

Emmanuele A. Jannini · Chris G. McMahon  
Marcel D. Waldinger *Editors*

# Premature Ejaculation

From Etiology to  
Diagnosis  
and Treatment

 Springer

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*To our wives, Susanna, Olivia, and Trudy  
For their support, encouragement, patience,  
and love*

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## Foreword

I was asked to write the foreword for *Premature Ejaculation* as the International Society for Sexual Medicine (ISSM) President and an expert on Sexual Medicine, but the main reason that made me accept this honor is my knowledge of the three leading authors of this important publication. I witnessed not only their vast publication trajectory but most importantly the intensive participation and commitment of Emmanuele A. Jannini, Chris McMahon, and Marcel D. Waldinger during all ISSM's activities on Premature Ejaculation, including the creation of the contemporary definition of lifelong premature ejaculation, the meeting on acquired premature ejaculation, the ISSM's Guidelines, and the International Consultation on Sexual Medicine.

This book is a landmark publication for any specialist on Sexual Medicine and clinicians with a special interest on Premature Ejaculation. The reader must understand that this is a quite young field and the approach to this condition is still pivotal, so much of the information included is new and provocative. The authors had chosen very carefully the worldwide experts in this condition making sure that every aspect is covered, from the history, anatomy, physiology, classification, pathophysiology, risk factors, evaluation, and treatment for both lifelong and acquired Premature Ejaculation.

The reader will benefit from this state-of-the-art book, which is a comprehensive review of this young and underexplored condition with a practical and didactic approach with a strong international flavor.

It is an honor for me to recommend this unique book to the Sexual Medicine specialist and those clinicians with a special interest on the field.

University of Buenos Aires, Argentina

Edgardo Becher

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## Preface

Premature ejaculation (PE) is a common—albeit only recently recognized—sexual symptom. However, it is still far from being a common reason to consult a doctor. The various reasons for this are discussed in this book.

An evidence-based definition of lifelong PE has been elaborated by the International Society for Sexual Medicine. On the other side of the coin, acquired PE is still awaiting an appropriate definition. Despite the large and ever-growing production of clinical reports and basic findings, some doctors still believe that the etiology of PE is unknown. In addition to the reluctance of sufferers to seek medical advice, then, the idea that “no etiology = no diagnosis” is another reason that PE is not a high priority for doctors.

There is yet another level of complication. While PE is objectively considered a male symptom, its perception is almost entirely related to the partner’s subjective pleasure. For this reason, I define couples where the man ejaculates earlier than desired by his partner as “asynchronous”. In such couples, sex is still possible, but the quality of the sexual relationship is lost. Alongside this is the fact that most couples still perceive PE as a psychological problem. I am afraid that all too many doctors share this opinion with their non-patients. Consequently, while doctors may feel required to treat the sexual dysfunction, they are not necessarily willing or able to intervene to improve the quality of the sexual relationship.

The result of all these intertwining factors is that some regulatory agencies still believe that a drug for PE is “just” a lifestyle treatment, thus demonstrating their profound ignorance of the tragic impact that PE can have on both quality of life and general health. This unhelpful attitude means that treating PE can itself be problematic. There is as yet just one approved oral treatment, dapoxetine, but even that is currently approved in relatively few countries. The pharmacological treatment of PE is thus often off-label.

The aim of this first textbook on PE, which I am honored to be editing with two giants in the field—Chris McMahon and Marcel D. Waldinger—is... politically incorrect. My aim is, in fact, to medicalize the symptom of PE! I am a molecular biologist with experience as an endocrinologist and andrologist, now holding the position of Professor of Sexology at the Faculty of Psychology in an Italian university. Given this background, I could not possibly be against a holistic perspective considering the failures of the body alongside the intrapsychological and

relational factors causing a loss of control over ejaculation. However, the medical world has spent more than a century looking for possible psychological causes of PE. I believe it is now time to consider it as a symptom caused by various organic and nonorganic risk factors (the term preferred in this book, over the more common “etiologies”) deserving medical care and attention. Premature ejaculation is, in fact, a true medical need, a multidimensional disorder comprising a physical dysfunction with psychosocial components. Its medicalization does not exclude the role of psychological factors in its pathogenesis.

The international team of authors we have chosen to collaborate with us in this reference book are the scientists and opinion leaders who have produced data in the field of PE. Their acknowledged authority is demonstrated by the fact that virtually all published articles dealing with this topic include their work in the bibliography.

In conclusion, readers of this book will discover the state of the art of basic research into PE and its taxonomy, epidemiology, etiology, diagnosis, treatment, and follow-up. This is a reference book, but it is also a work-in-progress. The field is, in fact, still in its infancy, but it is rapidly growing, expanding, and changing. I hope that the contents of this book may prove fertile ground for cultivating scientific thought, to the benefit of our real interest: the sexual health of couples.

Emmanuele A. Jannini



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Chris G. McMahon

As long as man has breathed, his fascination, pursuit and quest for the perfect sexual experience have remained one of his principal *raison d'être*. After thousands of years, millions of words and pictures, and billions of attempts, he still often finds the goal largely unobtainable. Until recently, our understanding of premature ejaculation (PE) was an eclectic mix and homogenization of ancient historical and culturally diverse influences. In many ancient cultures and times, there were many references to the importance of ejaculation and the art of love and sexuality.

The Bible states that semen was intended to be deposited only in vaginas and mainly for the purpose of procreation. Men were told: *Be fruitful, and multiply and replenish the earth* (Genesis 2). The punishment for not obeying God's Law was death, as Onan was to discover to his peril. Onan's father, Judah, forced him to marry his brother's widow Tamar, whom he did not love. Onan discovered that during coitus he could not ejaculate into Tamar: *he spilled it [semen] on the ground, and the thing which he did displeased the Lord: wherefore He slew him* (Genesis 38).

The Indian god Shiva, who has the power to destroy and create, is often represented with an erect phallus, a symbol of power and fertility. Because Shiva always holds back his seed, the "lingam" (penis) remains erect, as a potential creator [1]. Semen is considered to be a precious substance in Indian cultures and many myths have been created around it [2]. Atharva-veda, one of the ancient Indian religious books mentions that 100 drops of blood are required to make one drop of semen. Loss of semen was considered then (and still is) as a loss of

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strength. Male weakness caused by a loss of semen is called “mardana-kamzori” [2]; this and PE is collectively known as “Dhat syndrome” [3].

The *Kama Sutra* was written between the first and fourth centuries AD by Mallanaga, a bachelor belonging to the Vatsyayana sect. It is best described as the lifestyle book of its era which was devoted to personal discipline and offered a range of knowledge that the reader may acquire, to find (and keep) a partner. It gave suggestions on many subjects, from how to freshen the breath by chewing betel leaves to a range of sexual positions that *seems often to be addressed to a contortionist* [4]. Although initially published in Britain in 1876, it was considered by Victorian England to be far too lewd and was not officially available until 1963.

Part Two of the *Kama Sutra* deals exclusively with sexual intercourse and considers different lengths of time to ejaculation as having various merits. The author believed that *The first time of union the passion of the man is intense, but on subsequent union the reverse of this is true*. He observed that, *if a male be long-timed, the female loves him the more, but if he be short timed, she is dissatisfied with him*. He concludes that *males when engaged in coition, cease of themselves after emission and are satisfied, but it is not so with females*. This is a clear reference to the fact that PE causes bother, frustration, and relationship friction.

Chinese sexology can be traced back many dynasties. The Tang Dynasty (618–907 AD) was considered to be sexually free, and during this period sex was positively encouraged as the means to good health. Early Taoist philosophers saw frequent and long-lasting sex as promoting balance between the Yin (negative, dark, feminine) and Yang (positive, bright, masculine). Sex was considered the very essence of nature and harmony. It was also thought that to ejaculate (“chi”) made the man weak for the next sexual encounter. Delaying or suppressing ejaculation was felt to be beneficial, and a disciplined approach to delaying ejaculation became popular. In the Ming Dynasty (1368–1644), attitudes to sex became more restricted, and by the Qing Dynasty (1644–1911), sexuality was repressed and regulated [5].

In sixteenth century Tunisia, Sheikh Nefzawi, adviser to the Grand Vizier of Tunis, wrote a book on the art of love called *The Perfumed Garden*, the Islamic version of the *Kama Sutra*. He makes specific reference to PE, but offers no remedy for the problem. *When the mutual operation is performed, a lively combat ensues between the two actors who frolic and kiss and intertwine. Man in the pride of his strength, works like a pestle, and the woman, with lascivious undulations, comes artfully to his aid. Soon all too soon the ejaculation comes!*

Erotic life flourished at all levels of society in ancient Egypt [6]. Life, the afterlife, fertility, and creation are important parts of Egyptian history, and representations of such can be seen on many temple carvings and paintings. Of particular interest were the remedies that the ancient Egyptians considered useful for various sexual ailments and problems. The lotus flower was an important icon in ancient Egypt [7]. Magical properties have been associated with the lotus flower since it arose at the beginning of time from the waters of Nun (the original waters) [1]. It was immortalized in modern times when lotus and corn flowers were discovered in the coffin of Tut-Ankh-Amon. At the first ray of the Sun, the lotus

flower opens up and releases a hyacinth-like scent. When an Egyptian buried his nose in a lotus flower and kept it there for a while, the effect on him may have been considerable, and the scent may have been sufficient to achieve an alteration in consciousness [8]. This may have had the effect of reducing anxiety and possibly delaying ejaculation, although there is no specific mention of PE.

Recent neurobiological, clinical, epidemiological, and observational research has provided new insights into the neuroanatomy and neurobiology of ejaculation and the dimensions, epidemiology, psychosocial and relational effects, and pathophysiology of premature ejaculation by both clinicians and the pharmaceutical industry [9–14]. Our understanding of PE has evolved from the initial premise that PE was a psychosexual disorder to a new understanding. We now believe that ejaculatory latency is a genetically determined biological variable and that some men are born with a genetic propensity to ejaculate rapidly. In parallel with this new understanding, the way we classify, define, evaluate, diagnose, and treat PE has undergone a paradigm change.

The first contemporary multivariate evidence-based definition of lifelong PE was developed in 2008 by a panel of international experts, and characterizes lifelong PE as *...ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, the inability to delay ejaculation on all or nearly all vaginal penetrations, and the presence of negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy*. This definition is limited to heterosexual men engaging in vaginal intercourse. There is insufficient published evidence to propose an evidenced-based definition of acquired PE.

The PE treatment paradigm, previously limited to behavioral psychotherapy, has now expanded to include drug treatment [15, 16]. Animal and human sexual psychopharmacological studies have demonstrated that serotonin and 5-HT receptors are involved in ejaculation and confirm a role for selective serotonin reuptake inhibitors (SSRIs) in the treatment of PE [17–20]. Multiple well-controlled evidence-based studies have demonstrated the efficacy and safety of daily or on-demand administration of SSRIs in delaying ejaculation, confirming their role as first-line agents for the treatment of lifelong and acquired PE [21].

This textbook explores the conundrum of premature ejaculation and in doing so attempts to demystify the epidemiology, pathogenesis and etiology, dimensions, diagnosis, and management of this common sexual complaint.

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Marcel D. Waldinger

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## 2.1 Introduction

The history of premature ejaculation (PE) is a history of contrasting hypotheses, controversial debates among medical specialists and psychologists, many opinions, and ignorant and embarrassed patients, but it is also the history of independently thinking clinicians, and pioneering clinicians and neuroscientists, who all together and throughout the years contributed to a better insight in a syndrome that for a very long time has been neglected in medical sexology and general medicine.

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## 2.2 Historical Development of Premature Ejaculation

The phenomenon of PE is probably as old as humanity. Writings as early as Greek antiquity made mention of an *ejaculatio ante portas* [1]. But it was not until the late 19th century that the experience was described in the medical literature and conceived as a disorder [2].

In 1887, Gross [3] described what is presumably the first case of rapid ejaculation in the medical literature. A report of the German psychiatrist Krafft-Ebing [4] followed in 1901 and referred to an abnormally fast ejaculation but did not yet use the word “*praecox*” or “*premature*”.

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**Table 2.1** Major historical views on diagnosis, etiology, pathogenesis, and advocated treatment of PE

Authors	Postulated etiology and pathogenesis of PE	Advocated treatment of PE
Karl Abraham (1917)	PE is a neurosis, linked to unconscious conflicts	Psycho-analysis and psycho-analytic therapy
Bernhard Schapiro (1943)	PE is a psychosomatic disorder, linked to a weak genital system There are two PE subtypes (1943)	Topical anesthetic creams
William Masters and Virginia Johnson (1970)	PE is a behavioral disorder, linked to self-learned behavior	Behavioral treatment (squeeze technique)
Marcel Waldinger (1998)	Lifelong PE is a neurobiological-genetic disorder, linked to central serotonin neurotransmission dysfunctions There are four PE subtypes (2006)	Selective serotonin reuptake inhibitors (SSRIs)

Waldinger [5] distinguished four periods in the course of the past century, and three partly contrasting approaches—a somatic (urological or physiological), a psychological (psychoanalytic or behavioristic), and a neurobiological-genetic approach resulting in four major historical views (Table 2.1).

## 2.3 Chronological Classification

### 2.3.1 The First Period (1917–1950): Neurosis and Psychosomatic Disorder

In 1917 Karl Abraham [6] described rapid ejaculation which he called *ejaculatio praecox*. During the first decades of the 20th century, PE was viewed, especially in psychoanalytic theory, as a *neurosis* linked to unconscious conflicts [6, 7]. Treatment consisted of classical psychoanalysis. The somatic approach in those years was primarily urological and blamed PE on hyperesthesia of the glans penis, a too short frenulum of the foreskin and on changes in the posterior section of the urethra, at the verumontanum in particular. Advocated treatment ranged from prescription of an anaesthetizing ointment to incision of the frenulum, application of solutions of silver nitrate, or total destruction of the verumontanum by electrocautery. Such urological causes, however, were thought to be present in no more than 5 % of the cases [8].

In 1943, the pure psychological view of Karl Abraham was challenged by Bernhard Schapiro, a German endocrinologist, who argued that PE is a *psychosomatic disturbance* caused by a combination of a psychologically overanxious

constitution and “an inferior ejaculatory apparatus as a point of least resistance for emotional pressure” [8]. Schapiro described two types of premature ejaculation. Type B (the sexually hypertonic or hypererotic type), representing a continuously present tendency to ejaculate rapidly from the first act of intercourse, and Type A (the hypotonic type) leading to erectile dysfunction. Many years later both types became distinguished as the primary (lifelong) and secondary (acquired) form of premature ejaculation [9]. In those years, patients of Type A, were believed to respond well to nerve tonics, testosterone, prolonged sexual rest, sports, hydrotherapy, and electrotherapy. In contrast, patients of Type B were treated by sedatives. A good combination at the time was Camphora monobornata, belladonna, strypticine, and papaverine. Although Bernhard Schapiro has never suggested that PE was related to genetic factors, he had noted that male family members of such patients were often also troubled by PE [8].

### **2.3.2 The Second Period (1950–1990): Learned Behavior**

In the second period, William Masters and Virginia Johnson, two American sexologists, postulated that PE was the result of *learned behavior* [10], hereby firmly rejecting the psychoanalytic and psychosomatic view of Abraham and Schapiro. They argued that a rapid ejaculation was linked to initial rapid intercourse(s) that led to habituation and created performance anxiety. Support for this *behavioristic* view has been sought in physiological experiments in which the phenomenon of anxiety became emphasized. Although behavior therapy was still predominantly present in the literature, in the 1980s increasingly more publications on psychoactive drugs, such as clomipramine, as a treatment were published.

### **2.3.3 The Third Period (1990–2005): Neurobiology and Psychopharmacology**

In 1998, Waldinger et al. [11, 12] postulated that lifelong PE is a neurobiologically and genetically determined dysfunction, which is related to a diminished central serotonergic neurotransmission and activation or inhibition of specific 5-HT receptors. Waldinger thereby rejected the previous pure psychological and behavioristic views of the etiology and pathogenesis of lifelong PE. The new neurobiological view was based on the outcome data of a number of animal and psychopharmacological treatment studies on PE [13]. The introduction of the selective serotonin reuptake inhibitors (SSRIs) in the early 1990s, meant a dramatic change in the treatment of premature ejaculation [13]. The efficacy of these drugs to delay ejaculation, combined with the low side effect profile, have made them first choice, yet off-label, agents to treat PE both at a daily as well as on demand base. During the 1990s, the new neurobiological view on lifelong PE and its effective treatment by SSRIs appeared to be difficult to accept by many

sexologists, with only one exception. In 1994, it was Pierre Assalian, a Canadian psychiatrist, who wrote an article wondering whether PE is really always psychogenic there by suggesting peripheral nervous system involvement [14].

### **2.3.4 The Fourth Period (2005–Present): Pharmaceutical Industry and Genetics**

Due to new developments in DNA research, investigations of genetic polymorphisms have become more easy to perform in the laboratory. DNA research in men with lifelong PE [15] and male twin genetic research [16, 17] have started to show that some polymorphisms of the central serotonergic and dopaminergic system are associated with the duration of the IELT. It is in this period that for the first time a drug, namely dapoxetine, has become officially approved by the European Medicines Agency (EMA) for the treatment of PE [18] and that other companies show interest in drug treatment of PE.

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## **2.4 Authority-Based Versus Evidence-Based Research**

In contrast to the opinion- or authority-based approach of the last century [5], both the third and fourth period (1990–present) are characterized by emphasis on evidence-based animal and human research, which mainly pertains to psychopharmacological, genetic, neurophysiological, and clinical research.

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## **2.5 Historical Development of Sexual Psychopharmacology**

Sexual psychopharmacology is a relatively independent domain of psychopharmacology [19]. Sexual psychopharmacology engages in scientific research on animals and humans regarding the relationship between the central nervous system, sexuality, and psychopharmacological drugs. It also includes clinical research into drug treatment of sexual disorders [19].

Interestingly, the historical development of PE from being a rather peculiar phenomenon in the late 1880s towards a well-defined and subclassified ejaculatory disorder in our time, mirrors the historical development of sexual psychopharmacology [19]. However, the development of sexual psychopharmacology consists of three major periods. The first period lasted from 1919 until 1933; I have called it the period of the medical specialists [19]. The second period lasted from 1970 until 2000; it is the period of the neuroscientists [19]. Currently, we live in the third period, which has started around 2000, the period of the pharmaceutical companies [19].

### **2.5.1 The First Period (1919–1933): The Period of the Medical Specialists**

At the beginning of the last century, the origins of sexual psychopharmacology started in the “Institut für Sexualwissenschaft” (Institute for Sexual Science) in Berlin, Germany. This institute was founded in 1919 by the physician Magnus Hirschfeld, the dermatologist Friedrich Wertheim, and the neuropsychiatrist Arthur Kronfeld [20]. It was the first institute in which medical research on sexuality became common. The medical specialists of the institute were treating patients for sexual dysfunctions and performed scientific research into the effects of a number of drugs on sexual disorders. For example, Bernhard Schapiro, who cooperated with Magnus Hirschfeld developed the drug “Testifortan” [21] for the treatment of erectile disorder and the drug “Praejaculin” [22] for the treatment of hypersexuality. Both drugs were produced by the pharmaceutical company Promonta which was located in Hamburg. At the time, the institute was famous around the world and many medical specialists of the institute had published scientific articles. However, this most interesting first sexual psychopharmacological period ended abruptly when the Nazis had set on fire the whole library, as they argued that the work of the institute with its many Jewish doctors represented “eine entartete Jüdische Wissenschaft” (a degenerated Jewish science). It is very unfortunate that important knowledge and clinically relevant literature from this very interesting period has been lost and disappeared forever [19].

After the downfall of the institute, a very long period starts in which the literature only sporadically mentions a drug that perhaps may be applied to the treatment of a sexual disorder. However, genuine systematic pharmacological research was not anymore practiced from the 1930s until the 1970s [19].

### **2.5.2 The Second Period (1970–2000): The Period of the Neuroscientists**

The second period started in the 1970s with a few publications of medical specialists, but now mainly psychiatrists, on the successful treatment of PE by the tricyclic antidepressant clomipramine and other central nervous system drugs [23]. In the 1980s, urologists started to focus on drug treatment of erectile disorder by injectable vasodilatory drugs [24]. At the end of the 1980s, neuroscientists initiated basic research into the sexual behavior of rodents. A few psychopharmacologists started to investigate neurotransmitters that mediate male rat sexual behavior. Pioneering neuroscientists in the 1980s and early 1990s are Sven Ahlenius, Berend Olivier, Koos Slob, Jan Mos, Hemmie Berendsen, and Rik Broekkamp [25–28]. Also neuroanatomical studies, as published by Jan Veening give rise to new insights in the neuronal circuits and neurotransmitters that play a role in the sexual functioning of the rat [29].

In the beginning of the 1990s, sexual psychopharmacology gets an enormous impulse after the introduction of the SSRIs, and the coincident finding that these drugs strongly delay ejaculation [30]. Also our research group, contributed to the sexual psychopharmacological developments in this period. This period is important in that evidence-based design and methodology for drug treatment studies were developed and applied by independent researchers without interference by the pharmaceutical industry [31].

### **2.5.3 The Third Period (2000–Present): The Period of the Pharmaceutical Companies**

The third period started in 1998 when sildenafil was fabricated and produced Pfizer as first oral drug against erectile disorder [32]. However, as mentioned before, sildenafil actually was not the first oral drug against ED but rather testifortan in the 1930s [19]. In the course of just a few years, the availability and successful use of sildenafil has led to an enormous change in thinking about sexuality and erectile disorder in particular. It has also led to a new medical discipline, known as ‘Sexual Medicine’ openly addressing the medical approach and pharmacological treatment of sexual dysfunctions, and at the same time emphasizing psychological, sociological, and cultural factors which clearly play a crucial role in most sexual dysfunctions. Inspired by the success of sildenafil, several pharmaceutical companies became interested in developing drugs against male and female sexual disorders. This development will continue, though temporarily at a slower pace down due to financial and economic reasons. In essence, it is clear that already in the very first years of the scientific study of sexuality, i.e., at the beginning of the last century, one had attempted to treat sexual dysfunctions by drug treatment. The development of this type of drugs is therefore certainly not new, as generally assumed [19].

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## **2.6 The Historical Views on Premature Ejaculation**

The various and sometimes even conflicting views on the etiology and pathogenesis of PE have throughout the years resulted in a lack of consensus on its definition and classification. In order to get a better understanding of these conflicting ideas, it is important to be aware of the various ideas and approaches on PE that have emerged in the past century and which have influenced various generations of medical specialists, psychologists, and sexologists. These include the psychoanalytic, the psychosomatic, the behavioristic, the medical, the neurobiological-genetic, and the pharmaceutical company approach.

### 2.6.1 The Psychoanalytic Approach

In 1908, Sandor Ferenczi [33], at that time a student of Sigmund Freud, wrote the first psychoanalytic paper on PE. In that paper he paid specific attention to the consequences of PE for the female partner. It was in 1917 that Karl Abraham, an, at the time renowned psychoanalyst, published a now well-known paper on the presumed unconscious problems of men suffering from PE [6]. He also introduced the medical term *ejaculatio praecox* to denote this phenomenon. Since Abraham was of the opinion that PE was caused by unconscious conflicts he suggested that treatment ought to consist of classical psychoanalysis [6]. After Karl Abraham's publication, PE was generally believed to be a psychological disorder, i.e., a *neurosis*, related to unconscious conflicts. For many years psychoanalysis and psychoanalytic psychotherapy became the treatment of first choice. However, only a few publications on psychoanalytic treatment of PE were published [6, 7, 34]. Although it may seem rather odd nowadays to focus on merely psychoanalysis to treat PE, one should realize that in the 1920s hardly anything was known about PE, and that for example a distinction in lifelong and acquired PE had not yet been made. In retrospect it is undoubtedly the lack of neurobiological and psychoanalytic knowledge in those days that negatively biased the way Karl Abraham interpreted the free associations of his patients who suffered from PE at that time [35].

### 2.6.2 The Psychosomatic Approach

The purely psychoanalytical assumptions were challenged by Bernard Schapiro, a German endocrinologist, who in 1943 postulated that PE was not the expression of a neurosis but a psychosomatic disorder [8]. He argued that both biological and psychological factors contributed to rapid ejaculatory performances. Years ahead of his time, Schapiro advocated drug treatment in the form of anesthetic ointments to delay ejaculation. In addition, he is credited with identifying two types of PE recognized today as primary (lifelong) and secondary (acquired) PE. Because he was the first clinician to use a medical approach to PE, Bernhard Schapiro should be regarded as a major pioneer in researching this condition. Unfortunately, the accurate differential diagnosis and biological components of Schapiro's arguments were ignored in his time. Psychoanalytic treatment, mainly conducted by psychiatrists, prevailed throughout the 1940s and 1950s. Today, as a number of years ago, I would like to emphasize that for a good understanding of the pathogenesis of PE it is essential to get more insight in the unconscious processes of men with PE. Therefore, I encourage a revival of psychoanalytic research into PE [35].

