or somatic innervations to the MGT. Therefore, both emission and expulsion might be affected. However, if only sympathetic nerves are damaged, as in retroperitoneal lymph node dissection during extirpative surgery, the climax reaction can be preserved despite a lack of anterograde ejaculate (Vale, 1999). In this latter condition, DE is more similar to and difficult to distinguish from RE. For this reason, patients who underwent extirpative pelvic surgery were excluded from the analysis. It is noteworthy that, in our sample, neurological diseases are associated with severe rather than moderate DE.

An original finding of the present study is the significant association between MMDE and reduced androgenicity (reduced testosterone plasma levels and testis volume). In particular, hypogonadism doubles the RR for DE, even after adjustment for possible confounding factors such as reduced libido. The association between hypogonadism and DE, though anecdotically reported (Waldinger and Schweitzer, 2005), has never been demonstrated. How hypogonadism might influence the ejaculatory reflex, besides decreasing sexual desire, is rather difficult to explain. At a peripheral level, motility of the MGT is under negative influence of nitrergic transmission. In fact, mice lacking the gene for endothelial nitric oxide synthase (eNOS) show ejaculatory abnormalities characterized by an increased propensity to ejaculate on a reduced stimulus (Kriegsfeld et al, 1999). In addition, in several clinical studies, prolonging nitric oxide (NO) activity by blocking phosphodiesterase 5 (PDE5) resulted in a variable increase in ejaculatory latency (Abdel-Hamid et al, 2001; Salonia et al, 2002; Chen et al, 2003; Ekmekcioglu et al, 2005; McMahon et al, 2005). We originally demonstrated that PDE5 is expressed in several portions of the human MGT (Morelli et al, 2004) and is androgen dependent (Mancina et al, 2005). In particular, in an experimental model of hypogonadotropic hypogonadism, we found that in vas deferens NO degradation was reduced and PDE5 was less expressed and active (Mancina et al, 2005). Hence, it is possible that hypogonadism-associated DE is coupled with an increased inhibitory nitrergic tone on smooth muscle cells of MGT.

It is interesting to note that hypogonadism and other concurrent conditions that were associated with MMDE did not show any association with ASDE, except SSRI. It can be specified that neurological disorders that are often present in patients with ASDE have such a great impact in DE that the effect of others possible risk factors becomes irrelevant in more severe forms of DE.

It should be considered that this study was performed on patients referring to an andrology clinic for sexual dysfunction. For this reason, the sample cannot be considered representative of general male population or of subjects referring to general practices for sexual problems. However, there is no reason to believe that the relationship between ejaculation and gonadal function observed in the present study cannot be extended to a broader population.

In conclusion, several biological, intrapsychic, marital, and pharmacological conditions might negatively affect the ejaculatory process, partially or completely impairing it and therefore causing varying degrees of derangement in sexual intimacy, even disrupting the psychosexual equilibrium of the couple.

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References

Abdel-Hamid IA, El Naggar EA, El Gilany AH. Assessment of as needed use of pharmacotherapy and the pause-squeeze technique in premature ejaculation. *Int J Impot Res.* 2001;13:41–45.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed, text revision ed. Washington, DC: American Psychiatric Association; 2000.

Apfelbaum B. Retarded ejaculation. In: Leiblum SR, Rosen RC, eds. *Principles and Practice of Sex Therapy.* 3rd ed. New York, NY: Guilford Press; 2005:205–241.

Burnett AL, Johns DG, Kriegsfeld LJ, Klein SL, Calvin DC, Demas GE, Schramm LP, Tonegawa S, Nelson RJ, Snyder SH, Poss KD. Ejaculatory abnormalities in mice with targeted disruption of the gene for heme oxygenase-2. *Nat Med*. 1998;4:84–87.

Chen J, Mabjeesh NJ, Matzkin H, Greenstein A. Efficacy of sildenafil as adjuvant therapy to selective serotonin reuptake inhibitor in alleviating premature ejaculation. *Urology*. 2003;61:197–200.

Corona G, Mannucci E, Petrone L, Giommi R, Mansani R, Fei L, Forti G, Maggi M. Psycho-biological correlates of hypoactive sexual desire in patients with erectile dysfunction. *Int J Impot Res*. 2004;16:275–281.

Corona G, Petrone L, Mannucci L, Ricca V, Balercia G, Giommi R, Forti G, Maggi M. The impotent couple: low desire. *Int J Androl*. 2005;28(suppl 2):81–85.

Ekmekcioglu O, Inci M, Demirci D, Tatlisen A. Effects of sildenafil citrate on ejaculation latency, detumescence time, and refractory period: placebo-controlled, double-blind, crossover laboratory setting study. *Urology*. 2005;65:347–352.