### 2.6.3 The Behavioristic Approach

In 1956, James Semans [36], a British urologist, described the stop-start technique, a masturbation technique, to delay ejaculation. Although hardly noticed in the following decade, in 1970, William Masters and Virginia Johnson [10], came up with a modification of Semans technique, the so-called squeeze technique. They argued that PE was the result of self-learned behavior, as they stated that the initial intercourses in these men had been carried out in a hurry. They argued that behavioral treatment in the form of the squeeze technique could cure PE in the majority of cases [10]. However, there still is a paucity of evidence-based studies demonstrating hard data of its efficacy to delay ejaculation in men who for example ejaculate within a few seconds. In the psychological approach pathogenetic biological mechanisms remained unclear, but an increased sensitivity of the glans penis has been suggested. However, penile vibratory studies provided conflicting data about a pathogenetic penile hypersensitivity [37–39].

Not only the squeeze technique, but all sorts of psychotherapies ranging from thought stopping [40, 41], Gestalt therapy [42], transactional analysis [43], group therapy [44, 45] and bibliotherapy [46] have been suggested as treatments. Unfortunately, the effectiveness of these therapies has only been suggested in case reports, but have hardly been investigated in well-designed controlled studies. Of all these treatments, however, the squeeze method is said to provide short-term effectiveness. Two (not well-designed) studies did confirm initial effectiveness, but also showed that the ejaculatory control initially attained had virtually been lost after a 3-year follow-up [47, 48].

#### 2.6.3.1 Definition of Premature Ejaculation from a Psychological Point of View

In the psychological approach, consensus about a definition of PE has never been reached due to conflicting ideas about the essence of the syndrome. Masters and Johnson [10] and Kaplan [49] suggested qualitative descriptions, i.e., female partner satisfaction or man's voluntary control. Masters and Johnson defined PE as the man's inability to inhibit ejaculation long enough to satisfy his partner 50 % of the time [10]. This definition in terms of a partner's response is rather inadequate, since it implies that any male who is unable to satisfy his partner in 50 % of sexual events could be labelled a premature ejaculator and since it would also imply that females "should" be satisfied on 50 % of intercourses.

Another way to define PE is by using quantitative measures such as the duration of ejaculatory latency, or the number of thrusts prior to ejaculation. Definitions according to length of time prior to ejaculation, varied from within 1–7 min after vaginal intromission [50–59]. These cut-off points (1–7 min) were not derived by objective measurements, but were subjectively chosen by the various authors. PE was a matter of (many) minutes and men who ejaculated within seconds were qualified as serious cases.

Equally subjective cut-off points have been proposed for the number of thrusts as a criterion for PE: ejaculation within 8–15 thrusts [60–62].

### 2.6.3.2 Methodology of Psychological Studies

During the many years in which the psychological approach prevailed, the proposed psychological hypotheses and psychotherapeutic treatments failed to be proved in a methodologically adequate scientific study [13].

For example, an influential view that prevailed for about two decades was the opinion of Masters and Johnson [10] who argued that PE was conditioned by having one's first sexual intercourse in a rapid way (i.e., hurried contacts on back seats of cars or in places where detection was possible). However, hard clinical data to support their view have never been reported.

## 2.6.4 The Medical Approach

### 2.6.4.1 Pharmacotherapy

Since the 1940s, case reports have occasionally been published about various drugs that demonstrated efficacy in delaying ejaculation. Physicians tried to reduce penile sensation and delay ejaculation by applying *local anesthetics* to the glans penis [8, 63, 64]. Others tried to influence the peripheral sympathetic nervous system by prescribing *sympatholytic drugs* like the  $\alpha_1$  and  $\alpha_2$  adrenergic blocker phenoxybenzamine [65–67] or the selective  $\alpha_1$  adrenergic blockers alphuzosin and terazosin [68]. In the 1960s, case reports described the ejaculation delaying effects of some *neuroleptics*. For example, thioridazine [69, 70] and chlorprothixene [71] delayed ejaculation by blocking central dopamine receptors. In the same period case reports of the delaying effects of nonselective, irreversible *monoamine oxidase inhibitors* (MAOIs) such as isocarboxazid [72] and phenelzine [73] were published. The use of these various drugs, however, was often contraindicated by their disturbing and sometimes quite serious side effects.

In 1973, Eaton published the first report on clomipramine as an effective treatment for PE [23]. Later case reports and double-blind studies [74–80] repeatedly demonstrated the effectiveness of clomipramine in low daily doses in delaying ejaculation. In 1993, Segraves and coworkers published a double-blind placebo-controlled study demonstrating that clomipramine 25–50 mg can even be taken on an on-demand basis, approximately six hours prior to coitus [62]. The majority of these pharmacological studies, similar to psychological studies, were designed without a precise definition of PE and without any methodology for quantifying the effects of treatment.

In the 1980s, the efficacy of clomipramine was recognized by some sexologists but never reached international consensus. One may wonder why drug treatment has gone such a long way to become accepted by medical specialists and sexologists as an effective treatment for PE. Indeed, the psychological view and particularly behavior therapy has predominated the literature and the general view on PE for a number of



decades. On the one hand, it may well be that animal research data showing the neurobiological basis of ejaculation has hardly been integrated with clinical experiences regarding drug treatment, and clinicians' emphasis on the tremendous success ascribed to behavior therapy and/or on the presumed psychogenic nature of PE. This may have been due to the prevailing misconception of the 1970s and 1980s that psychopharmacotherapy only represses symptoms, while the essence of the disorder that had to be treated, i.e., PE, remains psychological [2]. A similar view that treatment with psychoactive drugs does not change the essence of a disorder also prevailed for a long time with respect to psychiatric disorders [81].

#### **2.6.4.2 Selective Serotonin Reuptake Inhibitors (SSRIs)**

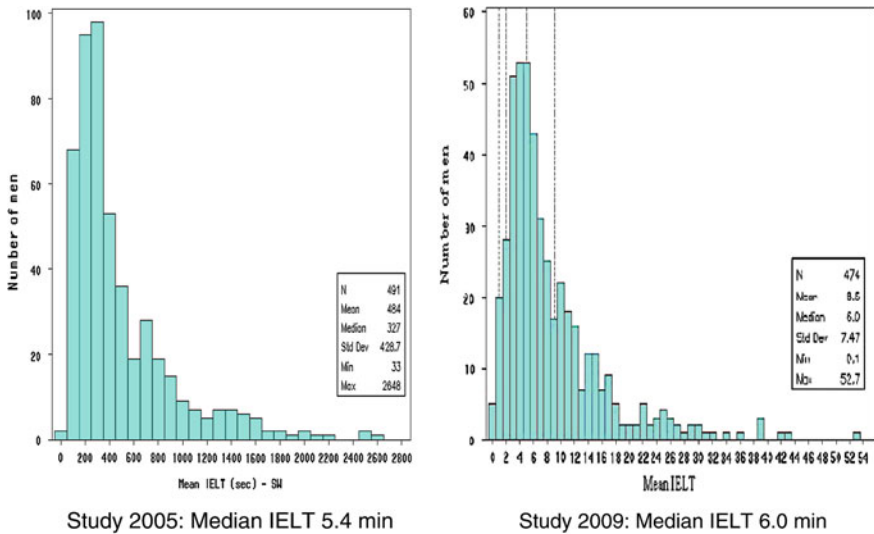
In 1994, successful treatment of PE by 40 mg paroxetine was for the first time reported by Waldinger et al. in a placebo-controlled study [30]. The efficacy of paroxetine in daily doses of 20–40 has been replicated in various other studies both at regular daily dose and on an “on-demand” regimen [82–84]. In addition, the efficacy of other SSRIs, such as 50–200 mg sertraline and 20 mg fluoxetine, in delaying ejaculation has been demonstrated in various studies [85–90]. The new methodology of these studies contributed to a better comparability of drug treatment study research and encouraged various clinicians to become interested in PE. An important parameter for comparing study results was the intravaginal ejaculation latency time (IELT), which as a measure was introduced by Waldinger et al. in 1994 [30] and became known as the IELT. The IELT was defined as the time between the start of intravaginal intromission and the start of intravaginal ejaculation. The stopwatch, originally introduced in 1973 by Tanner [91] as an accurate tool to measure ejaculation time, was reintroduced in 1995 by Althof [79], and has since become a standard tool for PE research.

#### **2.6.4.3 Differential Efficacy of SSRIs in Delaying Ejaculation**

By using the IELT, the stopwatch, and a 4-week baseline assessment at each intercourse, comparison of placebo-controlled studies has become possible and demonstrated that the various SSRIs differed in the extent in which they delayed ejaculation [31]. As such it was demonstrated that paroxetine 20 mg/day exerted the strongest ejaculation delay [31].

### **2.6.5 The Neurobiological Approach**

The development of accurate measurement of the ejaculation time by using the IELT and a stopwatch together with the availability of the SSRIs has stimulated both human and animal psychopharmacological research of PE. Particularly in the 1990s animal research in rodents using SSRIs contributed much to our understanding of why SSRIs delay ejaculation [92, 93]. The pharmacological knowledge about the mechanism of action of these SSRIs has become the cornerstone of an upcoming neurobiological approach. These animal studies have shown that



**Fig. 2.1** Two epidemiological stopwatch studies of the IELT in random sample of the general male population in five countries [99,100]

ejaculation is not only mediated by the central serotonergic system but also by dopaminergic and oxytocinergic pathways [94–96].

One of the major unanswered questions in the 1990s was the form of the distribution of the IELT in the general male population. Waldinger et al. [11] postulated that there is a continuum or biological variability of the IELT in men. This continuum of ejaculation latency was first recognized in male Wistar rats [97]. By investigation of large samples of male rats it appeared that in a sexual behavioral test of 30 min about 10 % of rats hardly or do not ejaculate, about 10 % of rats have a short ejaculation latency time and the majority have a normal ejaculation latency time. This phenomenon that is present in every large sample of male Wistar rats, has become the basis of a new animal model for the investigation of both lifelong premature and retarded ejaculation [98]. In 2005, it was the first time that an epidemiological stopwatch study measuring the IELT was performed in the general male population [99]. It confirmed the existence of a variability of the IELT, but is also showed that the IELT has a positive skewed distribution. In two similar studies, the same skewed distribution was found [18, 100] (Fig. 2.1). Both studies, showed that IELT values of less than 1 min are statistically aberrant compared to the IELT values in the general male population. Interestingly, both stopwatch and self-reported studies of the IELT in men with lifelong PE show that about 90 % of men ejaculate within 1 min, indicating that IELTs of less than 1 min give rise to bother and complaints and indeed are statistically abnormal [101].

The finding of a population-based variability of the IELT implicates that rapid ejaculation should be considered a biological phenomenon rather than a psychological aberration. This biological phenomenon is most probably differently

**Table 2.2** New preliminary classification and characteristics of four premature ejaculation subtypes on the basis of their IELT duration [105]

Lifelong PE	Acquired PE	Variable PE	Subjective PE
Ejaculation occurs too early, at (nearly) every intercourse. With (nearly) every woman. From about the first sexual encounters onwards. In 80 % within 1 min (mostly within 30 s). In 20 % between 1 and 2 min. Ejaculation remains rapid throughout the lifetime of the subject.	Early ejaculation occurs at some point in a man's life. The man had normal ejaculation experiences before. The onset is (usually) at later age. Ejaculation occurs within 1–2 min. Early ejaculation is result of urological, thyroid, or psychological problems.	Early ejaculations are inconsistent and occur irregularly. The ability to delay ejaculation may be diminished or lacking. From about the first sexual encounters or onset at later age. Ejaculation time may be short or normal. This is part of the normal variability of ejaculatory functioning.	Subjective self-perception of (in)consistent early ejaculations. The ability to delay ejaculation may be diminished or lacking. From about the first sexual encounters or onset at later age. Ejaculation time is in the normal range or may even be of longer duration. Early ejaculation is a subjective experience, independent of the actual (normal) ejaculation time.

appreciated among individuals, populations, and cultures. There are men and women who cope very well with rapid ejaculation and do not find it a major problem. But for other men and their sexual partners rapid ejaculation may become a psychological or emotional problem.

### 2.6.5.1 Classification and Definition of Premature Ejaculation

For many years, the various DSM definitions of PE were considered adequate for daily clinical use. However, together with the increasing research into PE of the last two decades, increasing criticism against the DSM definition was uttered by clinicians and neuroscientists [102]. It soon became well-known that the DSM definition of PE was not the result of evidence-based research but was based on the opinions of a few clinicians and therefore an example of authority-based medicine. In 2007, the International Society for Sexual Medicine (ISSM) organized a committee meeting of experts in Amsterdam resulting in a first evidence-based definition of lifelong PE [103]. Another major contribution of the ISSM was the publication in 2009 of the first evidence-based guideline for the treatment of PE [104]. Without doubt, both the new definition of lifelong PE and the guideline for PE treatment will form a new basis for further evidence-based research of PE. Apart from this new definition of lifelong PE, Waldinger et al. proposed a new classification of PE based on the duration of the IELT (Table 2.2). In this classification, there are four PE subtypes [105]. First of all, lifelong PE and acquired

PE. Both subtypes have become an integrated part of PE since their description by Schapiro in 1943 [8]. However, based on recent clinical and epidemiological stopwatch data, Waldinger postulated the existence of two other PE subtypes: natural variable PE or variable PE and premature-like ejaculatory dysfunction or subjective PE. Men with lifelong PE suffer from IELTs that are consistently shorter than about a minute in most sexual events, since puberty or adolescents. In men with acquired PE, PE may be caused by erectile dysfunction, thyroid disorders, inflammatory prostatitis or relationship problems. In men with (natural) variable PE, men suffer only sometimes of a very short IELT. In “subjective PE” men have a normal or even high IELT value, but still perceive themselves as having PE. Whereas it is postulated that the very short IELT values in men with lifelong PE result from neurobiological processes and genetic factors, it has been postulated that “subjective PE” is strongly associated with psychological and cultural factors. In these men, IELT is normal but the perception of the IELT is distorted or disturbed. Although there is no general consensus on this proposal for a new classification, Serefoglu et al. published two studies confirming the existence of the four PE subtypes in a Turkish population of men [106, 107].

### 2.6.6 The Genetic Approach

Although Bernhard Schapiro never argued that PE is related to genetic factors, he noticed, as described in his article of 1943, that men with PE seemed to have family members with similar ejaculatory complaints. Remarkably, this interesting observation has never been quoted in the literature until it was mentioned in 1998 in a study performed by Waldinger et al. [12] who routinely asked 237 men with PE about family occurrence of similar complaints. Due to embarrassment, only 14 of them consented to ask male relatives about their ejaculation. These 14 men were able to point out a total of 11 first degree male relatives with available information for direct personal interview. Indeed, ten of them also ejaculated within one minute or less. The calculated risk in this small selected group of men to have a first relative with PE was 91 % (CI: 59–99 %). The odds of family occurrence is therefore much higher compared to a suggested population prevalence rate of 2–39 %. Moreover, the high odds indicates a familial occurrence of the syndrome far higher than by chance alone. Based on this preliminary observation the influence of familial factors as formerly stated by Bernard Schapiro, gains substantial credibility. But this familial occurrence does not automatically mean that lifelong PE has genetic roots, as has been postulated by Waldinger et al. in 1998. Hard indications for that hypothesis only appeared in 2009, a decade later. In 2009, Janssen et al. [15] published the first DNA study in men with lifelong PE. It was found that polymorphism of the 5-HT transporter, the activity of which determines the 5-HT content in the synapse of central serotonergic neurons, is associated with the duration of the IELT in men with lifelong PE. This coincides well with animal research showing that a diminished serotonergic neurotransmission facilitates

ejaculation. However, Jern et al. [108] in a study in Finnish twins did not find an association of this polymorphism and the ejaculation time. However, in their sample of males, the majority of men had IELTs far longer than 1 min. Nevertheless, both the study of Janssen et al. in Dutch men with lifelong PE [15] and the studies of Jern et al. [16, 17, 108] in Finnish twins have become the basis for further genetic research of PE in men with lifelong PE and in twins in the general population.

## 2.6.7 The Pharmaceutical Industry's Approach

After the very successful introduction of sildenafil for the treatment of erectile disorder, pharmaceutical companies have become interested in sexual medicine. This has been a very fortunate development. One of the major tasks of sexual medicine is to provide medication to patients with sexual disorders. For that purpose, animal and human drug treatment research is pivotal. Between 2000 and 2012, a few companies have investigated existing compounds for the treatment of PE. Only the pharmaceutical company Johnson & Johnson was able to obtain a registration by the European Medicines Agency (EMA) for their drug dapoxetine, an SSRI with a short half life, for the on-demand treatment of PE [18]. This registration has led to increased epidemiological research of PE in large populations of men [109] and largely supported by the latter company. In general, the approach of the pharmaceutical industry consists of epidemiological studies in large samples of men. However, a limitation of these studies in large samples of men is the potential risk of including men who do not have PE according to officially defined criteria. Nevertheless, as dapoxetine has added to the existing off-label drug treatment options of PE, the introduction of new drugs for the treatment of PE is encouraged.

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## 2.7 Conclusion

Any scientific article promoting a new idea, view, or finding starts to describe the current ideas, views, or existing knowledge, followed by critical remarks on their limitations. This has also been the case in the scientific literature on PE. Articles on behavioral psychotherapy started with critical remarks on psychoanalytic therapy of PE. Articles on drug treatment of PE started with critical remarks on behavioral psychotherapy of PE. Articles on on-demand drug treatment of PE started with critical remarks on daily drug treatment of PE. The current reality, however, is that the whole history of PE can be applied to PE. This is nicely represented by the various drug treatments of and views on the different etiology and pathogenesis of the recently proposed four different subtypes of PE. In other words, to fully understand PE requires knowledge of its history. And the history of PE tells a story that can be distinguished in four time periods, each of them adding

new information on PE. However, it would be a mistake to think that the prevailing view of the last period is the best view on PE. For example, recently the genetic roots of PE have been investigated, but in daily clinical practice, a clinician with knowledge of psychoanalytic psychotherapy may better understand the sorrow of a man with PE, than a clinician who tells him that his complaint is the result of a genetic polymorphism.

Nevertheless, neurobiological, psychopharmacological, neurophysiological, and genetic research of the last decade has demonstrated that the classical purely psychological view of lifelong PE is no longer tenable as the golden standard. Moreover, the history of PE shows that from its onset a century ago being a rather unknown and peculiar phenomenon, PE has now become a well-known sexual disorder. Still, as in the old days, a taboo on PE still exists, but this may hopefully diminish in the next decades when our current time has become history as well.

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François Giuliano and Pierre Clément

## 3.1 Introduction

The human (female and male) sexual response was described by Masters and Johnson [59] as including four interactive phases: excitation, plateau, orgasm, and resolution. This definition has been subsequently revised by Kaplan [40] and Levin [50] to lead to a model widely accepted, consisting of desire, excitation, orgasm, and resolution. The different aspects of male sexual function include sexual desire, erection, ejaculation, and orgasm. Each of these phases is controlled by a complex and coordinated interplay of multiple components of the brain, spinal cord, and relevant peripheral organs.

Ejaculation is the final stage of coitus in mammalian males since it is followed by a refractory period during which sexual responses are inhibited. Ejaculation consists in the synchronized succession of physiological events that form two distinct phases: emission and expulsion. Emission corresponds to the secretion of the different components of the seminal fluid from accessory sex glands and testes. The seminal secretions are poured into the posterior urethra via phasic contractions of the glands and their respective ducti while the bladder neck is firmly closed to prevent backflow into the bladder. Expulsion is then triggered in the form of an intense burst of contractions of pelviperineal striated muscles. These two phases are intimately linked but they can be studied distinctively using specific

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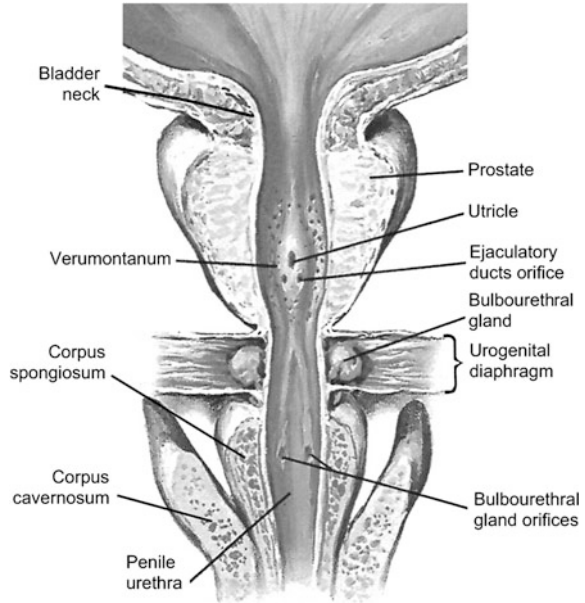
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**Fig. 3.1** Frontal section at the level of the prostatic and proximal penile urethra



physiological markers and can occur independently from each other in peculiar experimental paradigms and pathophysiological conditions.

## 3.2 Anatomical Organization of Sexual Organs Involved in Ejaculation

Anatomical structures belonging to the male reproductive tract (Fig. 3.1) that are involved in ejaculation can be divided into two main categories depending on the phase they participate in.

### 3.2.1 Organs of Emission

The epididymis is a long coiled tube of epithelial cells covered by connective tissue partly composed of smooth muscle cells. It consists of three parts: the expanded head (caput), the body (corpus), and the tail (cauda). Spermatozoa are produced in the seminiferous tubules of the testes and then translocated into the head of the epididymis. The spermatozoa in the seminiferous tubules and early epididymis are nonmotile but gain motion capacity after maturation (18–24 h) along the epididymis. Mature spermatozoa are stored in the tail of the epididymis and, as sexual arousal develops, are released in the contiguous seminal duct (ductus deferens). The volume of spermatozoa accounts for a very minor fraction (<0.1 %) of the total volume of the sperm.

*Ductus deferens.* The first portion of the ductus (or vas) deferens is very tortuous, but progressively becomes straighter. It passes through the inguinal canal and enters the pelvic cavity to join the excretory duct of the seminal vesicle, forming the ejaculatory duct. The ejaculatory duct traverses the prostate behind its middle lobe and opens into the prostatic portion of the urethra via the verumontanum (a 2–3 mm height intraluminal urethral crest in humans). As the ductus deferens reaches the posterior wall of the bladder base, it becomes enlarged to form the ampulla. During the emission phase of ejaculation, strong peristaltic contractions of ductus deferens smooth muscle cells bring spermatozoa into the ejaculatory duct and then into the urethra where they are mixed with seminal fluids.

The seminal vesicles are a pair of tubular glands lying between the posterior wall of the bladder base and the rectum. Each vesicle is formed by a unique coiled tube which gives off multiple diverticulae and joins with the ductus deferens as it enters the prostate to form the ejaculatory duct. Epithelial cells that constitute the inner layer of the seminal vesicle are responsible for the secretion of 50–80 % of the entire ejaculatory volume. Seminal vesicle secretions are thick, alkaline, and contain substances providing the spermatozoa with a protective and nutritive environment. During the emission phase of ejaculation, seminal vesicle fluid is expelled into the prostatic urethra via the excretory duct following contractions of smooth muscle cells which compose the intermediate layer of the gland. The external coat is constituted of fibrous connective tissue which maintains the structure of the glands.

The prostate gland which is located between the bladder neck and the external urethral sphincter, consists of three distinct zones. The central zone surrounds the ejaculatory ducts and represents around 25 % of the gland size; the transitional zone surrounds the proximal urethra and accounts for approx. 5 % of the gland size; the peripheral zone surrounds the distal urethra and accounts for up to 70 % of the prostate size. The structure of the prostate consists in branching glandular formations composed of epithelial cells that spread out into a matrix of fibromuscular stroma. A fibrous capsule encloses the gland preventing it to enlarge outwards. The prostate produces 15–30 % of the total volume of sperm. Prostatic secretions are milky, slightly alkaline, and enhance spermatozoa survival. During the emission phase of ejaculation, muscular elements of the gland contract and eject the secretions into the prostatic urethra via the prostatic ducts and the utricle opening into the verumontanum.

The bulbourethral or Cowper's glands are located posterolaterally to the membranous portion of the urethra at the level of the urogenital diaphragm. They are closely invested by a layer of striated muscle, namely bulboglandularis. Bulbourethral gland excretory ducts extend forward through the urogenital diaphragm and open into the cavernous urethra. Bulbourethral clear thick secretions are poured into the urethra as sexual arousal increases. Their role is dual: neutralizing urine acidic residues and lubricating the urethra before sperm passes through.

### 3.2.2 Anatomical Structures Participating in Expulsion

The bladder neck and the urethra play an important role in the occurrence of ejaculation. The bladder neck corresponds to the area where bladder and urethra connect and is composed of smooth muscle cells forming a circular collar which extends distally to encircle the proximal part of the urethra. The male urethra is a fibromuscular tube that extends from the bladder neck to the external urethral orifice, i.e., the meatus, and is divided into three portions, the prostatic, membranous, and penile (or spongy) portions. Upon the posterior wall of the prostatic urethra is the verumontanum where the orifice of the prostatic ducts and utricle, and the slit-like openings of the ejaculatory ducts are found. The inner layer of the urethra is a mucous membrane continuing the bladder mucous membrane and protecting subjacent epithelial cells from urine corrosion. The morphology of the epithelial cells evolves from transitional (prostatic urethra) to pseudostratified (membranous and proximal penile portions), and finally to stratified squamous (distal penile portion). Within the wall of the membranous urethra is the intrinsic striated muscle (external urethral sphincter or rhabdosphincter) which consists of an inner layer of smooth muscle bundles continuous proximally with those of the prostatic urethra, and an outer layer of circularly orientated striated muscle fibers. Strong contraction of the bladder neck prevents semen to flow backward in the bladder (retrograde ejaculation) and relaxation, preceded by rhythmic contractions, of the external urethral sphincter facilitates flowing of semen through the urethra in an anterograde way.

*Perineal striated muscles.* The pelvic floor striated muscles, and more particularly the bulbospongiosus and ischiocavernosus muscles, have a major role in the expulsion of semen from the urethra. The bulbospongiosus muscle encompasses the median part of the penile root (bulb). The muscle arises from the perineal body and from a central tendinous raphe and passes around the bulb to attach to the perineal membrane and dorsum of the penis. The ischiocavernosus muscles surround the lateral roots of the penis (crura). They arise from the medial surface of the ischial tuberosity and the ischiopubic ramus and insert on the corpus cavernosum and crura of the penis. Intense rhythmic contractions of those muscles during the expulsion phase of ejaculation compress the spongy urethra and corpus cavernosum leading to pulsatile expulsion of semen and providing further rigidity to the penis. Moreover, intense contractions of those muscles likely contribute to the orgasmic feeling in the human male.

All the anatomical structures listed above receive specific autonomic (both sympathetic and parasympathetic for most of them) and somatic innervations that drive messages for synchronized functioning of the organs involved in ejaculation.

### 3.3 Peripheral Neural Pathways

#### 3.3.1 Afferents

The dorsal nerve of the penis, a sensory branch of the pudendal nerve, carries impulses to thoracic, lumbar, and sacral segments of the spinal cord from sensory receptors harbored in the penile skin, prepuce, and glans [38, 76]. Encapsulated receptors (Krause-Finger corpuscles) have been found in the glans but the majority of afferent terminals are represented by free nerve endings [31]. Stimulation of the Krause-Finger corpuscles, which can be potentiated by sensory information coming from various peripheral areas such as penile shaft, perineum, and testes, facilitates the ejaculatory reflex. In various mammalian species, a relatively sparse sensory innervation of ductus deferens, prostate, and urethra has been evidenced which reaches the lumbosacral spinal cord via the pudendal nerve [39, 80]. A second afferent pathway is constituted by fibers travelling along the hypogastric nerve and, after passing through the paravertebral lumbosacral sympathetic chain, enters the spinal cord via thoracolumbar dorsal roots [8]. Sensory afferents terminate in the medial dorsal horn and the dorsal grey column of the spinal cord [61, 101].

#### 3.3.2 Efferents

The soma of the preganglionic sympathetic neurons are located in the intermediolateral cell column and in the central autonomic region (dorsal gray column) of the lower thoracic and upper lumbar segments of the spinal cord [68, 74]. The sympathetic fibers, emerging from the spinal column via the ventral roots, relay in the paravertebral sympathetic chain. In the majority of mammalian species, the fibers then proceed whether directly via the splanchnic nerves or after relaying in the celiac superior mesenteric ganglia via the intermesenteric nerves to the inferior mesenteric ganglia [78] or superior hypogastric plexus in humans. Emanating from the inferior mesenteric ganglia are the hypogastric nerves that form, after joining the parasympathetic pelvic nerve, the pelvic plexus from which arise fibers innervating the anatomical structures involved in ejaculation.

The cell bodies of the preganglionic parasympathetic neurons are located in the intermediolateral cell column of the sacral (lumbosacral in rodents) segments of the spinal cord, i.e., sacral parasympathetic nucleus (SPN) [73]. The SPN neurons send projections, travelling in the pelvic nerve, to the postganglionic cells located in the pelvic plexus (or inferior hypogastric plexus). Postganglionic parasympathetic neurons fibers follow the course of the blood vessels to reach the pelvic organs participating in ejaculation.

Efferents of somatic motoneurons, cell bodies of which are found at the lumbosacral spinal level (sacral level in the human male) in the Onuf's nucleus, exit the ventral horn of the medulla and proceed via the motor branch of the pudendal



nerve to the pelvic floor striated muscles, including bulbospongiosus and ischio-cavernosus muscles [86].

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## 3.4 Functional Considerations

The composition of the seminal fluid is complex and contains, besides spermatozoa, a variety of enzymes, sugars, lipids, oligo-elements, and other substances. This mixture provides spermatozoa with a nutritive and protective milieu promoting their survival and movement during their course through the female reproductive tract to the ovule. In human males, the fluid is released from the glands in a specific sequence during ejaculation. The first portion of the ejaculate consists of a small amount of fluid from the bulbourethral/Cowper's glands. This is followed by a low-viscosity opalescent fluid from the prostate containing a few spermatozoa. Then the principal portion of the ejaculate is expelled which contains the highest concentration of spermatozoa, along with secretions from the epididymis as well as prostatic and seminal vesicle fluids. The last fraction of the ejaculate consists of seminal vesicle secretions.

### 3.4.1 Sensory Nervous System

Sensory inputs have been shown sufficient to elicit expulsion reflex or even complete ejaculatory response (forceful expulsion of semen). In an experimental paradigm developed in anesthetized rats with complete transection of the spinal cord at T8 level, urethral distension by accumulating liquid infused into the urethra elicited rhythmic contractions of bulbospongiosus muscles [62]. In anesthetized and intact rats, pudendal nerve (motor branch innervating bulbospongiosus and ischiocavernosus muscles) firing was elicited in response to electrical stimulation of the dorsal nerve of the penis and pelvic nerve which convey sensory information from penis and urethrogenital tract, respectively [37].

In humans also, contractions of bulbospongiosus muscles identified with electromyographic electrodes were evidenced following electrostimulation of the penile dorsal nerve, mechanical distension of the posterior urethra, and magnetostimulation of the sacral roots [75, 77, 89]. These procedures can be used to evaluate the integrity of the reflex arc controlling expulsion and have also served as a basis for developing a method that produces ejaculation in patient with neurogenic anejaculation. This method, namely penile vibratory stimulation, consists in placing a vibration-delivering device on the glans of the penis, either the dorsum or frenulum, and applying 2.5 mm amplitude vibrations at an optimal frequency of 100 Hz for 5–15 min [13, 93]. Penile vibratory stimulation leads to complete ejaculatory response in a significant number of men with spinal cord injury [13].

### 3.4.2 Autonomic Nervous System

The importance of the autonomic nervous system in regulating the ejaculatory response is well documented. All of the organs participating in ejaculation receive a dense autonomic innervation composed of sympathetic and parasympathetic axons mainly originating in the pelvic plexus. The ganglia of the pelvic plexus, that are dispersed in amongst the pelvic organs in most animal species, contain fibers from both pelvic and hypogastric nerves and from the caudal paravertebral sympathetic chain [41]. In addition to adrenergic and cholinergic mechanisms of regulation of ejaculation, non-adrenergic/non-cholinergic (NANC) factors including ATP [4, 35, 69], neuropeptide Y (NPY; [30, 108], vasoactive intestinal peptide (VIP; [24, 25], and NO [16, 25] have been shown to have a direct participation in the peripheral control of ejaculation.

Both sympathetic and parasympathetic tones act in a synergistic fashion to initiate seminal emission by activating respectively smooth muscle contraction and epithelial secretion throughout the seminal tract.

From experimental studies carried out in different animal species, it has been demonstrated that activation of the sympathetic nervous system, whether by stimulating sympathetic nerves (hypogastric or splanchnic) or using sympathomimetic agents, elicited strong contractile responses in the ducti deferens [42, 44], seminal vesicle [27, 99], prostate [46, 104], and urethra [46]. Contractions induced by sympathetic nerve stimulation were blocked, only partially in ducti deferens and seminal vesicle [95], by  $\alpha 1$  adrenergic antagonists [44]. The functional role of parasympathetic cholinergic fibers conveyed by the pelvic nerves is still not fully defined likely because of the differences in gross and microscopic anatomy of the prostate among species that do not allow straightforward extrapolation between animals.

Contractions of the ductus deferens in rodents [44, 47], prostate [104], and urethra [23] in dogs were elicited by electrical stimulation of the pelvic nerves, although no appreciable emission of fluid was observed [104]. Pharmacological evidence relating to a cholinergic mechanism for both contraction and secretion of prostate and seminal vesicle exist [70, 91, 99]. Essentially, these glands were activated by cholinomimetic compounds acting on muscarinic receptors [49]. Altogether, the results of pelvic nerve stimulation and pharmacological cholinergic activation led to suggest—and converse to the conventional view of the organization of pelvic autonomic pathways—that sympathetic innervation to the prostate includes both adrenergic and cholinergic components.

In addition to adrenergic and cholinergic commands, peptidergic and purinergic regulations have been demonstrated in laboratory animals although the precise mechanisms remain to be clarified. Several lines of evidence have shown that VIP and NPY participate in contraction and secretion of prostate and seminal vesicle [70, 92, 95] by apparently modulating noradrenaline release [96]. The same regulatory role has been reported for NPY in ductus deferens contractions [96]. Finally, ATP, the main endogenous purine, was found to act as a cotransmitter

with noradrenaline to produce prostatic [102], seminal vesicle [64], and ductus deferens [2] contractions.

In humans, disruption of sympathetic pathways supplying the bladder neck, ductus deferens, and prostate is widely accepted to be the cause of postoperative anejaculation or retrograde ejaculation [60, 105]. The essential role of sympathetic innervation is best illustrated by surgical strategies that, by sparing sympathetic efferents, successfully preserve normal ejaculatory function in patients who have undergone retroperitoneal lymphadenectomy for testicular cancer or resection for rectal cancer [82, 97]. In addition, in paraplegic men whose ability to ejaculate is commonly severely impaired, semen was obtained upon electrical stimulation of the hypogastric plexus [15]. As far as we know, there is no clear clinical evidence for a functional role of parasympathetic innervation in the ejaculatory process.

### 3.4.3 Somatic Nervous System

The expulsion phase of ejaculation is commanded by the somatic nervous system though it is a reflex mechanism with no voluntary control. Forceful propulsion of semen out of the urethra via the glans meatus is caused by rhythmic contractions of pelvi perineal muscles. Owing to the fact that relatively non invasive measurement of pelvi perineal muscle activity is possible in humans, the expulsion phase has been shown to be characterized by synchronous activation of ischiocavernosus, bulbospongiosus and levator ani muscles, anal and urethral external sphincters [11, 28]. The contractions are regular, with an interburst interval starting at approx. 0.6 s and increasing by about 100 ms for each subsequent interburst interval. The typical number of bursts of contractions varies from 10 to 15 depending on the subject although each subject's pattern of contractions is reproducible [11]. In case of lesion of the pudendal nerves, as it may occur after trauma [29] or neuropathy related to diabetes [103], retrograde and/or dribbling ejaculation is observed. Besides being important for the expulsion of sperm, rhythmic contractions of pelvipерineal muscles seem associated with the orgasmic feeling inseparable from ejaculation (except in rare pathophysiological conditions like anorgasmia).

### 3.4.4 The Trigger for Expulsion

The initial phase of ejaculation (emission) develops as autonomic pathways are activated due to increasing sexual arousal and peripheral sex-related stimuli. What triggers the expulsion phase is unclear, however. The "pressure chamber" hypothesis by Marberger [53] states that accumulation of seminal emission within the proximal penile urethra (bulbous urethra), because of closed urethral proximal and distal sphincters, until a threshold level is reached triggers pelvi perineal striated muscle contractions which, together with external (distal) urethral sphincter episodic relaxation and continuous bladder neck (proximal sphincter)

contraction, propels sperm anterogradely. This hypothesis has however to be reassessed in view of the large body of contradictory data collected in laboratory animals and men (for review see [51]). The major argument is the observation that pharmacological inhibition of emission by adrenergic blockers or lack of emission following selective nerve injury or radical prostatectomy does not prevent pelvi perineal muscle contractions with a similar pattern than in the normal condition [9, 10, 28]. The occurrence of expulsion in absence of emission (known as dry ejaculation) clearly indicates that other mechanisms not related to the pressure chamber concept can trigger the expulsion phase of ejaculation. These mechanisms involve specific spinal cord and brain elements.

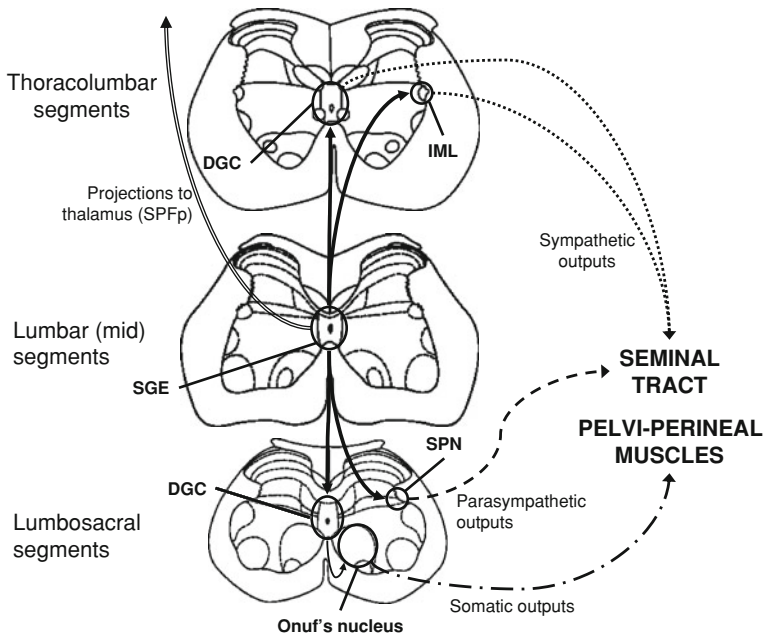
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## 3.5 Central Network

Synchronization of the activity of autonomic and somatic nervous systems, which is necessary for complete ejaculatory response to occur, takes place in the spinal cord with specific brain structures having a key role.

### 3.5.1 Spinal Cord

The soma of the neurons controlling the peripheral events of ejaculation are distributed in the thoracolumbar and sacral (lumbosacral in rodents) spinal cord as described in Sect. 3.3 (Fig. 3.2). Another spinal structure characterized in the male rat plays the role of a spinal generator for ejaculation (SGE) [100]. SGE is composed of cells that are located around the central canal, in laminae X and VII (medial part) of the lumbar segments 3 and 4 and that contain galanin, cholecystokinin, and enkephalin [22]. One component of the SGE, referred to lumbar spinothalamic (LSt) cells, connects to the parvicellular subparafascicular nucleus of the thalamus (SPFp). SGE neurons expressing galanin and/or neurokinin-1 receptors (SP preferential receptor) also project to the sympathetic and parasympathetic preganglionic neurons innervating the prostate as well as to the motoneurons of the dorsomedial nucleus innervating the bulbospongiosus muscle (Fig. 3.3; [106, 107]). In addition, fibers of the sensory branch of the pudendal nerve terminate close to LSt cells [61], although a direct connection remains to be demonstrated and their nature is unknown. One question still to be answered is about brain influence on SGE. Direct supraspinal projections onto SGE neurons have not been described to date although functional investigations provide evidence of brain outputs triggering ejaculation, likely by activating SGE (Clement et al. [18, 19, 43]). Finally, investigations in anesthetized male rats have demonstrated that electrical stimulation of SGE elicits a complete ejaculatory response allowing the collection of motile spermatozoa [12]. Altogether these data support a crucial role for LSt cells in orchestrating autonomic and somatic spinal centers. A plausible mechanism is that both peripheral and brain stimulatory and inhibitory



**Fig. 3.2** Schematic view of the spinal network of ejaculation. The spinal generator for ejaculation (SGE) projects to (i) thoracolumbar sympathetic centres (DGC, IML) (ii) lumbosacral parasympathetic centers (SPN), and (iii) lumbosacral somatic center (Onuf's nucleus). Those autonomic and somatic spinal centers innervate the seminal tract and pelvipereineal muscles participating in ejaculation. The SGE also projects to a thalamic structure; the parvocellular subparafascicular nucleus (SPFp)

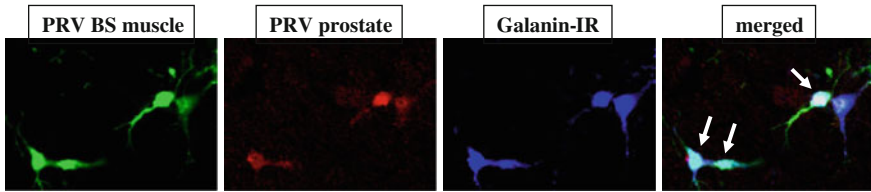
outputs are summated in SGE and, once an excitatory threshold is reached, a programed sequence is generated and activates autonomic and somatic spinal centers to produce ejaculation. Integrity of these spinal nuclei is necessary and sufficient for the expression of ejaculation as demonstrated by the induction of ejaculation after peripheral, spinal, or pharmacological stimulation in animals with spinal cord transection and men suffering from spinal cord injury [12, 13, 62, 94].

### 3.5.2 Brain

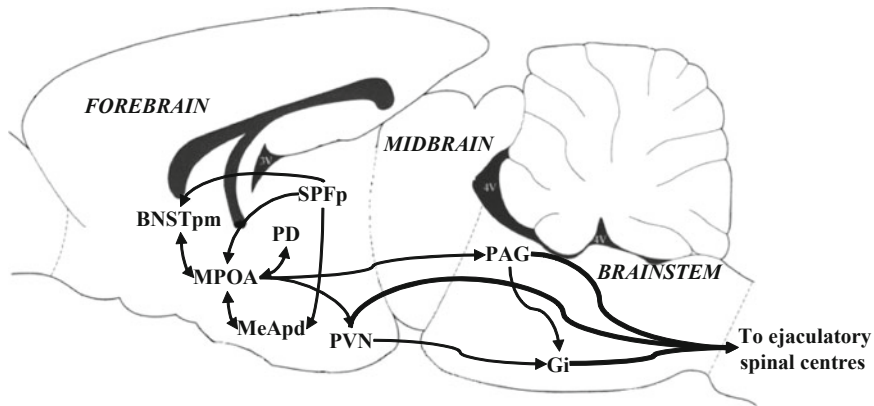
As a centrally integrated and highly coordinated process, ejaculation involves cerebral sensory areas and motor centers which are tightly interconnected.

#### 3.5.2.1 Animal Data

The use of Fos protein expression as a marker for neuronal activity together with well designed behavioral paradigms has been helpful for the identification of brain structures specifically involved in ejaculation [33, 34]. As a whole, experimental



**Fig. 3.3** Confocal microscope photographs of section of male rat third lumbar spinal segment (lamina X). Retrogradely transported and transynaptically migrating pseudo-rabies viruses (PRV) of two different strains were injected into the bulbospongiosus (BS) muscle (*green* signal) and the prostate (*red* signal). Neurons immunoreactive (IR) for the neuropeptide galanin (*blue* signal) were detected on the same spinal cord section. Triple-labelled neurons (*white* colored) indicated with *arrow* on the merged image project to both BS muscle and prostate and contain galanin. Adapted from [107]



**Fig. 3.4** Schematic view of the brain network of ejaculation. Abbreviations: *BNSTpm*—bed nucleus of the stria terminalis posteromedial; *Gi*—gigantocellular; *MeApd*—medial amygdala posterodorsal; *MPOA*—medial preoptic area; *PAG*—periaqueductal grey; *PD*—posterodorsal preoptic; *PVN*—hypothalamic paraventricular; *SPFP*—subparafascicular parvicellular. See details in the text

data collected in different species strongly suggest the existence of a cerebral network specifically related to ejaculation that is activated whatever the preceding copulatory activity, i.e., mounts and intromissions in rats. The brain structures belonging to this cerebral network comprise discrete regions located within the posteromedial bed nucleus of stria terminalis (BNSTpm), the posterodorsal medial amygdaloid nucleus (MeApd), the posterodorsal preoptic nucleus (PNpd), and the parvicellular part of the subparafascicular thalamus (SPFP). Reciprocal connections between those substructures and the medial preoptic area (MPOA) of the hypothalamus, a brain area known as essential in controlling sexual behavior [64], has been reported in anatomical and functional studies [20, 34].

The pivotal role of MPOA in ejaculation has been documented in several experiments where both emission and expulsion phases of ejaculation were abolished after MPOA lesion [5] and elicited after chemical [36, 79] or electrical [48, 56] stimulations of this brain area. Neuroanatomical studies failed to reveal the existence of direct connections between the MPOA and the spinal ejaculatory centers (autonomic or somatic nuclei or SGE). However, it was shown that MPOA projects to other brain regions involved in ejaculation such as the paraventricular hypothalamic nucleus (PVN) [90], the periaqueductal gray (PAG) [84], and the paragigantocellular nucleus (nPGi) [72]. The PVN has long been known as a key site for neuroendocrine and autonomic integration [98]. Parvocellular neurons of the PVN directly innervate autonomic preganglionic neurons in the lumbosacral spinal cord [52, 85] and pudendal motoneurons located in the L5–L6 spinal segment in rats [61]. PVN also sends direct projection to nPGi in the brainstem [7]. Bilateral chemical lesion of the PVN with NMDA was associated with 30 % reduction in the weight of the seminal material expressed [1]. Retrograde and anterograde tracing studies have shown that SPFP sends projections to BNST, MeA, and MPOA [17, 38] and receives inputs from LSt cells [22], suggesting a pivotal role for SPFP. The other forebrain structures which have been proposed, based on Fos protein patterns of expression, to take part in regulation of the ejaculatory process in rats are MeA, BNST, and PNpd [20, 32]. Their precise roles remain unclear but they are very likely involved in integration and relay of sexual cues (auditory, olfactory, and visual) and genital sensory signals to the MPOA.

In the brainstem, different nuclei have received increasing attention. A strong inhibitory role on ejaculation for nPGi, which projects to motoneurons and interneurons in the lumbosacral spinal cord [54, 55], has been suggested in several rat experimental models [54, 57]. Behavioral data provide further support to this view by showing increased expression of Fos protein in nPGi of copulating male rats but not in animals repeatedly ejaculating (more than twice) [21, 32]. An inhibitory influence on ejaculatory reflex was demonstrated for PAG [58]. Actually, as established in neuroanatomical studies, PAG constitutes a relay between MPOA and nPGi [20, 71]. Thus, it can be suggested that a basal brain inhibitory tone on the spinal mechanism of ejaculation exists and its release is required for ejaculation to occur. However, a brain excitatory influence on spinal control of ejaculation also likely exists since intracerebral administration of dopamine agonists can trigger ejaculation in anesthetised rats, without sexual context and in absence of genital stimulation [18, 19, 43]. Clearly, midbrain structures exert a regulating function on ejaculation but further investigations are required for revealing the details of their involvement.