Filippi S, Morelli A, Vignozzi L, Vannelli GB, Marini M, Ferruzzi P, Mancina R, Crescioli C, Mondaini N, Forti G, Ledda F, Maggi M. Oxytocin mediates the estrogen-dependent contractile activity of endothelin-1 in human and rabbit epididymis. *Endocrinology*. 2005;146:3506–3517.

Filippi S, Vannelli GB, Granchi S, Luconi M, Crescioli C, Mancina R, Natali A, Brocchi S, Vignozzi L, Bencini E, Noci I, Ledda F, Forti G, Maggi M. Identification, localization and functional activity of oxytocin receptors in epididymis. *Mol Cell Endocrinol*. 2002;193: 89–100.

Jannini EA, Lenzi A. Ejaculatory disorders: epidemiology and current approaches to definition, classification and subtyping. *World J Urol*. 2005;23:68–75.

Kaplan HS. *The New Sex Therapy*. London, United Kingdom: Bailliè Tindall; 1974.

Kriegsfeld LJ, Demas GE, Huang PL, Burnett AL, Nelson RJ. Ejaculatory abnormalities in mice lacking the gene for endothelial nitric oxide synthase (eNOS-/-). *Physiol Behav*. 1999;67:561–566.

Mancina R, Filippi S, Marini M, Morelli A, Vignozzi L, Salonia A, Montorsi F, Mondaini N, Vannelli GB, Donati S, Lotti F, Forti G, Maggi M. Expression and functional activity of phosphodiesterase type 5 in human and rabbit vas deferens. *Mol Hum Reprod*. 2005;11:107–115.

McMahon CG, Stuckey BGA, Andersen M, Purvis K, Koppiker N, Haughie S, Boolell M. Efficacy of sildenafil citrate (Viagra) in men with premature ejaculation. *J Sex Med*. 2005;2:368–375.

Montgomery S, Doyle JJ, Stern L, McBurney CR. Economic considerations in the prescribing of third-generation antidepressants. *Pharmacoeconomics*. 2005;23:477–491.

Morelli A, Filippi S, Mancina R, Luconi M, Vignozzi L, Marini M, Orlando C, Vannelli GB, Aversa A, Natali A, Forti G, Giorgi M, Jannini EA, Ledda F, Maggi M. Androgens regulate phosphodiesterase type 5 expression and functional activity in corpora cavernosal. *Endocrinology*. 2004;145:2253–2263.

Mulryan K, Gitterman DP, Lewis CJ, Vial C, Leckie BJ, Cobb AL, Brown JE, Conley EC, Buell G, Pritchard CA, Evans RJ. Reduced vas deferens contraction and male infertility in mice lacking P2X1 receptors. *Nature*. 2000;403:86–89.

Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet*. 1997;349:1498–1504.

Parelman MA. Regarding ejaculation, delayed and otherwise. *J Androl*. 2003;24:496.

Petrone L, Mannucci E, Corona G, Bartolini M, Forti G, Giommi R, Maggi M. Structured Interview on Erectile Dysfunction (SIEDY): a new, multidimensional instrument for quantification of pathogenetic issues on erectile dysfunction. *Int J Impot Res*. 2003;15: 210–220.

Ralph DJ, Wylie KR. Ejaculatory disorders and sexual function. *BJU Int*. 2005;95:1181–1186.

Rosen RC, Lane RM, Menza M. Effects of SSRIs on sexual function: a critical review. *J Clin Psychopharmacol*. 1999;19:67–85.

Rowland DL. Psychophysiology of ejaculatory function and dysfunction. *World J Urol*. 2005;23:82–88.

Rowland DL, Keeney C, Slob AK. Sexual response in men with inhibited or retarded ejaculation. *Int J Impot Res*. 2004;16:270–274.

Salonia A, Maga T, Colombo R, Scattoni V, Briganti A, Cestari A, Guazzoni G, Rigatti P, Montorsi F. A prospective study comparing paroxetine alone versus paroxetine plus sildenafil in patients with premature ejaculation. *J Urol*. 2002;168:2486–2489.

Vale J. Ejaculatory dysfunction. *BJU Int*. 1999;83:557–563.

Waldinger MD. Lifelong premature ejaculation: definition, serotonergic neurotransmission and drug treatment. *World J Urol*. 2005; 23:102–108.

Waldinger MD, Schweitzer DH. Retarded ejaculation in men: an overview of psychological and neurobiological insights. *World J Urol*. 2005;23:76–81.

Waldinger MD, Zwinderman AH, Schweitzer DH, Olivier B. Relevance of methodological design for the interpretation of efficacy of drug treatment of premature ejaculation: a systematic review and meta-analysis. *Int J Impot Res*. 2004;16:369–381.