### 3.5.2.2 Human Data

Emergence of non-invasive functional brain imaging techniques with relatively high spatial and temporal resolutions have led to the identification of brain areas involved in the human sexual response. The discrimination of the different components of the sexual response (e.g. arousal, erection, ejaculation) is difficult

because of the intimate relationship between them. However, carefully designed experimental paradigms render possible the specific study of neuronal activity in relation with ejaculation. One brain imaging study has been performed that aimed at investigating the changes in regional cerebral blood flow in humans during ejaculation [34]. This study used positron emission tomography (PET) in healthy male volunteers who received penile stimulation from their female partner until ejaculation occurred. At the time of ejaculation, the strongest activation was found in the mesodiencephalic transition zone including ventral tegmental area (VTA), SPFP, medial and ventral thalamus. Those thalamic areas are known to be associated with rewarding processes, visceral sensory responses, and control of pelvic floor motoneurons and sympathetic preganglionic neurons throughout the spinal cord. Notably, the VTA contains an A10 dopaminergic cell group belonging to the mesolimbic system and has previously been shown to be activated in humans during a cocaine or heroin rush [14, 88]. These observations make the VTA a key element of the neuronal substrate for orgasm. In addition, based on data collected in rats (as described in Sect. 3.5.2.1), the SPFP can also be suggested as an important relay in the human male orgasmic response. Quite unexpected is the intense increase in blood flow in an extended zone (vermis and cortex) of the cerebellum during ejaculation. In addition to its primary role in motor and coordination control as well as proprioception, the cerebellum has also been shown to be involved in sensory and emotional processing [67] and thus its activation concomitant to ejaculation may be related to the orgasmic response. In their PET imaging study, Holstege and collaborators noted that the amygdala was deactivated during ejaculation, as indicated by decreased blood flow. This element of the limbic system is essential for the processing of emotional reactions [3] and, as demonstrated in previous imaging studies in men, is also deactivated during cocaine rush [14] and in correlation with sexual arousal [83]. The release of amygdala influence on other brain areas may constitute the neuronal substrate for the euphoric state related to different contexts including orgasm. It is to be noticed that some results of the brain imaging study of Holstege and collaborators are in disagreement with data obtained in rodents using Fos immunohistochemistry [32, 33]. Most notably, BNST and subregions of the MPOA, which were found to be specifically activated in relation with ejaculation in male rats, did not display changes in blood flow. The lack of MPOA activation during ejaculation was also found in a Fos study performed in monkeys [66] and this suggests the lesser importance of this structure in the control of the ejaculatory response in primates. Human imaging studies have provided key data for understanding the brain functioning during ejaculation but also its participation to other aspects of the sexual response like erection and sexual arousal [6, 83].

Intimately associated with ejaculation and terminating it is an intense pleasurable feeling cerebrally driven, that is orgasm.



### 3.6 Orgasm

Orgasmic sensation systematically accompanies ejaculation although it must be distinguished from emission and expulsion and thus may be regarded, from a neurophysiological perspective, as a third phase in the ejaculatory process. This view is illustrated by cocaine and heroin users reporting orgasmic feeling during drug rush without any sexual stimulation [87]. Orgasm is a complex neuropsychophysiological process that translates in intense cerebral discharge but also whole-body physiological changes.

The exact site in the brain where orgasm is produced is not clearly defined. This is mainly due to the difficulty in developing animal models and in studying orgasm distinctly in humans. The rewarding property of ejaculation in the male rat [81] can be considered as analogous to orgasm and an experimental paradigm exploring that specific aspect of the male sexual response may lead to significant progress in our understanding of the neurophysiology and pharmacology of orgasm. The brain imaging study by Holstege and collaborators (2003) provided clarifications on the possible neuronal substrate of orgasm, as described in Sect. 3.5.2.2. Of particular interest is the observation of activation and deactivation of major components of the limbic system (VTA and amygdala, respectively) during ejaculation as well as concomitantly to cocaine and heroin rush [14, 88, 88]. Moreover, VTA was also found activated during orgasm in women as measured by functional magnetic resonance imaging [45]. In the brain of male rats, SPFP occupies a pivotal role as relaying ejaculation-related sensory stimuli from LSt to the limbic system. The same role is plausible in the human male, as supported by Holstege and collaborators' study (see Sect. 3.5.2.2), although spatial resolution of PET-scan techniques is not sufficient to delimit neuronal activity to such small areas.

What triggers orgasm is still unknown. The flow of sperm throughout the urethra brings pleasurable sensation although it has only a minor role. Indeed, lack of seminal emission (dry ejaculation) does not prevent orgasm as reported by the majority of the patients (54–73 %) having undergone radical prostatectomy—i.e., removal of prostate and seminal vesicles—[26, 65]. In addition, pharmacologically inhibited emission in volunteers had no effect on the orgasmic feeling [28]. Bursting contractions of pelvic perineal striated muscles have been associated with the subjective experience of orgasm but the matching is not 100 %. Orgasm begins just before muscles start to contract and continues for a short period after contractions end [11, 28]. Furthermore, voluntary contractions of pelvic perineal muscles are not accompanied with orgasm. While the peripheral event(s) triggering orgasm is (are) to be identified, it is established that 'orgasmogen' stimuli driven by pelvic perineal somato-sensory afferents enter the spinal cord via dorsal roots, and then reach the brain sites involved in orgasm. As suggested by the recent findings in the male rat (for review see Giuliano, 2007), LSt are likely involved in the orgasmic response as a relay for sensory stimuli from the periphery to the brain structures where the pleasurable feeling arises, and more notably, the first step in cerebral processing of an orgasm may reside in the SPFP.

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Ege Can Serefoglu

The recent increased interest in premature ejaculation (PE) has highlighted the need for better recognition of its epidemiology. However, determining the burden of this sexual problem is a challenging task. First of all, lack of universally acknowledged definitions, of criteria for diagnosis of PE, and of standards for designing observational studies at the time surveys were conducted has hampered an understanding of the true magnitude of this sexual disorder [1, 2]. Moreover, the sensitive nature of this condition may cause additional obstacles resulting in systematic biases, as men with PE may be reluctant to report this complaint due to their concerns of social stigmatization, especially during face-to-face interviews [3]. Conversely, healthy individuals may be tempted to self-report PE, because of believing that they may benefit from participating in a survey. Therefore, health-care professionals and researchers must be aware of the aforementioned limitations in epidemiologic PE studies while evaluating the presented data. After all, “the data speak for themselves” and physicians or scientists must appropriately interoperate their validity.

Prominent media attention, public interest, and various publications often funded by pharmaceutical companies have led to the public belief that the prevalence of PE is very high. However, most of these high prevalence reports are not based on large-scale, broadly representative epidemiologic studies with scientifically sound sampling methods [4]. This chapter aims to provide an up-to-date review and methodological critique of the published descriptive epidemiological data about PE with regard to their validity and reliability.

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Initial studies regarding the prevalence of sexual dysfunctions in the general population were suggestive of a high prevalence rates of PE and have drawn attention to this issue [3, 5]. The first large-scale, systematic survey of sexual dysfunctions in the general population was carried out in 1998 and a stratified random sample was selected from registries of four general practices in England [5]. There, 14 % of the recruited subjects complained about “having difficulty with ejaculating prematurely” in the past three months, whereas 31 % reported this to have happened at some point in their lives. It is interesting that the percentage of men who reported “difficulty in getting or maintaining erection” (26 and 39 % within the last three months and lifetime, respectively) was much higher than subjects reporting PE, probably due to the high age of the men recruited (mean age of 51 years).

A year later the results of a similar study, the National Health and Social Life Survey (NHSLs), were published in the USA, where 1,410 men of younger age (18–59) were recruited [3]. These men were asked whether they experienced “climaxing or ejaculating too rapidly during the past 12 months” and the ones who gave a positive reply to this single dichotomous question were accepted as having PE. Since men may have ejaculated “too rapidly” within the past year for several reasons, such as having sex with a new and sexually attractive partner or abstaining from sex for a longer period of time [6], the authors detected a very high prevalence rate (31 %) for PE [3]. Thereafter, PE has been consistently regarded as the “most common male sexual dysfunction”, in spite of the shortcomings of this study, i.e., of sampling method (63.8 % of subjects were under 40 years of age), improper outcome measure (single dichotomous question), and vague operational criteria (ejaculating too rapidly) .

In 2005, the same question was asked to men between 40 and 80 years old in the Global Study of Sexual Attitudes and Behaviours (GSSAB) survey, which was conducted in 29 countries funded by a pharmaceutical company, using personal and telephone interviews and self-completed mailed questionnaires [7]. There, the worldwide prevalence of PE was also found to be quite high (23.75 %) among the 13,618 men who responded. However, different from NHSLs, these middle-aged and older adults were also asked how often they experienced PE and only 4.26 % reported that they “frequently” ejaculate early. This study is the largest multinational survey that has ever been performed in the field of sexual medicine and several points are noteworthy: (1) As the authors indicated, selection biases (including only men who were over 40 years and using systematic sampling instead of stratified sampling) and a low overall response rate (19 %) hampers the accuracy of the results in this study, (2) The most widely accepted definition of PE at the time that GSSAB was carried out was from the Diagnostic and Statistical Manual of Mental Disorders IV-Text Revision (DSM-IV-TR), which defines PE as a ‘persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it’ [8]. Therefore, only the ones who experience this problem “frequently” (4.26 %) should have been classified as having PE [7]. Indeed, a recent study which used almost the same methodology on a large representative sample of the Danish population, confirmed

**Table 4.1** The prevalence rates of premature ejaculation in population-based cohort studies

Date	Author	Method of data collection	Method of sample recruitment	Specific operational criteria	Prevalence rate (%)	Number of men
1998	Dunn et al. [5]	Mail	General practice registers—random stratification	Having difficulty with ejaculating prematurely	14 (past 3 mo) 31 (lifetime)	617 618
1999	Laumann et al. (NHLS) [3]	Personal interview	National Representative (18–59 years)	Climaxing or ejaculating too rapidly during the past 12 months	31	1410
2002	Fugl-Meyer and Fugl-Meyer [16]	Interview	Population register (18–74 years)	Oftenly ejaculating very shortly after intromission during the past 12 months	9	1475
2004	Rowland et al. [15]	Mailed questionnaire	Internet panel	DSM IV	16.3	1158
2004	Nolazco et al. [20]	Interview	Invitation to outpatient clinic	Ejaculating fast or prematurely	28.3	2456
2005	Laumann et al. (GSSAB) [7]	Telephone-personal interview/ Mailed questionnaires	Random (systematic) sampling	Reaching climax too quickly during the past 12 months	23.75 (4.26 frequently)	13,618
2005	Basile Fasolo et al. [14]	Interview (Clinician-based)	Invitation to outpatient clinic	DSM IV	21.2	12,558
2005	Stulhofer et al. [21]	Interview	Stratified sampling	Oftenly ejaculating in less than 2 min	9.5	601

(continued)

Table 4.1 (continued)

Date	Author	Method of data collection	Method of sample recruitment	Specific operational criteria	Prevalence rate (%)	Number of men
2007	Porst et al. (PEPA) [10]	Web-based survey	Pre-existing internet panels	Control over ejaculation Distress	22.7	12,133
2009	Brock et al. [13]	Web-based survey + telephone interview	Internet panel (random sampling from a representative cohort)	DSM III	16	3816
				Control	26	
				Distress	27	
2010	Traesen and Stigum [17]	Mailed questionnaire + internet	Population register (random sampling)	Having PE frequently during the past 12 months	26-27	11,746 + 1671
2010	Amidu et al. [18]	Questionnaire	Random sampling	N/A	64.7	255
2010	Liang et al. [19]	Questionnaire	Random sampling	ISSM definition	15.3	7372
2010	Park et al. [23]	Mailed questionnaire	Stratified sampling	Suffering from PE	27.5	2037
2011	Serefoglu et al. [22]	Interview	Stratified sampling	Complaining about ejaculating prematurely	20.0	2593
2011	Christensen et al. [9]	Interview + questionnaire	Population register (random sampling)	Having PE frequently within the year before, and perceiving it as a problem (DSM IV)	7	5552

the rightfulness of this criticism [9]. In this study, the authors distinguish PE as a “sexual difficulty” (experiencing PE within the past year) from PE as a clinically relevant “sexual dysfunction” (experiencing PE frequently and perceiving it as a problem). Accordingly, with the prevalence of 7 %, PE was the most frequent “sexual dysfunction”, however this prevalence was much less than PE as a “sexual difficulty” (54 %).

The results of another international study, namely the Premature Ejaculation Prevalence and Attitudes (PEPA) survey, were published in 2007 [10]. Like GSSAB, this study was also funded by a pharmaceutical company and the prevalence of PE, which was assessed according to two criteria (control and distress) of DSM-IV definition was found to be very high (22.7 %). Inherently, this study was not without shortcomings. First of all, although 12,133 multinational volunteers from three pre-existing internet panels were invited to participate with various incentives, only 12 % participated in this study. However, the characteristics of these samples somehow matched the census data in each of the three countries, in spite of the low response rate. This is of interest because it is well known that in almost every cross-sectional study, volunteers have different characteristics from the real population as they tend to be overrepresented with the “worried well” and/or with people who believe they will benefit from participation (volunteer bias). Furthermore, individuals recruited from internet panels, who can afford to buy a computer, use the internet, and check their e-mails do not represent the population secondarily to their higher income status and educational level. Finally, the reward system which had been used to promote participation in PEPA was another source of selection bias, further deteriorating the reliability of its results.

Volunteer couples, who were recruited by radio/newspaper ads and compensated financially, were again part of two observational studies performed in the USA [11] and five European countries [12]. Both of these studies aimed to characterize men with and without PE by seeking the relation between intravaginal ejaculatory latency time (IELT) and patient reported outcome measures (PROs). As the authors of these observational studies did not intend to determine the prevalence of PE in a cross-sectional setting with an appropriate sampling method (i.e. stratified sampling), the percentage of men with PE (USA: 13 % and Europe: 18 %) recorded in these studies cannot be considered to be the prevalence of PE among the general male population.

In several other publications, the prevalence of PE was mainly reported between 9–27 % [13–23], depending on the definition and methodology utilized (Table 4.1). However, only a few of these studies successfully measured the prevalence of PE in a representative population with valid operational criteria and acceptable response rates, obtaining results that could be generalized to the entire population. Additionally, it is of importance that many concerns have been raised regarding the reliability of former definitions of PE, as they were not based on evidence, did not have specific operational criteria, and applied vague and inadequate terminology such as ‘complaints’ or ‘marked distress’ [24–28].

Considering the shortcomings of these former PE definitions, Waldinger and Schweitzer highlighted the importance of distinguishing PE as a “complaint” from

PE as a “syndrome” [24]. These authors draw attention to the misconception that PE has always been regarded as a male sexual syndrome, although it can also be a normal variation of normal ejaculatory response [29]. Furthermore, in addition to the previously defined lifelong and acquired PE syndromes [30], they proposed the existence of two additional PE syndromes, referred to as natural variable PE and premature-like ejaculatory dysfunction. Both of these new syndromes are assumed to be responsible for the previously reported high prevalences of PE [29]. On the other hand, PE complaints of patients with these latter two syndromes are not as severe as lifelong and acquired PE patients, therefore they do not actively seek treatment although they appear in epidemiologic studies [22, 26, 29, 31, 32].

A recent cross-sectional field survey investigated the prevalence of these four PE syndromes with strata being selected by the proportional (stratified) sampling method [22]. Of the 2,593 men involved, 2.3, 3.9, 8.5, and 5.1 % were diagnosed as having lifelong, acquired, natural variable PE syndromes, and premature-like ejaculatory dysfunction, respectively. This confirmed that the prevalence of actual PE patients requiring medical treatment is much lower than the prevalence of men who occasionally complain about ejaculating too rapidly. However, it is noteworthy that although the International Society for Sexual Medicine (ISSM) managed to develop an evidence-based definition for lifelong PE [25], such a definition has not yet been generated for other PE syndromes. Therefore, the remaining three PE syndromes are considered to be provisional but are also thought to be beneficial for health-care professionals in addressing the concerns of men with PE complaints that do not meet the ISSM criteria for lifelong PE [33].

In summary, enhanced attention towards PE has resulted in an increase in published data regarding epidemiology of this sexual disorder over the last decade. However, physicians and researchers must consider the limitations of the epidemiologic methods used while evaluating the quality of these data, most of which were not gathered with well-designed cross-sectional studies, in addition to having their internal/external validities hampered by both information and selection biases. Although, the prevalence of PE has been repeatedly reported to be around 20–30 %, this mainly reflects the proportion of men who occasionally complain from ejaculating prematurely, while the percentage of real PE patients with either lifelong or acquired PE seems to be no more than 8-10%. Similar to the one developed for lifelong PE, evidence-based definitions for acquired PE, natural variable PE, and premature-like ejaculatory dysfunction should be designated in order to conduct further epidemiologic research and confirm whether these rates reflect reality. Moreover, not only descriptive epidemiology but also analytic epidemiology of different PE syndromes must be studied to ascertain the according etiology, pathogenesis, and clinical course and to elucidate potential risk factors for these sexual dysfunctions. Thereafter, target populations for screening PE can be established and appropriate preventive and therapeutic interventions can be set. Since “the data speak for themselves”, one must have an appropriate epidemiologic perspective in order to translate the data to form a meaningful and applicable understanding.

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# Taxonomy of Ejaculatory Disorders and Definitions of Premature Ejaculation

# 5

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## 5.1 Classification of Premature Ejaculation

In 1943, Schapiro proposed a distinction of premature ejaculation (PE) into Types A and B [1]. Men with Type B have always suffered from a very rapid ejaculation (or short latency), whereas in Type A, the rapid ejaculation develops later in life and is often associated with erectile dysfunction (ED). In 1989, these types were respectively referred to as lifelong (primary) and acquired (secondary) PE [2]. Over the years, other attempts have been made to identify various classifications of PE, including several that have been incorporated PE definitions (e.g., global vs. situational, the effect of a substance, etc.). In 2006, Waldinger [3–5] proposed a classification of PE according to a “syndromal” approach and suggested adding two new categories, “Natural Variable Premature Ejaculation” and “Premature-like Ejaculatory Dysfunction” (Table 5.1). In the category of Natural Variable Premature Ejaculation, men suffer only occasionally from rapid ejaculations or short latencies. This pattern might be regarded as part of the normal variability of ejaculatory performance in men rather than a symptom of an underlying psychopathology. In the category of Premature-like Ejaculatory Dysfunction, men subjectively experience and/or voice complaints of PE, while having typical or even long ejaculatory latencies of 4–20 min. Thus, including the longstanding “lifelong” and “acquired” classifications, four PE syndromes are defined [6].

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**Table 5.1** Classification of premature ejaculation

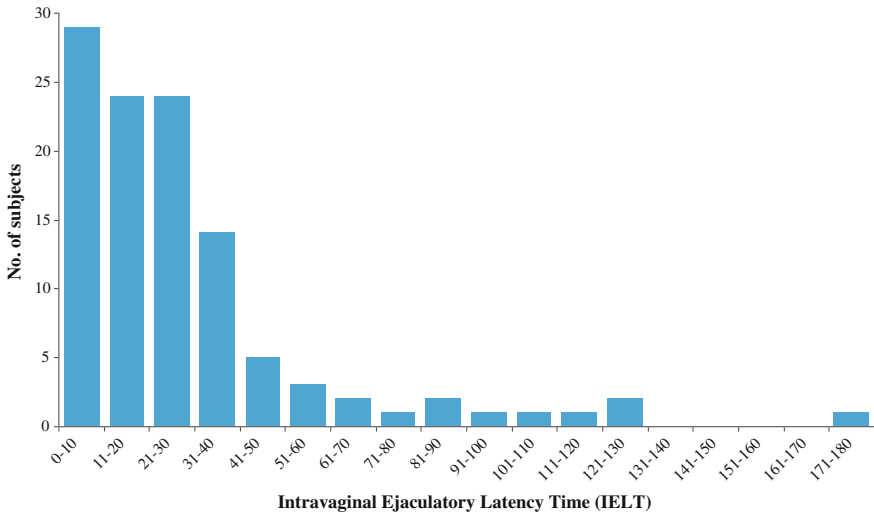
Variable	Lifelong premature ejaculation	Acquired premature ejaculation	Natural variable premature ejaculation	Premature-like ejaculatory dysfunction
IELT	Very short IELT (<1–1.5 min)	(Very) short IELT (<1.5–2 min)	Normal IELT (3–8 min)	Normal or long IELT (3–30 min)
Frequency	Consistent	(In)consistent	Inconsistent	(In)consistent
Etiology	Neurobiological and genetic	Medical and/or psychological	Normal variation of ejaculatory performance	Psychological
Treatment	Medication with or without counselling	Medication and/or psychotherapy	Psycho-education, reassurance	Psychotherapy
Prevalence	Low (?)	Low (?)	High (?)	High (?)

### 5.1.1 Lifelong Premature Ejaculation

With lifelong PE, ejaculation occurs too early at nearly every intercourse, with (nearly) every woman, and from about the first sexual encounters onwards. Based on self-selected samples, the majority of these men (80–90 %) ejaculate intravaginally within 30–60 s, and most of the remainder (10 %) between 1 and 2 min (Fig. 5.1). As the prevalence of an intravaginal ejaculatory latency time (IELT) of less than 1 min in unselected male cohorts in mainly Western countries is about 1–3 %, the prevalence of lifelong PE may be rather low [7]. The ejaculation remains rapid during life in the majority (70 %) of these men or may be aggravated during the course of aging (30 %). Some men ejaculate during foreplay, before penetration (ejaculatio ante portas), or as soon as their penis touches the vagina (ejaculatio intra portas). No accepted cure for lifelong PE is known, but various drugs (including SSRIs) and psychotherapy treatments may be effective in postponing the ejaculatory response [6].

### 5.1.2 Acquired Premature Ejaculation

Complaints of men with acquired PE differ in relation to the underlying somatic or psychological problem. In these men, PE occurs at some point in a man's life after experiencing normal ejaculatory latencies; the onset may be either sudden or gradual. Acquired PE differs in that sufferers develop early ejaculation at some point in their life having previously had normal ejaculation experiences. Acquired PE may be due to sexual performance anxiety [8], psychological or relationship problems [8, 9], ED [10], prostatitis [11], hyperthyroidism [12], or during withdrawal/detoxification from prescribed [13] or recreational drugs [14, 15]. In a study of 1,326 consecutive men with PE, lifelong PE was present in 736 men (74.4 %), and acquired PE was



**Fig. 5.1** Intravaginal ejaculation latency time (IELT) measured with stopwatch in 110 men with lifelong premature ejaculation, of whom 90 % ejaculated within 1 min after vaginal penetration, including 80 % within 30 s

present in 253 men (25.6 %) [16]. The acquired form of PE may be cured by medical and/or psychological treatment of the underlying cause [6].

### 5.1.3 Natural Variable Premature Ejaculation

Men exhibiting this pattern experience short ejaculatory latencies only in certain situations. This type of response should not be regarded as a symptom or manifestation of underlying psychopathology but of normal variation in sexual performance. The syndrome is characterized by the following symptoms. (i) short ejaculatory latencies are inconsistent and occur irregularly, (ii) the ability to delay ejaculation, that is, to withhold ejaculation at the moment of imminent ejaculation, may be diminished or lacking, and (iii) the experience of diminished control of ejaculation is associated with either a short or normal ejaculation time, that is, an ejaculation of less or more than 1.5 min. Treatment of these men should consist of reassurance and education that this pattern of ejaculatory response is normal and does not require drug treatment or psychotherapy [6].

### 5.1.4 Premature-Like Ejaculatory Dysfunction

Men under this classification experience or complain of PE while the ejaculation time is in the normal range, i.e., around 2–6 min, and in some instances the ejaculatory latency may even be of very long duration, i.e., between 5 and 25 min [6].

This response should not be regarded as a symptom of an underlying medical or neurobiological pathology although psychological and/or relationship problems may underlie the complaint. The syndrome is characterized by the following symptoms: (i) subjective perception of consistent or inconsistent short ejaculatory latency during intercourse, (ii) preoccupation with an imagined early ejaculation or lack of control of ejaculation, and (iii) the IELT is in the normal or even long range (i.e., an ejaculation that occurs between 3 and 25 min), and (iv) the ability to delay ejaculation may be diminished or lacking.

As the duration of the ejaculation latency in these men is normal, the experience of the response is not related to a medical or neuro-biological disturbance [6]. Rather, there is either a misperception of the actual ejaculation time, for various reasons, or the ejaculation latency is too short for the female partner to attain an orgasm. Complaints of these men may be alleviated by the various sorts of psychotherapy and treatment should not a priori assume the use of pharmaceuticals. However, evidence-based controlled trials are required to investigate the optimal treatment for couples affected by this pattern of responding.

In 261 potent men with self-reported PE, Serefoglu et al. found that the majority of the men were diagnosed with lifelong PE (62.5 %); the remaining men were diagnosed as having acquired (16.1 %), natural variable PE (14.5 %), or premature-like ejaculatory disorder (6.9 %) [17]. Men with lifelong PE had significantly lower mean self-reported IELT ( $20.47 \pm 28.90$  s), whereas men with premature-like ejaculatory dysfunction had the highest mean IELT ( $286.67 \pm 69.96$  s,  $p = 0.001$ ).

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## 5.2 Definitions of Premature Ejaculation

Research into the treatment and epidemiology of PE is heavily dependent on how PE is defined. The medical literature contains several univariate and multivariate operational definitions of PE. [18–26], (Table 5.2). Each of these definitions characterize men with PE using all or most of the accepted dimensions of this condition: ejaculatory latency, perceived ability to control ejaculation, and negative psychological consequences of PE including reduced sexual satisfaction, personal distress, partner distress, and interpersonal or relationship distress. The major criticisms of the extant definitions included their failure to be evidenced-based, lack of specific operational criteria, excessive vagueness, and reliance on the subjective judgment of the diagnostician.

### 5.2.1 Traditional Definitions

The first official definition of PE was proposed in 1980 by the American Psychiatric Association (APA) in the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) [27]. This definition was progressively revised as the DSM-III-R, DSM-IV, and finally DSM-IV-TR definitions to include the “shortly after penetration” as an ejaculatory latency criterion, “before the person wishes it” as a control criterion

**Table 5.2** Definitions of premature ejaculation

Definition	Source
A male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within 1 min of vaginal penetration, and the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress bother, frustration and/or the avoidance of sexual intimacy	International Society of Sexual Medicine [45]
Persistent or recurrent ejaculation with minimal sexual stimulation, before, on or shortly after penetration and before the person wishes it. The condition must also cause marked distress or interpersonal difficulty and cannot be due exclusively to the direct effects of a substance	DSM-IV-TR [29]
For individuals who meet the general criteria for sexual dysfunction, the inability to control ejaculation sufficiently for both partners to enjoy sexual interaction, manifest as either the occurrence of ejaculation before or very soon after the beginning of intercourse (if a time limit is required, before or within 15 s) or the occurrence of ejaculation in the absence of sufficient erection to make intercourse possible. The problem is not the result of prolonged absence from sexual activity	International Statistical Classification of Disease, 10th edn. [20]
The inability to control ejaculation for a “sufficient” length of time before vaginal penetration. It does not involve any impairment of fertility, when intravaginal ejaculation occurs	European Association of Urology. Guidelines on Disorders of Ejaculation [23]
Persistent or recurrent ejaculation with minimal stimulation before, on, or shortly after penetration, and before the person wishes it, over which the sufferer has little or no voluntary control, which causes the sufferer and/or his partner bother or distress	International Consultation on Urological Diseases [24]
Ejaculation that occurs sooner than desired, either before or shortly after penetration, causing distress to either one or both partners	American Urological Association Guideline on the Pharmacologic Management of Premature Ejaculation [22]

(continued)

Table 5.2 (continued)

Definition	Source
The man does not have voluntary, conscious control, or the ability to choose in most encounters when to ejaculate	Metz and McCarthy [21]
The Foundation considers a man a premature ejaculator if he cannot control his ejaculatory process for a sufficient length of time during intravaginal containment to satisfy his partner in at least 50 percent of their coital connections	Masters and Johnson [18]
Men with an IELT of less than 1 min (belonging to the 0.5 %) have “definite” premature ejaculation, while men with IELTs between 1 and 1.5 min (between 0.5 and 2.5 %) have “probable” premature ejaculation (Fig. 5.2). In addition, an additional grading of severity of premature ejaculation should be defined in terms of associated psychological problems. Thus, both definite and probable premature ejaculation need further psychological subclassification in nonsymptomatic, mild, moderate, and severe premature ejaculation	Waldinger et al. [44]

and “causes marked distress or interpersonal difficulty” as a criterion for the negative psychological consequences of PE [19, 28, 29]. Although DSM-IV-TR, the most commonly quoted definition, and other definitions of PE differ substantially, they are all authority-based, i.e., expert opinion without explicit critical appraisal, rather than evidence-based, and have no support from controlled clinical and/or epidemiological studies [30]. The DSM definitions are primarily conceptual in nature, vague in terms of operational specificity, multi-interpretable, fail to provide any diagnostic IELT cut-off points and rely on the subjective interpretation of these concepts by the clinician [31, 32]. The absence of a clear IELT cut-off point in the DSM definitions has resulted in the use of a broad range of subjective latencies for the diagnosis of PE in clinical trials ranging from 1 to 7 min [33–41]. The failure of DSM definitions to specify an IELT cut-off point means that a patient in the control group of one study may very well be in the PE group of a second study, making comparison of studies difficult and generalization of their data to the general PE population impossible.

This potential for errors in the diagnosis of PE was demonstrated in two recent observational studies in which PE was diagnosed solely by the application of the DSM-IV-TR definition [42, 43]. Giuliano et al. diagnosed PE using DSM-IV-TR criteria in 201 of 1,115 subjects (18 %) and predictably reported that the mean and median IELT was lower in subjects diagnosed with PE compared to non-PE subjects. There was, however, substantial overlap in stopwatch IELT values between the two groups. In subjects diagnosed with PE, the IELT range extended from 0 s (ante-portal ejaculation) to almost 28 min with 48 % of subjects having an IELT in excess of 2 min and 25 % of subjects exceeding 4 min. This study demonstrates that a subject diagnosed as having PE on the basis of DSM-IV-TR criteria has a 48 % risk of not having PE if a PE diagnostic threshold IELT of 2 min, as suggested by community-based normative IELT trial, is used [44].

## 5.2.2 Lifelong Premature Ejaculation

The first contemporary multivariate evidence-based definition of lifelong PE was developed in 2008 by a panel of international experts, convened by the International Society for Sexual Medicine (ISSM), who agreed that the diagnostic criteria necessary to define PE are: time from penetration to ejaculation, inability to delay ejaculation and negative personal consequences from PE. This panel defined lifelong PE as a male sexual dysfunction characterized by... “...ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, the inability to delay ejaculation on all or nearly all vaginal penetrations, and the presence of negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy” [45].

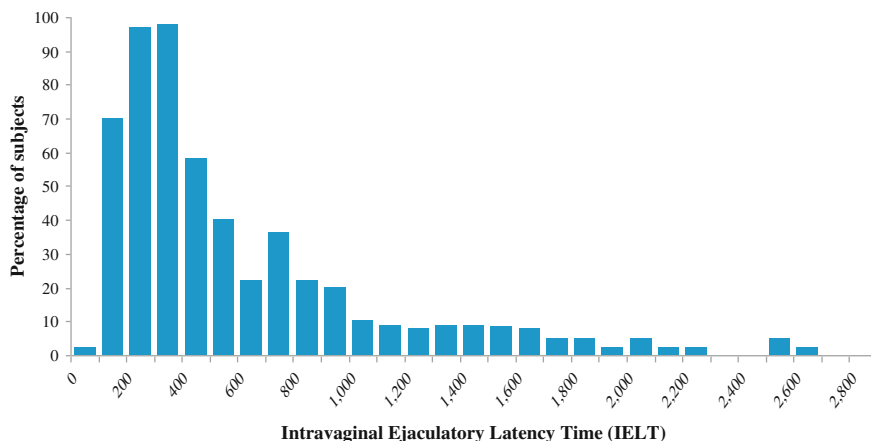
This definition is supported by evidence from several controlled clinical trials.

*Evidence to support inclusion of the criterion of “...ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration ...” (Table 5.3).*

**Table 5.3** Findings of key publications regarding the time-to-ejaculate in PE

Author/s	Summary of primary findings
Waldinger et al. [51]	110 men with lifelong PE whose IELT was measured by the use of a stopwatch 40 % of men ejaculated within 15 s, 70 % within 30 s, and 90 % within 1 min
McMahon [16]	1,346 consecutive men with PE whose IELT was measured by the use of a stopwatch/wristwatch 77 % of men ejaculated within 1 min
Waldinger et al. [52]	88 men with lifelong PE who self-estimated IELT 30 % of men ejaculated within 15 s, 67 % within 30 s, and 92 % within 1 min after penetration Only 5 % ejaculated between 1 and 2 min
Waldinger et al. [44]	Stopwatch IELT study in a random unselected group of 491 men in five countries IELT had a positive skewed distribution Application of 0.5 and 2.5 % as disease standards 0.5 % equated to an IELT of 0.9 min and 2.5 % to an IELT of 1.3 min
Althof [47]	IELT estimations for PE men correlate reasonably well with stopwatch-recorded IELT
Pryor et al. [48]	IELT estimations for PE men correlate reasonably well with stopwatch-recorded IELT
Rosen et al. [49]	Self estimated and stopwatch IELT as interchangeable Combining self-estimated IELT and PROs reliably predicts PE

- Operationalization of PE using the length of time between penetration and ejaculation, the IELT, forms the basis of most current clinical studies on PE [46]. Intravaginal ejaculatory latency time can be measured by a stopwatch or estimated. Several authors report that estimated and stopwatch IELT correlate reasonably well or are interchangeable in assigning PE status when estimated IELT is combined with PROs [47–49].
- Normative multinational (Netherlands, United Kingdom, United States, Spain, and Turkey) reports of IELT been only recently been published [7]. The median IELT was 5.4 min (range, 0.55–44.1 min) and the distribution of the IELT in all five countries was positively skewed (Fig. 5.2). The median IELT decreased significantly with age, from 6.5 min in the 18–30 years group, to 4.3 min in the group older than 51 years. Median IELT varied between countries, with Turkey having the lowest IELT. The median IELT value was independent of condom use or circumcision status (except in Turkey). A similar study conducted a few years later reported congruent results with a median IELT of 6 (range 0.1–15.2 min) [50].
- Several studies suggest that 80–90 % of men seeking treatment for lifelong PE ejaculate within 1 min (Fig. 5.1) [16, 51, 52]. Waldinger et al. [51] reported IELTs <30 s in 77 % and <60 s in 90 % of 110 men with lifelong PE with



**Fig. 5.2** Distribution of intravaginal ejaculatory latency times (IELT) values in a random cohort of 491 men with a median IELT of 5.4 min [37]

only 10 % ejaculating between 1 and 2 min. These data are consistent with normative community IELT data, support the notion that IELTs of <1 min are statistically abnormal and confirm that an IELT cut-off of 1 min will capture 80–90 % of treatment seeking men with lifelong PE [44]. Further qualification of this cut-off to “about one minute” affords the clinician sufficient flexibility to also diagnose PE in the 10–20 % of PE treatment seeking men who ejaculate within 1–2 min of penetration without unnecessarily stigmatising the remaining 80–90 % of men who ejaculate within 1–2 min of penetration but have no complaints of PE.

*Evidence to support inclusion of the criterion of “...the inability to delay ejaculation on all or nearly all vaginal penetrations...”* (Table 5.4).

- The ability to prolong sexual intercourse by delaying ejaculation and the subjective feelings of ejaculatory control comprise the complex construct of ejaculatory control. Virtually all men report using at least one cognitive or behavioral technique to prolong intercourse and delay ejaculation, with varying degrees of success, and many young men reported using multiple different techniques [53]. Voluntary delay of ejaculation is most likely exerted either prior to or in the early stages of the emission phase of the reflex but progressively decreases until the point of ejaculatory inevitability [54, 55].
- Several authors have suggested that an inability to voluntarily defer ejaculation defines PE [56–59]. Patrick et al. reported ratings of “very poor” or “poor” for control over ejaculation in 72 % of men with PE compared to 5 % in a group of normal controls [42]. Lower ratings for control over ejaculation were associated with shorter IELT with “poor” or “very poor” control reported by 67.7, 10.2, and 6.7 % of subjects with IELT <1 min, >1, and >2 min respectively.



**Table 5.4** Findings of key publications regarding ejaculatory control in PE

Author/s	Summary of primary findings
Grenier and Byers [53]	Relatively weak correlation between ejaculatory latency and ejaculatory control ( $R = 0.31$ ) Ejaculatory control and latency are distinct concepts
Grenier and Byers [60]	Relatively poor correlation between ejaculatory latency and ejaculatory control, sharing only 12 % of their variance suggesting that these PROs are relatively independent
Waldinger et al. [51]	Little or no control over ejaculation was reported by 98 % of subjects during intercourse Weak correlation between ejaculatory control and stopwatch IELT ( $p = 0.06$ )
Rowland et al. [63]	High correlation between measures of ejaculatory latency and control ( $R = 0.81, p < 0.001$ )
Patrick et al. [42]	Men diagnosed with PE had significantly lower mean ratings of control over ejaculation ( $p < 0.0001$ ) 72 % of men with PE reporting ratings of “very poor” or “poor” for control over ejaculation compared to 5 % in a group of normal controls Intravaginal ejaculatory latency time (IELT) was strongly positively correlated with control over ejaculation for subjects ( $R = 0.51$ )
Giuliano et al. [64]	Men diagnosed with PE had significantly lower mean ratings of control over ejaculation ( $p < 0.0001$ ) “Good” or “very good” control over ejaculation in only 13.2 % of PE subjects compared to 78.4 % of non-PE subjects Perceived control over ejaculation had a significant effect on intercourse satisfaction and personal distress IELT did not have a direct effect on intercourse satisfaction and had only a small direct effect on personal distress
Patrick et al. [65]	Effect of IELT upon satisfaction and distress appears to be mediated via its direct effect upon control
Rosen et al. [49]	Control over ejaculation and subject assessed level of personal distress are more influential in determining PE status than IELT Subject reporting “very good” or “good” control over ejaculation is 90.6 % less likely to have PE than a subject reporting “poor” or “very poor” control over ejaculation

- However, control is a subjective measure which is difficult to translate into quantifiable terms and is the most inconsistent dimension of PE. Control has yet to be adequately operationalized to allow comparison across subjects or across studies. Grenier and Byers failed to demonstrate a strong correlation between ejaculatory latency and subjective ejaculatory control [53, 60]. Several authors report that diminished control is not exclusive to men with PE and that some men with a brief IELT report adequate ejaculatory control and vice versa, suggesting that the dimensions of ejaculatory control and latency are distinct concepts [42, 53, 61]. Furthermore, there is a higher variability in changes in control compared to IELT in men treated with SSRIs [62].

- Contrary to this several authors have reported a moderate correlation between the IELT and the feeling of ejaculatory control [42, 49, 63, 64]. Rosen et al. report that control over ejaculation, personal distress and partner distress was more influential in determining PE status than IELT [49]. In addition, the effect of IELT upon satisfaction and distress appears to be mediated via its direct effect upon control [65].
- However, despite conflicting data on the relationship between control and latency, the balance of evidence supports the notion that the inability to delay ejaculation appears to differentiate men with PE from men without PE [42, 66].  
*Evidence to support exclusion of the criterion of sexual satisfaction*
- Men with PE report lower levels of sexual satisfaction compared to men with normal ejaculatory latency. Patrick et al. reported ratings of “very poor” or “poor” for sexual satisfaction in 31 % of subjects with PE compared to 1 % in a group of normal controls [42, 64].
- However, caution should be exercised in assigning lower levels of sexual satisfaction solely to the effect of PE and contributions from other difficult to quantify issues such reduced intimacy, dysfunctional relationships, poor sexual attraction, and poor communication should not be ignored. This is supported by the report of Patrick et al. that despite reduced ratings for satisfaction with shorter IELTs, a substantial proportion of men with an IELT <1 min report “good” or very good” satisfaction ratings (43.7 %).
- The current data is limited but suggests that sexual satisfaction is of limited use in differentiating PE subjects from non-PE subjects and was not included in the ISSM definition of PE [42].

*Evidence to support inclusion of the criterion of “... the presence of negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy” (Table 5.5).*

- Premature ejaculation has been associated with negative psychological outcomes in men and their women partners [8, 42, 43, 66–77]. Patrick et al. reported significant differences in men with and without PE in the PRO measures of personal distress (64 vs. 4 %) and interpersonal difficulty (31 vs. 1 %), suggesting that this personal distress has discriminative validity in diagnosing men with and without PE.
- The personal and/or interpersonal distress, bother, frustration and annoyance that results from PE may affect men’s quality of life and partner relationships, their self-esteem and self-confidence, and can act as an obstacle to single men forming new partner relationships [8, 42, 43, 66–77]. McCabe reported that sexually dysfunctional men, including men with PE, scored lower on all aspects of intimacy (emotional, social, sexual, recreational and intellectual) and had lower levels of satisfaction compared to sexually functional men ( $p < 0.001$  or  $p < 0.01$ ) [72]. Rowland et al. showed that men with PE had significantly lower overall health-related quality of life, total Self-Esteem and Relationship Questionnaire (SEAR) scores and lower confidence and self-esteem compared to non-PE groups [70]. PE men rated their overall health-related quality of life lower than men without PE ( $p \leq 0.001$ ).

**Table 5.5** Findings of key publications regarding the negative personal consequences of PE

Author/s	Summary of Primary Findings
Patrick et al. [42]	Using the validated Premature Ejaculation Profile (PEP), 64 % of men in the PE group vs. 4 % in the non-PE group reported personal distress
Giuliano et al. [64]	On the Premature Ejaculation Profile (PEP) 44 % of men in the PE group vs. 1 % of men in non-PE group reported personal distress
Rowland et al. [70]	Men in highly probably PE group reported greater distress vs. men in non-PE group on PEP scale On the Self Esteem and Relationship Questionnaire (SEAR) men with highly probable PE had lower mean scores overall, for confidence and self-esteem vs. non PE men
Rowland et al. [66]	30.7 % of probable PE group, 16.4 % of possible PE group vs. 7.7 % of non-PE group found it difficult to relax and not be anxious about intercourse
Porst et al. [67]	Depression reported by 20.4 % of PE group vs. 12.4 % of non-PE group Excessive stress in 28 % of PE group vs. 19 % of non-PE group Anxiety in 24 % of PE group vs. 13 % on non-PE group
McCabe [72]	Sexually dysfunction men, including those with PE, scored lower than sexually functional men on all measures of intimacy on the Psychological and Interpersonal Relationship Scale (PAIRS)
Symonds et al. [69]	68 % reported self esteem affected by PE. Decreased confidence in sexual encounter Anxiety reported by 36 % (causing PE or because of it) Embarrassment and depression also cited due to PE
Dunn et al. [68]	Strong association of PE with anxiety and depression on the Hospital and Anxiety Scale
Hartmann et al. [8]	58 % of PE group reported partner's behavior and reaction to PE was positive and 23 % reported it was negative.
Byers et al. [73]	Men with PE and their partners reported slightly negative impact of PE on personal functioning and sexual relationship but no negative impact on overall relationship

This definition should form the basis for the office diagnosis of lifelong PE. It is limited to heterosexual men engaging in vaginal intercourse as there are few studies available on PE research in homosexual men or during other forms of sexual expression. The panel concluded that there is insufficient published evidence to propose an evidenced-based definition of acquired PE [45]. However, recent data suggests that men with acquired PE have similar IELTs and report similar levels of ejaculatory control and distress, suggesting the possibility of a single unifying definition of PE [78].

The evidence suggests that the multivariate evidence-based ISSM definition of lifelong PE provides the clinician a more discriminating diagnostic tool. The IELT cut-off of about one minute captures the 90 % of men with PE who actively seek treatment and ejaculate within 1 min but also affords the clinician sufficient flexibility to also diagnose PE in the 10 % of PE treatment seeking men who ejaculate within 1–2 min of penetration. This definition fails to specify the duration of symptoms required to diagnose PE. This is of paramount importance in adolescents and young men who complain of rapid ejaculation due to performance anxiety during their first sexual experiences and may incorrectly categorising as suffering from lifelong PE. Data from Oberg et al. indicate that the requirement of 6 months' duration might be used to separate transient from chronic complaints [79].

If the ISSM definition is used, men who ejaculate in <1 min but report adequate control and no personal negative consequences related to their rapid ejaculation do not merit the diagnosis of PE. Similarly, men who have IELTs of 10 min but report poor control, dissatisfaction and personal negative consequences also fail to meet the criteria for PE. It is likely that the constructs and criteria of the ISSM definition of lifelong PE will be adopted as modifications to the criteria sets for PE by the DSM-V committee [80].

### 5.2.3 Acquired Premature Ejaculation

At this point of time, there is insufficient published evidence to propose an evidenced-based definition of acquired PE [45]. Although no logical reasons exist for suspecting substantial differences in IELTs and patient reported outcomes (PROs) in patients with lifelong or acquired PE, the lack of evidence-based IELT and PRO data has thus far frustrated the efforts of scientific societies and consensus conferences to reach a definition of acquired PE. The only consensus at this juncture is that acquired PE occurs after a period of normal ejaculatory latency and control. However, recent unpublished data suggests that men with acquired PE have similar IELTs and report similar levels of ejaculatory control and distress to men with lifelong PE, suggesting the possibility of a single unifying definition of PE [78].

A post hoc analysis of subject baseline characteristics from two randomized, double-blind, placebo-controlled, phase 3 dapoxetine clinical trials demonstrated that baseline IELT and the PROs of control, ejaculation-related personal distress, and interpersonal difficulty were similar in men with acquired and lifelong PE [78]. Although a marginally shorter mean IELT was observed among men with lifelong PE, the difference in IELT values between men with acquired and lifelong PE is not considered large enough to suggest that IELT could be applied as a discriminating factor for PE subtype. Besides duration of PE, the analyses of baseline demographics and sexual history revealed no differences in patient characteristics that might have diagnostic utility in discriminating between acquired and lifelong. Patient age and the reported duration of the sexual

relationship was similar between men with acquired and lifelong PE. In addition, there was no difference in circumcision status, marital status, or intercourse frequency.

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Marcel D. Waldinger

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## 6.1 Introduction

A major contribution to the field of premature ejaculation (PE) was the distinction of PE in Type A and B by Bernhard Schapiro in 1943 [1]. In 1989, Godpodinoff renamed these subtypes as primary (lifelong) and secondary (acquired) PE [2]. However, despite this distinction, all DSM versions maintained a single definition of PE. This persistence to maintain a single definition of PE is unfortunate but understandable, as for many decades the core clinical features of both lifelong and acquired PE had not been systematically investigated. However, the situation changed after the introduction of the selective serotonin reuptake inhibitors (SSRIs) in the early 1990s. In addition, the nearly complete absence of objective measures for PE research and the need for evidence-based data necessitated the development of an evidence-based operational definition of lifelong PE for daily SSRI treatment studies in men with lifelong PE. Therefore, the data that led to the new ISSM definition of lifelong PE [3] originates in the SSRI treatment studies of lifelong PE in the mid-1990s.

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## 6.2 Intravaginal Ejaculation Latency Time

The first requirement for an evidence based operational definition of both lifelong and acquired PE was an objective clinical measure for the ejaculation time. For this purpose, Waldinger et al. introduced the intravaginal ejaculation latency time (IELT) in 1994 [4]. The IELT was defined as the time between vaginal intromission and intravaginal ejaculation [4]. This measure with its clear starting and endpoint, has highly contributed to more objective research of the ejaculation time in heterosexual men with and without PE. Waldinger also proposed the masturbation ejaculation latency time (MELT), oral ejaculation latency time (OELT), and anal ejaculation latency time (AELT) as measures for research in homosexual men and heterosexual men without partners [5], but so far only the IELT has been used in PE research of heterosexual males.

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## 6.3 IELT in Men with Lifelong PE

In a clinical study of 110 Dutch men with lifelong PE, recruited by advertisement, the duration of the IELT was measured by a stopwatch operated by the female partner [6]. According to the participating couples, the use of a stopwatch did not interfere with sexual intercourse. The study showed that 40 % of men ejaculated within 15 s, 70 % within 30 s, and 90 % within 1 min after penetration. Only 10 % ejaculated between 1 and 2 min. McMahon reported similar results in 1,346 consecutive men with PE and a mean IELT of 43.4 s [7]. The same results were also obtained in a third clinical study of 88 men with lifelong PE, in which the participating men were actively seeking medical treatment at an outpatient clinic for sexual disorders [8]. In this study, the IELT was not measured by a stopwatch but evaluated as a self-perceived patient reported outcome (PRO). The study showed that 30 % of men ejaculated within 15 s, 67 % within 30 s, and 92 % within 1 min after penetration. Only 8 % ejaculated between 1 and 2 min. These clinical studies demonstrate that the majority of men with lifelong PE who were seeking medical treatment, ejaculate within 1 min after penetration with only approximately 10 % ejaculating between 1 and 2 min. As such, it appears that the majority of men (90 %) who ejaculate between 1 and 2 min do not seek medical treatment for their complaints. Notably, as lifelong PE is not a life-threatening disorder, it is not necessary to set the threshold at 100 %. On the contrary, in order not to stigmatize the majority of men who ejaculate within 1 and 2 min and who have no complaints of PE, it is better to choose a 90 % cut-off point of the IELT. By using a 90 % cut-off point, lifelong PE can be operationally defined by the (very) short ejaculation time criterion of 1 min after penetration. Interestingly, this 1 min criterion which was established by Waldinger et al. in 1998 [6] confirmed the criterion of about 1 min, that was used by psychoanalysts in the 1930s to the 1960s, but was rejected by Masters and Johnson [9] who were of the opinion that the duration of the ejaculation time was not a clinical marker of PE at all. Their

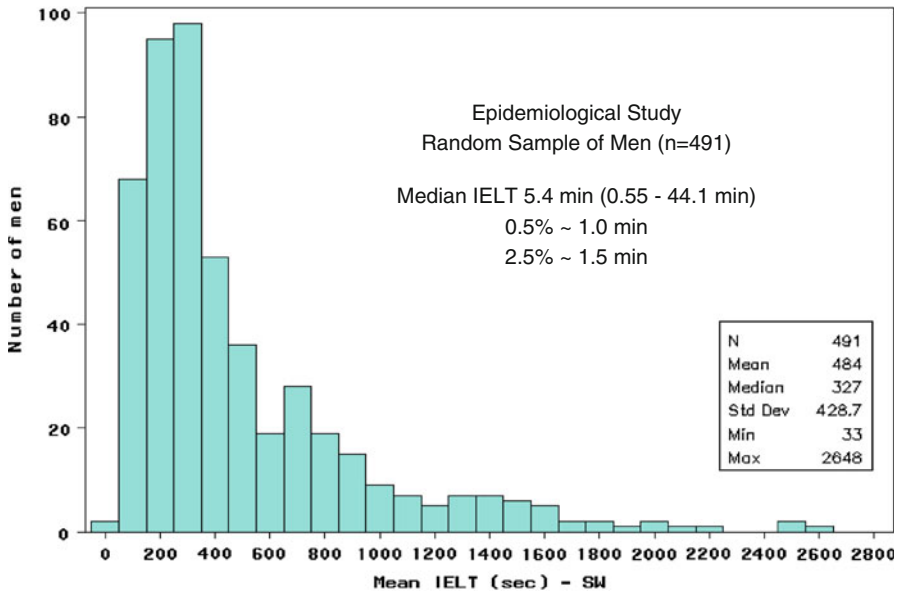


Fig. 6.1 Epidemiological stopwatch study in general male population in five countries [12]

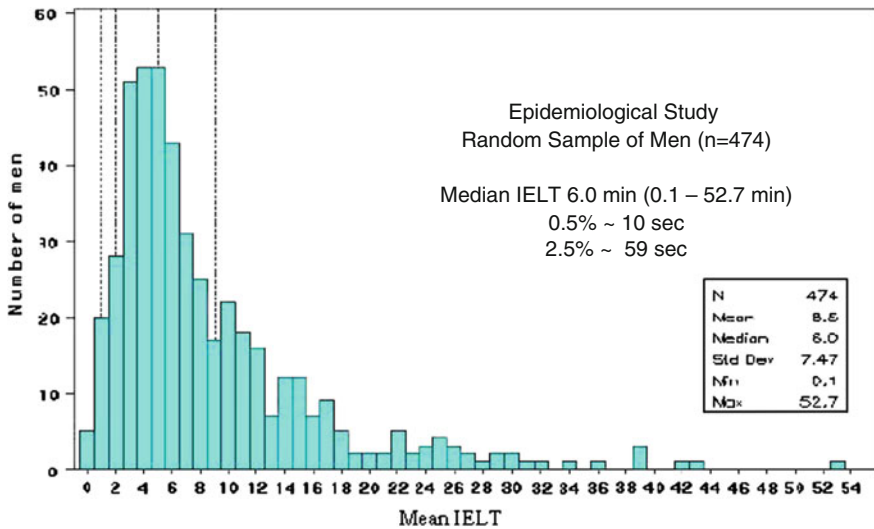


Fig. 6.2 Epidemiological blinded-stopwatch study in general male population in five countries [13]

rejection of it and the uncritical acceptance of their “opinion” by sexologists in the 1970s and 1980s has contributed to a dispute that still exists today among professionals.

## 6.4 Variability of the IELT

Until the late 1990s, no data existed on the mean IELT and the sort of IELT distribution in the general male population. However, in 1998, Waldinger et al. [10] postulated that there was a variability of the IELT in the general male population. Such a variability of the ejaculation latency time was for the first time shown in male Wistar rats [11]. And a few years later, in 2005, such a continuum of the IELT was also for the first time demonstrated in a stopwatch study in a random sample of males in five countries (Fig. 6.1), [12]. Moreover, in 2009 the study was repeated in another random sample of men in the same countries, but now by using a blinded stopwatch so that the volunteers had no idea of the value of the IELT that they had measured. Remarkably, this study provided nearly identical IELT values (Fig. 6.2), [13]. Both studies showed that there is a variability of the IELT in the general male population, with about 2.5 % of men ejaculating within 1 min. According to statistics this means that 2.5 % of males experience ejaculation times that from a statistical point of view are abnormal compared to the ejaculation times of the general male population. Although the methodology of both studies did not allow to make such a conclusion, it may well be that the 2.5 % of men suffered from lifelong PE. But what is the cause of this variability of the IELT?

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## 6.5 Neurobiology and Genetics of the IELT

In 1998, Waldinger et al. [10] postulated that the variability of the IELT is caused by neurobiological and genetic factors, e.g., that the persistently short IELTs in men with lifelong PE are associated with diminished serotonin (5-hydroxytryptamine, or 5-HT) neurotransmission, a hypersensitivity of 5-HT<sub>1A</sub> receptors, and/or a hypofunction of 5-HT<sub>2C</sub> receptors. Notably, due to an absence of selective 5-HT<sub>1A</sub> and 5-HT<sub>2C</sub> receptor ligands for safe human usage, this hypothesis has so far not been confirmed.

It should be noted that a characteristic feature of lifelong PE is the inability of a man to control the duration of his IELTs. Whatever the man would do, whatever techniques applied, whatever he thinks, or feels, his IELT is nearly always a matter of seconds, without much variation. However, usually these men mention that an IELT is sometimes longer than usual for unknown reasons. Actually, the affected man with lifelong PE is victim of his own very short IELTs and he is not able to change it. Men with lifelong PE have a rigid pattern of very short IELTs, without having the capability to change this rigidity. What causes this rigid pattern of short IELTs? The answer to this question is related to central neurobiological mechanisms and may also be related to genetic aberrations in certain neurotransmitters and neurotransmitter receptor functioning.

## 6.6 Genetic Polymorphism in Lifelong Premature Ejaculation

In 2009, Janssen et al. [14] published the first (quantitative) case-control association study in men with lifelong PE, defined in terms of an IELT of less than 1 min. Janssen et al. [14], investigated 89 men who actively sought medical treatment for lifelong PE. In these men, the IELT was measured with a stopwatch. It was shown that the IELT duration in men with LPE is associated with 5-HTLPR polymorphism, indicating the presence of a disturbance of central serotonin neurotransmission, which is regulated by the activity of the 5-HT transporter. The study showed that the prevalence of LL, SL, and SS genotypes in LPE is comparable with the normal Dutch population. However, subjects with LL genotype (geometric mean IELT 13.2 s) ejaculated 100 % faster ( $p < 0.027$ ) than men with SS genotype (geometric mean IELT 26 s) and SL genotype (geometric mean IELT 25.3 s) [14]. The strength of this study is that by using a stopwatch, accurate measurement of the IELT was performed which made it possible to find an association between the IELT and the investigated genotypes. However, a limitation of this case-control design is that by using this method one cannot investigate the influence of genetic polymorphism on the median IELT of about 6 min in the general male population. Interestingly, this finding is in line with pharmacological knowledge, indicating that a diminished serotonergic neurotransmission facilitates ejaculation.

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## 6.7 Different Levels of Pathophysiology

From a statistical point of view it is just bad luck to have an IELT of less than 1 min, as this is just one end of the variability of the IELT in men in the general population. However, from a genetic point of view, there is now some preliminary evidence that the persistent short IELTs in men with lifelong PE may be due to genetic polymorphism of central serotonergic neurotransmission. And from a neurobiological point of view lifelong PE is possibly related to dysfunction of 5-HT<sub>1A</sub> and 5-HT<sub>2C</sub> receptors in brain areas that are specifically involved in ejaculatory functioning [10]. But what exactly is the problem in lifelong PE? Clearly, the neurophysiology of ejaculation itself is not disturbed in lifelong PE [15]. Rather, it is the timing of ejaculation that is persistently disturbed in men with lifelong PE [16]. And the timing of ejaculation is associated with a multitude of variables that have not yet been fully investigated. For example, how is timing related to the sensory information system of the peripheral and central nervous system? How is timing related to the motoric output system of both nervous systems? How is timing associated with genetic polymorphisms? The answers to these questions are essential for a deeper understanding of the pathophysiology of lifelong PE. New research into these questions is warranted. So far however, there are indications that the timing of ejaculation is related to the central nervous system.

## 6.8 Serotonergic Modulation of the Spinal Ejaculatory Reflex

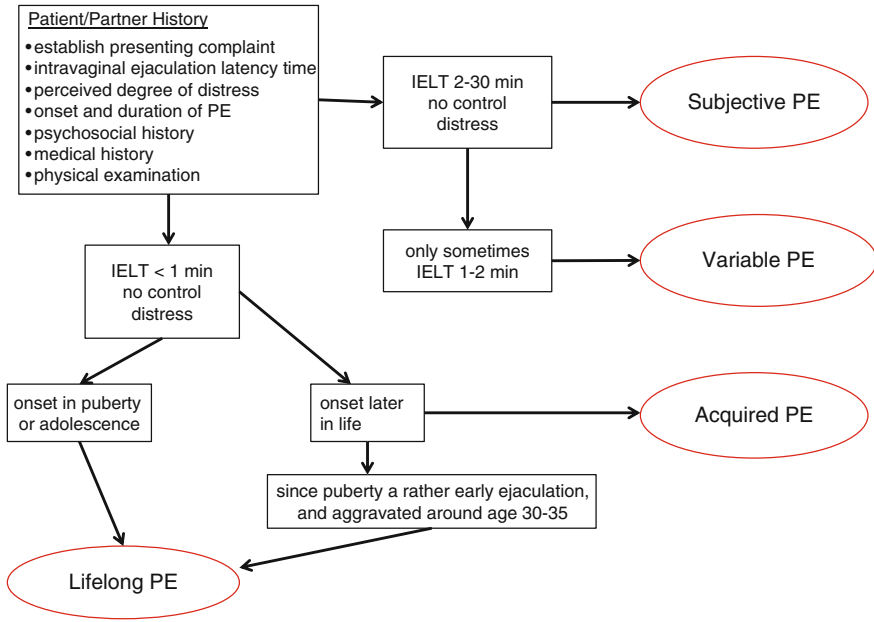
Data derived from animal research suggest a major role of the central serotonergic system in modulating the spinal ejaculatory reflex [17]. This serotonergic modulation of ejaculation may result in a faster or more delayed ejaculation, whereas the ejaculation itself is probably not only under direct influence of the serotonergic system, but rather under the influence of other neurotransmitter systems in the spinal cord [16]. I would like to underline that this “modulation” is an important feature of the central serotonergic system that has hardly been discussed in the literature. However, it is pivotal for genetic research of PE and for a good understanding of the pathophysiology of lifelong PE. For example, it may be assumed that the modulation of ejaculation among men is variable; it can be strong, moderate, weak, or even absent. In the latter case, the serotonergic system in the brainstem is unable to modulate the ejaculation reflex in the lower spinal cord. In that case, a male is not able to or hardly able to change the duration of his ejaculation time; he has a rigid pattern of his ejaculation time without any variability. Even by using SSRIs, this person may still not be able to change the duration of his ejaculation time. Although never systematically investigated, it is clinically well known that a subgroup of men with lifelong PE do not respond with ejaculation delay to any SSRI treatment [16]. I therefore suggest that in these men, the serotonergic system is unable to modulate the ejaculation reflex [16]. The view that serotonin modulates ejaculation may have important implications for genetic and psychopharmacological research, because it may imply that in a certain cohort of men, an unknown number has no or hardly any ability to modulate ejaculation irrespective of the presence of functional serotonergic polymorphisms [16]. Consequently, irrespective of the presence of these polymorphisms, these men will not show any change in IELT duration when modulation of the IELT is not 100 % associated with such serotonergic polymorphisms.

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## 6.9 Symptoms of Lifelong PE

Considered as a syndrome, i.e., as a cluster of symptoms, lifelong PE is characterized by the following symptoms [18]:

- (1) Early ejaculation exists from the first or nearly first sexual intercourses.
- (2) Is present with (nearly) every female partner in more than 80–90 % of events of intercourse.
- (3) Remains similar in rapidity during aging, or aggravates in 25–30 % of the patients with aging at around the age of 30–35 years.
- (4) Occurs within 30–60 s after vaginal penetration at nearly every coitus in the majority, i.e., >90 % of men affected by the dysfunction. However, about 10 % of men complaining of lifelong PE ejaculate within 1–2 min.



**Fig. 6.3** Algorithm for the diagnosis of the four premature ejaculation subtypes [19–21]

## 6.10 Different Subtypes with Different Etiology and Pathogenesis

Based on clinical and epidemiological stopwatch data, Waldinger recently postulated the existence of two PE subtypes that had not been identified previously [19, 20]. Adding to lifelong and acquired PE, there are two other PE subtypes: (natural) variable PE and premature-like ejaculatory dysfunction or “Subjective PE”. The clinical symptomatology of the subtypes is different with regard to the duration of the IELT, the course of the IELT duration throughout life, the frequency of occurrence of short IELTs, and the cognitive experience of the IELT. Apart from the clinical symptomatology, the etiology and pathogenesis of the four subtypes is different [21]. Men with lifelong PE suffer from IELTs that are consistently less than 1 min since puberty or adolescence. Acquired PE may be caused by erectile dysfunction, thyroid disorders, acute inflammatory prostatitis or relationship problems [22–24]. In “Variable PE”, the IELT is only sometimes very short. In “Subjective PE” men have a normal or even long IELT duration, but still perceive themselves as having PE. It has been postulated that “Subjective PE” is strongly associated with psychological and cultural factors. Although there currently is no general consensus on the value of this new classification, Serefoglu et al. published two studies confirming the existence of the four PE subtypes in a Turkish population of men [25, 26].

Although one may not fully exclude the possibility that lifelong PE may have a psychological etiology in some men [27], the pathogenesis of lifelong PE is currently thought to be primarily of neurobiological and genetic origin [28]. It should be noted that its pathogenesis is different from the pathogenesis of acquired PE. For example, although thyroid dysfunction is associated with acquired PE [22], a large study in Dutch men with lifelong PE has shown that lifelong PE is not associated with thyroid dysfunction [29]. A diagram of how to integrate the four PE subtypes in daily clinical practice is shown in Fig. 6.3.

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## 6.11 Necessity of distinct Definitions of Premature Ejaculation Subtypes

The aforementioned differences in clinical symptomatology, etiology and pathogenesis of the four PE subtypes, necessitates distinct definitions of these PE subtypes. This is not only required for daily clinical practice, but is also pivotal for clinical, genetic, epidemiological and psychopharmacological research on PE. Only recently has there been agreement on a separate definition for lifelong PE. With more research ahead, we will soon be able to distinctly define acquired PE and the two other PE subtypes.

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## 6.12 Definition of Lifelong PE

In October 2007, the International Society of Sexual Medicine (ISSM) convened a meeting in Amsterdam of international experts in PE and agreed upon the following evidence-based definition of lifelong PE [3]. Premature ejaculation is a male sexual dysfunction characterized by: Ejaculation which always or nearly always occurs prior to or within about 1 min of vaginal penetration, and the inability to delay ejaculation on all or nearly all vaginal penetrations, and with negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy. Currently, the available objective evidence on PE is limited to men with lifelong PE who engage in vaginal intercourse. By using this definition, clinical research into the pathophysiology of lifelong PE will provide answers to the many questions that remain to be elucidated.

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## 6.13 Conclusion

The symptomatology, etiology and pathogenesis of lifelong PE is different from the characteristic features of acquired PE, variable PE and subjective PE. Although the neurophysiology of ejaculation in men with lifelong PE is not genuinely different from the neurophysiology in men who do not complain of premature ejaculation, it is the timing of ejaculation that is persistently disturbed in these



men. The timing is dependent of serotonergic modulation of the ejaculation reflex. In addition, there is preliminary evidence that genetic polymorphism of the 5-HT transporter and also from 5-HT<sub>1A</sub> and 5-HT<sub>2C</sub> receptors [30, 31] is associated with the duration of the IELT in heterosexual men with lifelong PE. Although, in the last two decades, progress has been made in understanding the pathophysiology of lifelong PE, many questions are still unanswered. For example, what is the role of the prefrontal cortex or the somatosensory system in the timing of ejaculation? Brain imaging studies, genetic and pharmacologic research as animal research will probably tell us the answers to these questions in the next two decades.

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## 7.1 Introduction: Definition and Epidemiology

The definition of acquired premature ejaculation (A-PE) is an ongoing process. While it has been relatively easy to define lifelong PE (LL-PE) on the basis of existing data on intravaginal ejaculation latency time (IELT) and patient reported outcomes (PROs) [1], similar objective parameters have not been so far produced for the acquired form of PE. Although no logical reasons exist for suspecting substantial differences in intravaginal timing and patient's outcome in patients with LL- and A-PE, the lack of evidence-based IELT and PRO so far frustrated the efforts of scientific societies and consensus conferences to define A-PE, which can be now simply recognized as a PE occurring after a period of normal ejaculatory control. The obvious inferring of this is that LL-PE is more likely (but not necessarily) to be sustained by congenital causes, while the acquired form must be grounded on psychological events or organic *noxae* able to affect the complex mechanism of ejaculation. It would be thus mandatory to search and eventually treat such possible pathologies.

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For operational purposes, although not directly based on specific evidence, but on clinical experience, we proposed in the past to the European Academy of Andrology (EAA) in a mailed consensus involving 71 scientist worldwide, selected as having published at least one paper in the field of PE, and to the International Society of Sexual Medicine (ISSM) the following definition of A-PE:

Acquired premature ejaculation is a male sexual dysfunction occurring after a period of normal ejaculatory performance, in which ejaculation occurs within about 2 minutes after vaginal penetration, with the feeling of loss of control over ejaculation and induction of symptom-related stress. The inability to delay ejaculation can be either: (i) a symptom of organic diseases; (ii) correlated to psychological difficulties; (iii) a co-morbidity with other sexual dysfunctions; or (iv) idiopathic.

The advantage of such a definition—the first paragraph of which can be hardly questioned—is that it recognizes the known risk factors of PE, both organic and non-organic, the possibility of a correlation with other sexual dysfunctions and the chance, quite frequent indeed, that the physician is unable to find causes underlying A-PE, as in the idiopathic PE. Hence, the definition has an evident operational aim. Finally, the figure of a 2 min cutoff seemed more realistic in the real life clinical perspective with respect to the stringent—and criticized [2]—cutoff of about 1 min proposed in the ISSM definition of LL-PE.

When formulated, the main weakness of this definition was the absence of epidemiological data on the IELT of the patients with A-PE. These epidemiological data have been the evidence-based background of the ISSM definition of LL-PE (see [Chaps. 5 and 6](#)).

Recognizing these difficulties, the ISSM elaborated an interim position statement on A-PE where:

Acquired PE is a subtype of PE characterized by: (i) a substantial decrease in time-to-ejaculation compared to a man's previous sexual experience (\*), and the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy.

The Society stressed the need for the third construct (\*) required for PE definition, i.e., temporal range of IELT. Moreover, the experts of the ISSM stated that further clinical research is required to obtain IELT and PRO data for A-PE.

Although not designed to ascertain difference in median IELT in patients with LL-PE or A-PE, recent findings suggested a substantial identity between the two subsets of PE patients. In fact, in a cohort of 1,470 men with LL-PE, the average IELT was 0.91 min, while the mean IELT of 750 subjects with A-PE was 1.07 [3]. The same article did not find differences between the LL- and A-PE in the measures that assess constructs similar to those represented in the ISSM definition of lifelong PE (i.e., control over ejaculation and distress related to ejaculation) (see [Chap. 5](#)); high degrees of impairment with similar magnitude were observed for both subgroups. Hence, the EAA definition of A-PE seems, at the moment, the best available option.

**Table 7.1** The risk factors for acquired premature ejaculation (from [7], modified)

Group of diseases	Diseases
Psychorelational	Anxiety, relational and marital problems
Neurological	Penile hypersensitivity
Endocrine	Hyperthyroidism
Urologic	Prostate inflammation/infection
Other sexual symptoms	Comorbid with erectile dysfunction, hypoactive sexual desire, female sexual dysfunction

Despite the lack of a unique and shared definition of A-PE, epidemiological hypotheses have been formulated. In fact, the prevalence of LL-PE vs. A-PE has been investigated in a recent cross-sectional field survey [4]. Of the 2,593 men involved, 2.3 and 3.9 %, were diagnosed as having real LL-PE and A-PE, respectively. Earlier literature concentrated almost exclusively on LL-PE. Now more attentions needs to be directed at A-PE.

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## 7.2 Pathophysiology of A-PE

The pathophysiology of A-PE appears to be both organic (endocrine, urologic, neurobiologic) and non-organic in nature [5]. In other words, A-PE is a psycho-neuroendocrine and urological symptom with a possible comorbidity with another sexual disturbance; in fact, A-PE has been correlated to psychological, neurological, hormonal, and urological diseases and to other sexual symptoms such as impotence.

Exactly as for the psychological aspects of PE [6], none of the neurological, endocrine, and urological pathologies here listed has been demonstrated to be a direct cause of A-PE. All these must be considered, at the best, as pathological conditions associated with PE, deserving medical attention and treatment in order to maximize the therapeutic efforts of PE. In other words, the best way to consider the candidate etiologies of A-PE here listed is to regard them as organic **risk factors** for A-PE (Table 7.1).

Basically, the final aim of this chapter is to summarize with different words and in a different perspective what is individually discussed in several chapters of this textbook.

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## 7.3 Psychological Risk factors

While for impotence the list of etiological causes is large and growing, for PE the according list is still relatively short (Table 7.1), with the psychological causes being the most studied. Premature ejaculation has long been viewed exclusively as

a psychological concern, although recent research also focuses on the organic underpinnings of the symptom [8].

Intrapsychic and relational derangement can be a risk factor for both LL- and A-PE, confirming that the two subsets of PE patients are not necessarily different in the pathophysiological mechanisms. Hence, systematic use of psychopathological procedures is a determining aid in diagnosis of various PE subtypes [9].

Distortions of belief and false convictions about sexuality are established in childhood as a consequence of adverse influences on sexual behavior. Destructive attitudes are usually exerted by parents but also by other dominant persons within and outside the family [10]. This, in a Freudian perspective, may lead to sexual dysfunction such as PE.

Classic psychoanalytic theories identified a sadistic or narcissistic behavior in PE [11]. For other psychoanalysts, however, men who ejaculate prematurely are typically passive and masochistic in their marriage and obsessive–compulsive in character [12]. These theories were the basis of Helen S. Kaplan's first idea, that PE is the result of an unconscious hatred of women [13, 14]. By ejaculating quickly, a man symbolically and physically "steals" the woman's orgasm. However, the same researcher rejected her own theory when she found that men with PE do not have any particular neuroses or personality disorders [14].

Premature ejaculation has been considered frequent, if not normal, during early sexual experiences. To this concept, Masters and Johnson added other connected etiologial causes: the risk of unwanted discovery (such as copulating in a car), experiences with prostitutes, and anxiety due to poor sexual education (e.g., absence of adequate knowledge of contraceptive methods) can worsen ejaculatory control, already physiologically poor at a young age [15].

Kaplan's original etiologic explanation is also connected with the role of early experiences: the man with PE has not allowed himself to receive the sensory feedback of those sensations occurring immediately before orgasm which would enable him to bring his ejaculatory reflex under voluntary control [13]. She compares this etiologic mechanism to the control of enuresis obtained when a child recognizes the sensation of a full bladder. In the same way, lack of awareness of pre-ejaculatory sensations may lead to PE.

More recent findings correlate PE with psychological problems. Subject-reported personal distress most strongly indicated PE. Partner's and personal distress better correlate with PE than IELT alone [16].

The role of anxiety (for sexual performance generally, but also for other, extrasexual reasons) has been frequently raised as a cause [17]. This is in keeping with Kaplan's theory: anxiety may block pre-ejaculatory sensations. Premature ejaculation has been associated with a psychological state of mind measured by the hospital anxiety and depression scale (HADS) [18]. Furthermore, the role of anxiety has been seen as variable, interacting with the somatic vulnerability of the individual to determine orgasmic latency [19]. Finally, Corona et al. elegantly demonstrated high levels of free-floating anxiety in A-PE [20]. It should be noted, however, that anxiety may also be the effect rather than the cause of PE.

Social phobia can be a feature characterizing both LL-PE and A-PE. Premature ejaculation was the most common sexual dysfunction in male social phobic patients [21]. Moreover, PE was highly associated ( $p = 0.015$ ) with social phobia, with an odds ratio of 2.55 [22].

Alexithymia is a deficit in identifying and communicating emotions that is presumed to play an important role in psychosomatic diseases. Alexithymic features, and in particular, an externally oriented cognitive style, can be seen as possible risk and/or maintenance factors for PE. Alexithymia could represent a variable to be assessed for an integrated diagnosis and treatment of PE [23].

In conclusion, the etiological approach of psychology to PE in general and to A-PE in particular should be re-thought. In fact, psychological involvement can be either a cause or may be caused by A-PE.

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## 7.4 Neurological Risk Factors

Although logical, the association between PE and hypersensitivity is still under debate. The sensitivity of the glans, the organ triggering ejaculatory reflex, undoubtedly has an important role in the ejaculatory mechanism, and possibly in some forms of PE. Penile sensation is unique when compared to other body regions [24]. The human glans penis is covered by stratified squamous epithelium and a dense layer of connective tissue, equivalent to the dermis of normal skin. The most numerous nerve terminals are free nerve endings (FNEs), which are present in almost every dermal papilla, as well as scattered throughout the deeper dermis. The FNEs are characterized by an incomplete Schwann cell investment and contain irregularly scattered neurofilaments and neurotubules, clusters of mitochondria, vesicles of variable size, and various inclusions. The unique corpuscular receptor of the glans penis consists of axon terminals that, at an ultrastructural level, resemble a tangled bunch of FNEs. Simple, Pacinian, and Ruffini corpuscles have been occasionally identified, predominantly in the corona glandis [25].

On this anatomical basis it has been shown that patients with PE, not necessarily with the acquired form, may have hypersensitivity and hyperexcitability of the glans penis, which may give rise to uncontrolled ejaculation and are believed to be organic implications for PE [26].

Evoked sacral potentials have in fact been used to study the bulbo-cavernous reflex in patients with PE [27]. In perineal and perianal measurements, the amplitudes of the evoked responses were much greater in these patients with respect to controls. This suggests a reflex hyperexcitability or an impaired “modulation” of the motor neurons of the pudendal nucleus in patients with PE. On the glans penis and penile shaft, the values in patients with PE have been found significantly less than those in normal potent men [28]. Furthermore, using somatosensory evoked potential, patients with PE showed a greater cortical representation of sensory stimuli from the genital areas than normoejaculators [29]. However, Rowland et al. found thresholds for premature ejaculators to be

commensurate with controls, while men with erectile dysfunction or combined erectile dysfunction and PE showed significantly elevated thresholds [30]. Although patients with PE did not show penile hypersensitivity, there was a significant correlation in this group between ejaculation latency and threshold. Overall, these findings argue against a primary role for penile sensitivity in ejaculation latency, and suggest that other somatic factors or cognitive factors may play a more critical role in PE. Furthermore, faster conduction along the pudendal sensory pathway or a greater cortical representation of the sensory stimuli from the genital area or hyperexcitability of the BC reflex were not always confirmed in patients with PE [31]. This was further confirmed using a vibrometer with a precision and reproducibility higher than analog-type biothesiometers [32]. This suggests that the electrophysiological approach is probably not sufficient to clarify some causes of both LL- and A-PE. A more extensive investigation may give better results in this area [33].

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## 7.5 Endocrine Risk Factors

Hormones play a central role in the machinery of emission–ejaculation [34]; this implies that pathological hormonal levels may directly or indirectly affect the ejaculatory control [35], as in the case of thyroid hormone, but may also be affected or simply modified by the condition of PE. This seems the case of testosterone and prolactin levels in A-PE.

*The role of sex steroids* Low serum testosterone levels have been inconsistently associated with PE [36, 37]. However, others have anecdotally suggested that hypogonadism can be considered a possible cause of delayed ejaculation (DE). Testosterone plays a crucial role in male sexual response, acting at both the central and peripheral levels, and is a clear determinant of motivation to seek sexual contact. Several studies in hypogonadal men have demonstrated that testosterone replacement has an unequivocal role in restoring sexual desire, spontaneous sexual thoughts and attraction to erotic stimuli. The testosterone dependency of type 5 phosphodiesterase (PDE5) expression and activity has also been demonstrated in other parts of the male genital tract (MGT) such as the vas deferens, a critical effector for semen emission and ejaculation [38]. Recent data suggest that testosterone plays a facilitatory role in the control of the ejaculatory reflex [39]. Different testosterone levels identify different subsets of ejaculatory disturbance. While a higher testosterone level characterizes PE, DE is associated with lower levels. Taken together, these data suggest a role for androgens in the mechanism of ejaculation [39].

Both central and peripheral mechanisms have been advocated to explain this association. The first explanation is psychoendocrinal. Testosterone level, in addition to its action on sexual response, profoundly influences male behavior. High testosterone levels in human adults are associated with leadership, toughness, personal power, and aggressive dominance [40]. Rowland considers DE to be



essentially characterized by the uncoupling of a decreased subjective and a preserved genital reaction in sexual arousal [41]. It could thus be speculated that hypogonadism and related reduction in sexual confidence and aggressiveness could play a critical role in the control of ejaculation timing, reducing the internal cues for reaching orgasm and ejaculation.

The second hypothesis is neurological. Recent data from animal models seem to support the central action of testosterone in the control of the ejaculation reflex. Keleta et al. [42] demonstrated that long-term testosterone treatment in rats significantly decreased 5-HT in the brain. Another intriguing possibility involves the possible peripheral role of testosterone in regulating MGT motility. In rabbit hypogonadism, it was found that PDE5 is less expressed and biologically active in the vas deferens [43]. Testosterone administration completely reversed these alterations. Hence, it is possible that hypogonadism-associated DE is due to an increased inhibitory nitrenergic tone on MGT smooth muscle cells. A “mechanical” action of testosterone in the ejaculation control can also be possible. A hypogonadism-induced reduction in semen volume may perturb the dynamics of the seminal bolus propulsion, possibly explaining ejaculation difficulties in some subjects. In fact, low testosterone directly reduces ejaculate volume, which may result in a lack of stimulation of accessory glands such as the prostate and seminal vesicles, which are well-known androgen targets. Finally, it cannot be excluded that the demonstrated testosterone differences are the consequence of sexual disturbances mirroring differences in sexual behavior, such as copulation frequency [44].

In conclusion, several possible mechanisms may connect androgen levels with the complex machinery of ejaculation. Clinical studies are currently in progress to further establish the role of testosterone in ejaculatory dysfunction.

*The role of prolactin* In a consecutive series of 2,531 patients interviewed using SIEDY structured interview (a 13-item tool for the assessment of erectile dysfunction-related morbidities) [45], and Middlesex Hospital Questionnaire [46], for the evaluation of psychological symptoms, low prolactin (PRL) levels are associated with PE and anxiety symptoms [47]. Low PRL seems an effect, rather than a cause of PE. In fact, many psychological disturbances (such as stress and frustration for chronic or acquired inability to enjoy sex) are able to provoke a neuroendocrine imbalance, such as that of the central serotonergic system, mirrored by the relative hypoprolactinemia found in patients with PE.

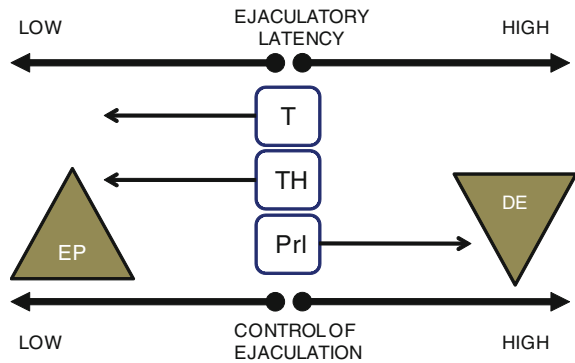
*The role of thyroid hormones* The impact of thyroid hyper- and hypo-function in male sexual function has been studied only very recently. This is probably the consequence of: (i) the apparently low clinical significance given to male sexual symptoms in comparison with the systemic effects of thyroid hormone excess and defect; (ii) the paucity of clinical studies- as thyroid disease is less common in men; (iii) the embarrassment of patients and physicians when discussing sexual dysfunction in the “traditional” setting of the endocrine outpatient clinic [48]. However, a high prevalence of A-PE in hyperthyroid patients has been found, whereas in hypothyroid subjects the main sexual complaint was DE [20, 49]. Both ejaculatory dysfunctions reverted on achievement of euthyroidism in the absence of any other treatment for the sexual symptom. Interestingly, suppressed levels of

TSH (as a marker of hyperthyroidism) have been demonstrated in A-PE [20] but, obviously, not in patients with LL-PE [50]. All these data suggest a direct involvement of thyroid hormones on the physiology of ejaculation.

As the relationship between thyroid hormones and ejaculatory mechanisms is currently unknown, three possible sites of action have been suggested: the sympathetic nervous system, the serotonergic pathway, and the endocrine/paracrine system. Most manifestations of thyrotoxicosis and sympathetic nervous system activation overlap. This may suggest a similar action on ejaculation, a reflex largely dependent on sympathetic and parasympathetic tone. However, plasma catecholamines and their urinary metabolites are usually normal in hyperthyroidism [51]. On the other hand, some studies have found that thyroid hormones augment sensitivity to  $\beta$ -adrenergic agonists by increasing  $\beta$ -adrenoceptor density and  $G_s/G_i$  protein ratio through an over-activation of adenylate cyclase [52]. This leads to increased sympathetic activity with normal circulating catecholamine levels. In hyperthyroid patients, the increased adrenergic tone may trigger both PE and DE, either acting directly on smooth muscle contractility/relaxation or indirectly on anxiety and irritability. The opposite may occur in hypothyroid patients [53]. Considering the neuropsychological reactions to thyroid hormone excess (hyperkinesia, nervousness, anxiety, emotional lability), PE may be also a non-specific disease-related complaint, disappearing when a euthyroid state is achieved. However, in light of the widespread distribution of thyroid hormone nuclear receptors within the brain, it can be hypothesized that iodothyronines specifically alter the central serotonergic pathway [54], leading to diminished ejaculation control. In animals with experimentally induced hypothyroid states, increased serotonin turnover in the brainstem is consistently reported [55] and thyroid hormone replacement is associated with increased cortical serotonin concentrations and augmentation of serotonergic neurotransmission by desensitization of the serotonin inhibitory 5-HT<sub>1A</sub> (auto-inhibition) [55]. Finally, DE is a common and therapeutically useful side effect of serotonergic drugs, indicating that this pathway is fundamental for ejaculatory control.

Another way that thyroid hormones may affect the ejaculatory mechanism could be through estrogen metabolism. Hyperthyroidism increases levels of sex hormone binding globulin (SHBG), which binds androgens with higher affinity than estrogens, leading to a relative hyperestrinism. It has been demonstrated in hypogonadic rabbits that estrogens, but not androgens, fully restore oxytocin-induced epididymal contractility, up-regulating oxytocin receptor gene and protein expression, and that deprivation of endogenous estrogens induces oxytocin hyporesponsiveness [56, 57]. As oxytocin is closely involved in the ejaculatory mechanism [58], both centrally [59] and peripherally [60], this may account for the close correlation between hyperthyroidism and PE. As an ancillary possibility, thyroid hormone receptors have been described in the animal [61] and human testis [62], and may also be present in other male genital tract structures, triggering ejaculation. Finally, although excluded in the original report [49], some cases of PE in hyperthyroidism are comorbid with impotence, which may in turn exacerbate the loss of ejaculatory control [63].

**Fig. 7.1** The hormonal regulation of the ejaculatory continuum. T = testosterone; TH = thyroid hormone; Prl = prolactin; PE = premature ejaculation; DE: delayed ejaculation



*Role of hormones in delayed ejaculation* More insights on the role of hormones in the pathogenesis of A-PE can be obtained from experimental evidence produced on DE [64]. When comparing DE and PE, PRL as well as TSH levels progressively increased from patients with severe PE towards those with anejaculation. Conversely, the opposite was observed for testosterone levels. All of these associations were confirmed after adjustment for age. When these hormonal parameters are introduced in the same regression model, adjusting for age, general psychopathology and use of selective SSRIs, they are independently associated with ejaculatory problems [65]. This indicates endocrine system is involved in the control of ejaculatory function and that PRL, TSH (as a marker of thyroid activity), and testosterone play an independent role.

In conclusion, from a psychoneuroendocrine perspective, PE and DE can be considered two ends of a single *continuum*, spanning from severe PE to extreme DE (Fig. 7.1). In addition, although endocrine regulation of the ejaculatory reflex is still in its infancy, evidences so far produced indicates that it should grow rapidly to help in shedding light on often occurring but seldom-studied conditions like ejaculatory disturbances.

## 7.6 Urologic Risk Factors

For unexplained reasons, the role of the largest gland involved in the mechanism of ejaculation has been ignored by the majority of urologists [66]. This is particularly surprising, since the main function of the prostate is to store and secrete the clear, slightly basic fluid that constitutes up to one-third of the volume of semen. The prostate also contains some smooth muscle that helps to expel its secretions during ejaculation.

*The role of the prostate.* The emission, the first phase of the ejaculatory process (see Chap. 3), is mediated by contractions of the smooth muscle in the capsules of the testes, seminal tract, and genital glands including the prostate [67]. It has been

reported that electric waves discharged from the prostate at rest seem to produce prostatic contractions that appear to be responsible for increases in the prostatic urethral pressure [68]. Shafik [69] noted that, at ejaculation, the intermittent and significant increase in wave variables and urethral pressure coincided with the ejaculatory spurts and apparently denotes intermittent prostatic smooth muscle contractions. These prostatic contractions seem to squeeze the prostatic secretions into the prostatic urethra. However, some important experimental evidence are against the notion that the “distension” of the prostatic urethra by the entering semen is the probable trigger for the ejaculation reflex: (i)  $\alpha$ -adrenergic blocking agents (phenoxybenzamine, phentolamine) prevent the discharge of semen into the urethra but they do not inhibit the initiation of ejaculation. This may occur also in absence of fluid to ejaculate (dry orgasms) and without changes in the subjective experience of orgasm [70]. Moreover, healthy person could experience a dry emission/orgasm with a complete absence of secretions. (ii) it has been reported that a decrease in echogenicity of the prostatic urethra during the pre-ejaculatory phase signifies the secretion and movement of prostatic fluid to the prostatic urethra, which in turn leads to the inevitability of expulsion [71] and that prostatic urethra distends 3–5 s before the start of seminal expulsion [72]; however, observing eight normal healthy volunteers, the expulsion of the contents of the seminal vesicles into the inframontanal urethra always occurs without prior ballooning of the prostatic urethra [73]. This may suggest that a “pressure chamber” does not appear to be formed before prostatic contractions take place. (iii) in copulating male rats, urethral stimulation by the ejaculate does not contribute to the activation of the striated muscle component of the ejaculation reflex [74], further suggesting that candidate sites for the ejaculation “trigger” could be present in the penile glans, spinal cord, and/or the brain.

Although the formation of the “pressure chamber” in the prostatic urethra is currently under debate, it is well know that the antegrade propulsion of seminal fluid into the distal urethra requires coordinated dynamic changes at the bladder neck, prostatic urethra, and external sphincter [75].

*Effects of prostatic disorders on the ejaculatory process.* Prostate inflammation/infections have been anecdotally correlated with PE in the past [76]. Jannini and coworkers firstly demonstrated, by the Meares and Stamey test [77], a relatively high prevalence of prostatic inflammations/infections in men with PE. Furthermore, it has been found that this sexual symptom is in turn common in subjects with prostatitis [78]. After this paper, the European Association of Urology (EAU) Guidelines on Ejaculatory Dysfunction recognized that “PE may be strictly organic (e.g. prostatitis-related)”, prescribing the rectal examination with evaluation of the prostate in patients with ejaculatory disturbances [79].

If a causal correlation exists, prostatic inflammation may alter sensations arising from the male genital tract, so that the male is unable to recognize the emission phase [80]. Prostatic inflammation/infections (variously demonstrated or simply admitted by patients in a population survey) has been found in a total of 3,115 patients with PE (variously defined) examined in several countries with a prevalence ranging from 15 to 64 % (Table 7.2).

**Table 7.2** Prevalence of prostate inflammation in patients with PE (summary)

Reference	Number of patients	Prevalence (%)
[78]	46	48–56
[81]	106	40–46
[82]	2,658	15
[83]	153	52–64

**Table 7.3** Prevalence of PE in patients with prostatitis/LUTS (summary)

Reference	Number of patients	Prevalence (%)
[78]	26	61.5
[81]	120	47.5
[86]	1,749	33.7
[87]	66	92
[88]	399	55.5

Vice versa, PE has been found in 2,360 patients with prostatitis and/or lower urinary tract symptoms (LUTS) (Table 7.2). Note that LUTS have been also related with retarded/painful ejaculation [84, 85] (Table 7.3).

The possible relationship between prostatitis and PE is probably complex. Signs and symptoms of prostatitis have been found more common in patients with varicocele, who more often complain of PE [89]. On this basis, it has been suggested that PE should be considered a marker underlying organic diseases including varicocele. Chronic prostatitis could be the link between the two conditions.

One may argue that the correlation, if any, between prostatitis and PE can be mediated via the prostatitis-induced erectile dysfunction [90]. The physiological correlation between the machinery of erection and prostate is not fully understood. On the contrary, considering the physiological role of the prostate, the correlation between ejaculation and this gland is definitively robust. The possibility that the EP found in patients with prostatitis is due to erectile dysfunction cannot be ruled out, at least in patients with such a comorbidity (see later). However, several authors were able to cure PE just with a specific antibiotic treatment against the bacteria responsible of prostatitis [91–94].

Interestingly, as firstly demonstrated by Screponi et al. [78], prostatitis does not seem exclusively correlated with of A-PE. Inflammatory prostatitis was found in 155 men with A-PE and in 55 with LL-PE [94]. In this experimental set, antibiotics were given to 184 men for 4 weeks, guided by sensitivity tests. Twenty-six men refused or did not comply with the antimicrobial therapy and were used as the untreated group. Two of the 26 men (7.7 %) from the untreated group experienced an increase in their ejaculatory latency compared with 109 of the 184 men

(59.0 %) who received antimicrobial therapy. The treatment was most effective in men with A-PE and when there are 19 pus cells per high-power field in the expressed prostatic secretion analysis [94].

Thus, the examination of the prostate, which should be always considered in the correct andrological setting, seems mandatory during assessment of patients with PE (see Chap. 25) [95].

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## 7.7 Comorbidity of A-PE with Other Sexual Dysfunctions

As discussed later in Chaps. 23 and 25, a sexual dysfunction can have a causative role in PE or can be caused by PE. For this reason, any case of PE should be carefully evaluated for having another sexual symptom. The same seems important for the partner of the patient. It is in fact mandatory to fix other possible sexual dysfunctions before starting any treatment for PE [96].

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## 7.8 Idiopathic A-PE

The percentage of patients having PE of unknown cause is currently not available. It was frequent in the recent past to consider these patients as psychogenic. However, this is not correct and the term psychogenic should be replaced by “idiopathic” PE [97]. Future research will provide new pathophysiological elements and the number of subjects with idiopathic PE—probably the majority at the moment—will decrease progressively.

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## 7.9 Conclusion

In conclusion, although the absence or deficiency of control in ejaculation is the most common sexual symptom [98], the acquired subtype of PE is still underdiagnosed and under-treated, despite the fact that it can be successfully cured [99]. However, increased medical awareness, careful diagnosis and subtyping, recognition of the pathogenetic mechanism in individual patients, and the forthcoming availability of new drugs specifically designed for PE will give the expert in sexual medicine a new opportunity to treat the severe suffering of many patients.

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# Risk Factors for Premature Ejaculation: The Intrapsychic Risk Factor

8

David L. Rowland and Stewart E. Cooper

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## 8.1 General Introduction

The term “intrapsychic” has no specific definition or meaning within the fields of either psychology or medicine—indeed, the terminology is unconventional or unfamiliar in many psychological or biomedical circles. However, for this chapter, we use the term to refer to all the psychological factors, tendencies, and processes associated with premature ejaculation (PE).

Thus, intrapsychic factors would encompass all those elements comprising the person’s psychological past and present that ultimately underlie his attitudes, beliefs, values, expectations, attributions, cognitions, thoughts, emotions, and behaviors. These processes may be affected by inherent dispositions having a biological/genetic basis, developmental-learning experiences which vary across individual men, or sociocultural environments which not only vary across but also within cultures, countries, peoples, and nations. Additionally, intrapsychic factors may be enduring and trait-like (suggesting an underlying personality characteristic), or they may be transient and state-like (suggesting a response to a specific situation or crisis). Finally, the psychological processes may be occurring within a relatively normal range (e.g., a man who is *upset* or bothered by his condition of rapid ejaculation) or they may extend beyond the normal range such that they become “clinically

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significant” (e.g., a man who becomes *obsessed* with his condition to the point where it affects relationships, work, sense of well-being, etc.).

Despite the broad scope of these intrapsychic factors, surprisingly little is known about their relationship to premature ejaculation. Much of the current understanding of these processes comes from several sources: (1) small-scale studies investigating a specific psychological area of interest in relationship to premature ejaculation; (2) clinical impressions garnered through intake interviews and psychosexual histories on men with PE; and (3) the general psychological literature relating these processes to general functional impairment or non-PE-related sexual impairment. Regarding the last source of information, the basic assumption is that many of the psychological processes involved in PE share common elements with those underlying other types of bio-behavioral dysfunctions (e.g., eating disorders, addictions, anxiety, sleep disorders, obsessions, and so on).

As suggested above (#2), an important source of information to the understanding of any functional impairment is the individual’s own experience of the condition. In specific, the individual experience of PE emerges from the reciprocal interaction of four components: (1) the *actual level of sexual performance*, for example, the frequency, duration, and intensity of sex especially as it relates to ejaculation, plus the level of verbalized partner satisfaction or dissatisfaction with sex; (2) the man’s *self-assessment of his sexual performance shortcoming*, including whether real or not, chronic or situational, or lifetime or short-term; (3) *secondary interpretations of his self-assessed functioning* as influenced through the filter of internalized beliefs which may be particularly detrimental when combined with distorted styles of thinking such as expectations of perfection; and (4) *the resulting emotions and behavioral accommodations* made in the attempt to meet his sexual performance expectations. The interactions among these four components can take place very rapidly at times, such as when a man with PE is having sex and feels an unwanted ejaculation is imminent, or they may play out more slowly as repetitive entrenched acting-thinking-feeling patterns, including when a man with PE avoids sex due to the anxiety of disappointing his partner. Such general processes are common to many psychological disorders and are likely to become part of the PE man’s intrapsychic constitution.

Finally, the term “risk factors” suggests that such psychological processes contribute in some way to the functionally impaired response, in this case the inability to delay ejaculation for some unspecified time interval. Thus, from a theoretical perspective, these risk factors might contribute to the etiology of the dysfunction, maintain it, or make it worse. Identifying and understanding such risk factors by both the clinician and patient may increase the patient’s openness to treatment, enhance the therapeutic effects of whatever treatment is prescribed (whether pharmacological or psychosexual), and sustain the treatment effect through increased compliance and relapse-recovery. Unfortunately, and as implied previously, data supporting the elaborate schema provided herein for the understanding of intrapsychic risk factors is sparse and fragmentary; what we do not know comprises a much larger domain than what we do know.

## 8.2 Historical Perspective

For decades, PE was considered an intrapsychic disturbance, and intrapsychic explanations have traditionally (though not exclusively) suggested the need for a psychoanalytic treatment approach. To the extent that psychoanalytic approaches delved into the developmental sexual histories of the patient, they may have been successful in providing some patients with insight into their problem. However, the wide variation in potential intrapsychic explanations together with a lack of standard treatment protocols rendered psychoanalytic strategies non-replicable and questionable in terms of treatment success. Against this backdrop, Masters and Johnson reframed PE as a learning/behavioral problem, where the dysfunctional response—presumably developed through conditioning—could be modified through appropriate counter-conditioning measures of stimulus control and reinforcement. For the past 40 years, their behavioral approach—which included interactive elements with the partner—was considered the mainstay treatment for this dysfunction. Their approach, as well as that of Kaplan, most frequently used behavioral strategies designed to attenuate or counter penile stimulation, respectively the ‘stop-squeeze’ technique described by Masters and Johnson in 1970 [1] and the ‘start-stop’ method described by Kaplan in 1974 [2]. These techniques, [Chap. 11](#), involved engaging in sexual foreplay until before the point of ejaculation and then either squeezing the head of the penis or stopping sexual activity until the urge to ejaculate subsided [1–3].

Partly because classic behavioral studies such as those by Masters and Johnson and later Kaplan initially reported high success rates, research on other kinds of psycho-behavioral explanations for PE essentially withered, and the idea that PE resulted from deep-seated developmental-relationship experiences was abandoned altogether. Although subsequent studies were less successful than Masters and Johnson’s initial reports [3, 4], behavioral approaches to the treatment of PE have, on the whole, generally shown moderate efficacy in terms of both improved sexual satisfaction and long-term efficacy [5]. Yet, interestingly—and perhaps highlighting the lack of ongoing intrapsychic exploration of PE—despite the moderate success of various behaviorally based techniques, even today an underlying psychophysiological explanation for the inhibiting effects of the “squeeze” technique on ejaculation has not been elucidated.

Nevertheless, throughout the years, a handful of studies have attempted to differentiate men with PE from sexually functional men along a number of psychological dimensions. Broadly speaking, these dimensions have typically fallen within the social-cognitive and affective realms. [Chapter 10](#) of this book expands on the social-cognitive realm by addressing relationship risk factors.

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## 8.3 Psychological Characteristics of Men with PE

The question whether men with PE are somehow fundamentally different from other men has long been a topic of interest. For example, early research suggested that men with PE were narcissistic and uncaring toward their partner (as discussed

in [1]), an idea that has received little or no support from contemporary analysis [6]. Yet, several studies do suggest that men with PE may have heightened social-cognitive or affective vulnerability.

### 8.3.1 Anxiety and Negative Emotionality

Anxiety, a construct considered central to many psychological disorders, has also been postulated to have a role in psychogenic sexual dysfunction, including premature ejaculation. Indeed, recent studies have identified depression, anxiety, apprehension, and neuroticism as key dimensions along which men with sexual dysfunction—in this case primarily ED—were different from controls [7–9].

With respect to PE, the research is less robust, yet a similar pattern seems to emerge. Men with PE on average display more trait-based anxiety and depression [10, 11] than the general population. Other research has indicated that men with PE approach psychosexual stimuli (such as visual sexual stimulation) with greater overall negative affect than controls [12]. Specifically, men with PE report higher embarrassment/guilt and worry/tenseness; when the dysfunctional response was mitigated with 3 weeks of treatment with an ejaculatory-retarding drug, the overall level of negativity decreased in men with PE, yet remained substantially elevated compared with controls. Such findings suggest that the negative emotionality in these men is fairly deeply entrenched, although it is likely that at least some negativity (e.g., embarrassment/guilt) is specific to the situation and not a characteristic trait of the individual.

A number of other studies have affirmed the psychological burden experienced by men with PE. These men report higher personal distress and interpersonal difficulty, lower self-positive image, and diminished quality of life compared with controls [13–16]. Furthermore, men with PE show higher general emotional distress, feelings of inadequacy, self-esteem problems, and disappointment than controls [14, 17, 18]. However, these differentiating characteristics quite clearly *result* from the functional impairment rather than contribute to the PE etiology. Nevertheless, because they become part of the man's individual experience of sexuality and intimacy, and because such psychological/experiential processes are likely to impact somatic function [19], they have strong potential to maintain or exacerbate the condition.

What remains unresolved is the reason or cause for the anxiety itself—is it genetically or developmentally predispositional (e.g., [20])? Is it general anxiety tied specifically to social interaction? Is it the consequence of feelings of inadequacy and failure with the sexual partner? Is it the fear of future poor sexual performance?

### 8.3.2 Other Emotional Disturbances: Alexithymia and Social Anxiety

Perhaps not surprising in view of the emotional characteristics and disturbances discussed above, recent research has identified men with PE as having a higher severity of alexithymia [21]. Alexithymia is a disorder characterized by an

inability to recognize, interpret, and verbalize signs of emotional arousal in oneself or others—that is, such persons are “not in touch with themselves emotionally.” The men with PE were particularly high on one specific subscale, namely a “stimulus bound externally oriented cognitive style.” Such men, rather than relying on their own inner feelings, depend heavily on external cues for expression and action [22].

Not inconsistent with the above findings, men with PE appear to be overrepresented among clinical populations exhibiting Axis I psychiatric disorders (DSM-IV). Two recent studies, for example, have shown a link between PE and social anxiety: one reported that 65% of a sample of PE men exhibited Axis I disorders, with the most common being social phobia or anxiety [23], and the other reported a high prevalence of PE in a sample of men with social phobia [24]. This social phobia often manifested before the PE, suggesting an etiological contribution to the PE.

Although the studies cited above warrant further replication and expansion, these findings, along with those dealing with anxiety and neuroticism, beg for a coherent and unified interpretation. One such interpretation is that the heightened risk for affective problems, inhibited social confidence, and amplified impact of external influencers—including social norms and/or partner feedback—suggests susceptibility to error or greater variation along the “social-affective axis,” at least for a subpopulation of men with PE. Although these differences between men with and without PE tend not to reach the level of clinical significance, this social-affective vulnerability may well heighten the probability for developing and intensifying negative (and counterproductive) thought patterns—patterns which are known to contribute to, maintain, or exacerbate functional impairments in many psychological realms, including PE [25].

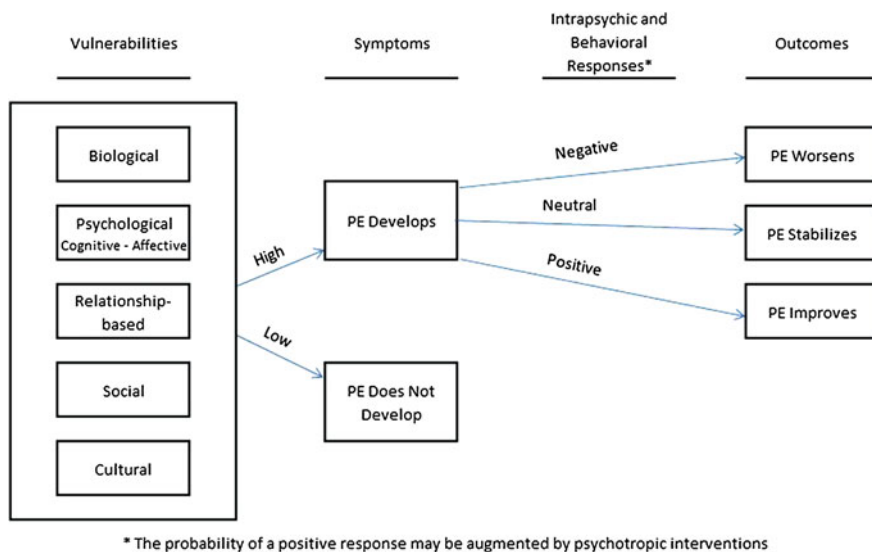
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## 8.4 Psychological Processes in Men with PE

The ways in which a patient thinks and feels about his impairment can become part of the dysfunction itself—in this case, the PE. Such psychological processes can be examined in two domains—those that are *etiologically* significant and those that are *restoratively* significant. Etiologically Significant Factors

The challenge in showing etiological contribution to PE is one endemic to much of the psychological research on clinical disorders; the collection of longitudinal data prior to, during, and after the emergence of the dysfunction is for all practical purposes impossible [26]. Nonetheless, there is little reason to believe that PE does not operate in much the same way as most other clinical problems; specifically, an individual’s biopsychosocial vulnerability interacts with specific developmental and current experiences and manifests as a specific disorder [27], in this case the PE symptomatology (see Fig. 8.1). The particular biological, psychological, and social (e.g., relational, cultural) vulnerabilities related to developing, maintaining, or exacerbating PE—as well as their relative balance—are idiosyncratic. Yet a *general* tendency towards vulnerability may be characteristic of specific subgroups, such as men who are predisposed towards anxiety responding, men with





**Fig. 8.1** Biopsychosocial model showing etiology of PE and effect of psychological-behavioral responses to the condition

perfectionistic performance expectations, men whose partners are highly critical, etc. [28].

The individual's pattern of responding to performance failures also has a significant influence in the development of PE. For example, attributions of external reasons for a PE experience—such as consuming too much alcohol—are less likely to lead to anticipatory anxiety than internal attributions such as interpretations of loss of endurance and thus manliness, or of an age related and inevitable functional loss [29]. As a further example, those having a low tolerance for risk may be more likely to avoid sexual encounters and, when these do occur, to experience feelings of pressure and monitoring of performance—both counterproductive to functional sexual response. Such factors suggest that intrapsychic factors may be the most central ones in determining whether the PE, once initially manifested, is sustained and intensified [28].

### 8.4.1 Restoratively Significant Factors

Although little is known about intrapsychic factors that contribute to the etiology of PE, the fact that psychosexual therapy has the potential to reduce or attenuate PE suggests that specific maladaptive affective-cognitive-behavioral patterns may complicate the dysfunctional sexual response. Indeed, although data are lacking, we agree with the general line of thinking that an integrated approach toward the treatment of PE, where medication and psychosexual therapy are combined, is likely to provide added value to the overall treatment process and efficacy [28, 30].

However, we also subscribe to the idea that, in some instances, psychosexual therapy might be initially attempted to ascertain whether this strategy by itself can achieve positive long lasting change in the man with PE [28]. Such a process could enable more control over the ejaculatory process without the patient's reliance on medication which, in addition to treating only PE symptomatology, imparts adverse effects along with the intended positive effect.

So what are these maladaptive (or alternatively, non-productive) cognitive-affective-behavioral patterns presumably associated with PE and what are the means by which they can be countered through therapy? Conceptually, conducting psychotherapy with men with PE can be divided into a focus on "process" interventions—those that cross therapy schools and approaches; and a focus on "technique" interventions—those that have emerged from various counseling theories and research [31]. There are five "process" elements of integrative therapy that are most relevant to PE, and these have been discussed in detail in a recent review on practical tips for the psychosexual treatment of PE [28]. The first three of these include (1) developing the therapist–patient relationship, (2) expressing empathy, genuineness, and positive regard, and (3) developing motivation to change, a process that typically involves working through patient resistance. Each of these typically leads to higher positive outcomes, including overall patient satisfaction, improved communication and coping skills, and greater compliance/adherence with therapy [3, 28, 31].

The fourth and fifth processes, and the ones most related to the question posed above, are those of (4) identifying PE-related affects, cognitions, and behaviors (including interactional patterns with partners) that sustain or intensify the problem, and (5) supporting self-efficacy in the patient. Although these issues are discussed in [Chaps. 16 and 17](#), it is worth noting here that these intrapsychic patterns often become one of the focal points of psychosexual counseling *because* they become part of the larger PE problem.

#### **8.4.2 Cognitive-Affective-Behavioral Patterns**

To a large extent, behavioral treatments for PE include strategies that enable the patient to gain control over the timing of his ejaculatory response. This goal is most often achieved by reducing stimulation through a combination of position adjustment and patient/partner initiated strategies (e.g., pause or squeeze [1, 2]) and by helping the patient become more attuned to his premonitory ejaculatory response [30, 32]. In addition, adjustments to the overall sexual response cycle may be introduced by altering the amount and type of foreplay for the patient and his partner, by encouraging a pre-intercourse ejaculation, and so on. Sexual behaviors associated with PE may sometimes (though not always) work against increasing ejaculatory latency, and therefore the behavioral treatment strategies may counteract these PE-supporting behaviors. However, treatment strategies are also intended to introduce new, alternative behaviors designed to optimize ejaculatory latency and control.

The cognitive domain focuses on changing responses by changing thoughts and beliefs. Interventions such as Desibels, Counters, Rational-Emotive Behavioral (REBT), and Self-Instructional techniques [31] are examples of cognitive interventions that have been empirically supported as effective means for countering distorted thinking and beliefs in general. As such, they can provide a potentially useful approach to countering beliefs that may contribute to, maintain, or exacerbate PE. Specifically, helpful cognitive strategies that attenuate negativity surrounding PE include (1) identifying faulty or irrational beliefs and attitudes, (2) developing steps to counter them with accurate information, and (3) replacing negative inner dialogue with positive thinking. For example, a man who has experienced rapid, uncontrolled ejaculation on several occasions may begin to develop high anxiety about any and all sexual interactions with his partner—he may assume that the pattern will repeat itself and obsess about “what if it happens again.” Or the man may internalize irrational (and often self- or performance-destructive) thoughts that are often embedded in culture. For example, in US culture, these thoughts may include “I must be the perfect lover” or “I must be sexually successful or I am a failure.” Men in other cultures, such as Japan, may hold self-destructive beliefs such as “I should always control my feelings.”

Affective domain interventions, as illustrated by emotion-focused therapy (EFT), seek to promote emotional awareness, regulate emotion, and transform negative emotion into positive emotion [33]. Accessing and expressing emotion as integrated with a cognitive processing is central. Specifically, while cognitive strategies often relieve distress, attending to and then directly working through negative emotions, particularly those that lead to counterproductive behaviors such as avoidance, may provide a needed opportunity to resolve emotional issues surrounding the problem.

The relational domain, while “interpersonal” rather than purely intrapsychic, always includes an intrapsychic aspect so it is mentioned briefly here (and taken up in greater detail in [Chap. 10](#)). It is generally agreed that including the partner in the treatment of PE has greater potential to produce rapid and substantial therapeutic change [3, 28]. For example, to improve long-term outcomes, cognitive and sexual therapy approaches rely on effective communication between the man and his partner regarding all aspects of sexual interaction, whether functional or dysfunctional. Besides more effective communication for the PE couple, use of other relationship therapy techniques including reframing, symptom prescription, use of paradox, and giving directives may be productive in alleviating PE.

Each of the restorative strategies above, by focusing on a particular intrapsychic domain of the man with PE, seeks to counter maladaptive thoughts, feelings, behaviors, and partner interactions that through time and experience may have become inseparable from the PE condition itself. They also promote strategies that replace counterproductive patterns with ones more likely to enhance the positive outcomes of ejaculatory control and, subsequently, to enhance overall sexual and relationship satisfaction.

### 8.4.3 Supporting Self-Efficacy

According to Bandura, the primary mechanism of behavioral change is mediated through self-efficacy, essentially the belief and conviction that a person has to and can change his/her behavior in order to achieve certain outcomes [34]. Often men with a sexual problem such as PE feel helpless and discouraged or become avoidant and fatalistic about their condition. They may not believe that the ability to do something about their problem lies within their own control [35], and so the problem becomes self-perpetuating. Thus, when counseling a patient with PE, the therapist encourages the patient to make positive statements about change, as this fosters a belief in the intrinsic ability to seek solutions to the problem and effect change as and when it is needed or appropriate. The therapist can also empower the couple by encouraging them to find their own solutions, thereby supporting a stronger sense of self-efficacy [36].

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## 8.5 Summary and Conclusions

This chapter has elucidated a number of intrapsychic factors that are etiologically and clinically related to the development, exacerbation, and alleviation of symptoms in men with chronic or situational PE. Research in this field is in its infancy due in part to lack of funding, but also to the differentially greater attention paid to biological and behavioral factors. The lack of any longitudinal research particularly limits generalizations. Nevertheless, the available evidence suggests that intrapsychic variables may play key roles in increasing a man's vulnerability to the development, maintenance, or intensification of PE symptoms; on the positive side, such variables are amenable to the influence of therapeutic processes. Future studies should focus on all three areas of unknowns: What and how do intrapsychic variables contribute to the development of PE in men? Which intrapsychic factors are the most likely to lead to an exacerbation of the PE symptoms once they emerge? And, what is the efficacy of therapeutic interventions targeting intrapsychic mediators and how do they work?

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# Risks Factors in Premature Ejaculation: The Genetic Risk Factor

# 9

Marcel D. Waldinger

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## 9.1 Introduction

In order to answer the question whether there are genetic risk factors for premature ejaculation (PE), we first need to know what is actually meant by premature ejaculation. In 1943, Bernhard Schapiro [1] distinguished two subtypes that many years later were renamed as lifelong and acquired PE [2]. Measurement of the intravaginal ejaculation latency time (IELT) [3], showed that men with lifelong PE ejaculate within about 1 min in more than 90 % of intercourses. Studies also showed that men with acquired PE ejaculate within seconds. The complaints of PE in men with normal IELT values had not been taken into account. By also considering these men, Waldinger et al. [4–6] suggested in 2006 that apart from lifelong PE and acquired PE, there are also two other PE subtypes: natural variable PE or Variable PE and premature-like ejaculatory dysfunction (or subjective PE). The four PE subtypes are distinguished on the basis of the IELT duration. In variable PE, men only occasionally suffer from early ejaculations. In subjective PE men experience or complain of PE while actually having a normal or even a long IELT duration of, 5–20 min [6–8]. Variable PE is considered a normal variation of ejaculatory performance. Subjective PE is considered to be caused by psychological, cultural, or interrelationship factors. On the other hand, it has been suggested that lifelong PE is mediated or even caused by neurobiological and

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genetic factors, where as the cause of acquired PE is either medical or psychological. Importantly, Waldinger emphasized that the four PE subtypes are characterized by different etiology and different pathogenesis and therefore should be defined indivally [6–8]. It was assumed that the prevalence of lifelong and acquired PE is low in the general male population but high in outpatient urological clinics [6–8], whereas the prevalence of variable PE and subjective PE is high in the general male population but rather low in urological outpatient clinics [6–8]. In addition, it was argued that the sum of the prevalences of these four PE subtypes constitutes the 20–30 % prevalence of PE often reported in epidemiologic studies [6–8]. Serefoglu et al. [9, 10] investigated the prevalence of the four PE subtypes in Turkey and confirmed the existence of the four PE subtypes in both an outpatient urological clinic and in the general male population. Moreover, the self-reported IELT values in their study indeed showed a continuum, with the shortest IELTs in lifelong PE and the longest IELTs in subjective PE. Also the prevalence rates of the four PE subtypes were in accordance with the hypothesis of Waldinger. The prevalence of lifelong PE was low in the general male population but high in the outpatient urological clinic , giving support to the validity of this proposal for a new PE classification.

### 9.1.1 Lifelong Premature Ejaculation and Genetics

The International Society for Sexual Medicine (ISSM) defined lifelong PE as an ejaculation that occurs within about 1 min after penetration in the majority of sexual encounters, with an inability to delay ejaculation and with associated negative personal consequences such as bother and avoidance of sexual activity [11]. In 1998, Waldinger et al. postulated that there is a continuum of the IELT in the general male population and that this variability in the IELT is influenced by neurobiological mechanisms and genetic factors [12]. In addition, it was postulated that the persistently short IELTs in men with lifelong PE are associated with diminished serotonin (5-hydroxytryptamine, or 5-HT) neurotransmission, a hypersensitivity of 5-HT<sub>1A</sub> receptors, and/or a hypofunction of 5-HT<sub>2C</sub> receptors [12]. Notably, due to an absence of selective 5-HT<sub>1A</sub> and 5-HT<sub>2C</sub> receptor ligands for safe human usage, this hypothesis has sofar not been confirmed.

### 9.1.2 Investigation of Genetic Risk Factors

There are a number of clinical and behavioral genetic methods that are effective for establishing whether and to what degree genetic factors influence a trait [13]. These methods are family studies (is the phenotype familial?), twin and adoption studies (what are the relative contributions of genes and environment?), but also molecular genetic methods to identify specific genes mediating familial transmission of a trait through linkage analysis (where are the genes located?), and association analysis (what are the responsible genes?).



### 9.1.3 Rationale and Method of Family Study

The basic design of a family study begins with the ascertainment of a group of subjects who are affected with the particular disorder and a comparable group of control subjects who do not have the disorder [13]. Next, the biological relatives of these subjects, or probands, are ascertained and evaluated for the presence of the disorder. The rate of the disorder among family members of affected probands is then compared with the rate of the disorder among family members of control probands to determine the familial risk or relative risk.

If a disorder has a genetic etiology, then biological relatives of case subjects should have a higher likelihood, compared with relatives of control subjects, of carrying the gene or genes that influenced illness in their relative, and thus they should be at greater risk for the illness themselves [13]. In addition, the risk to relatives of cases should be correlated with their degree of relationship to the proband, or the proportion of genes they share. First-degree relatives such as parents, siblings, and children, share 50 % of their genes, on average, with the proband. Thus, first-degree relatives of case subjects should be at greater risk for the disorder than second-degree relatives (grandparents, uncles, aunts, nephews, nieces, and half-siblings), because second-degree relatives share only 25 % of their genes with the proband [13].

If the results of the family study indicate that the phenotype is not familial, then there is little reason or need to research the issue further with genetic methods, as absence of familiarity argues strongly against a genetic component in the etiology of a disorder. If the phenotype is found to be familial, then there is some basis to suspect that it may also be heritable and, thus, that a gene or genes underlie this transmission. However, it is critical to understand (and convey to clients) that familiarity does not establish heritability [13]. For example, religion and language are familial traits, as often all members of the same family practice the same religion and speak the same language. These facts are due not to the transmission of “religion genes” or “language genes” through the family, but rather to the common environment and upbringing that those family members share.

### 9.1.4 Familial Occurrence of Lifelong Premature Ejaculation

Although Bernhard Schapiro, a German endocrinologist, never postulated that PE is a genetic disorder, he noted in 1943 that family members of men with PE also suffered from PE [1]. This remarkable clinical observation was never quoted in sexological literature until 1998 when Waldinger et al. published a study on the familial occurrence of PE [14]. In this study, 237 men with lifelong PE were routinely asked whether they were willing to ask family members about the occurrence of PE. Due to embarrassment, only 14 of them consented to ask male relatives about their ejaculation time. These 14 men found a total of 11 first degree male relatives with available information for direct personal interview. Indeed, ten of them also ejaculated within one minute or less. The calculated risk in this small

selected group of men to have a first-degree relative with PE was 91 % (CI: 59–99 %). The odds of family occurrence is therefore much higher compared to a suggested population prevalence rate of 2–39 %. Moreover the high odds indicates a familial occurrence of the syndrome far higher than by chance alone [14]. However, a limitation of this study is the lack of a control group. Nevertheless, based on this preliminary observation the influence of familial factors as formerly stated by Bernard Schapiro, has gained some credibility. But unfortunately, since 1998 there has not been any other study investigating the familial occurrence of PE. Therefore, although it may have some face validity, there is insufficient evidence today that being a first-degree family member of a person with lifelong PE can be considered a risk factor for lifelong PE.

### **9.1.5 Limitation of Family Studies for Research of Premature Ejaculation**

The aforementioned study of Waldinger et al. [14] also demonstrated the immense taboo that exists among PE sufferers to openly talk about their complaints of PE. As long as such a taboo exists, and realizing that it is quite difficult to admit to suffer from PE, family studies on PE are rather impossible to perform today, and I fear also in the next decade.

### **9.1.6 Rationale and Method of Twin Studies**

Twin studies are performed to investigate the relative contributions of genes and environment [13] and can be used to determine whether a disorder is attributable to the inheritance of genes or to shared familial and other environmental factors. If a genetic contribution of the disorder is detected, it is also important to quantify that contribution relative to that made by environmental factors.

In a twin study design, identical (monozygotic [MZ]) and fraternal (dizygotic [DZ]) twin-pairs are ascertained if at least one member of the pair is affected with the disorder of interest. Twin-pairs are deemed concordant if both members of the pair have the disorder and are deemed discordant if only one member of the pair is affected [13]. The ratio of concordant to discordant MZ twin-pairs is then compared with the ratio of concordant to discordant DZ twin-pairs.

Monozygotic twins are derived from the same zygote and thus share 100 % of their genetic material. In contrast, DZ twins result from separate fertilizations and thus share, on average, 50 % of their genes—no more or less than any other pair of siblings. Thus, a typical MZ twin-pair will have 50 % more genes in common than a typical DZ twin-pair. The degree of similarity in environmental exposures between members of a MZ twin-pair should be no different than that between members of a DZ twin-pair, however. Thus, any difference in concordance for a

disorder between the two types of twin-pairs can be attributed to the effects of the additional gene-sharing in the MZ twins. In other words, sharing 50 % more genes in common can be considered to be the sole factor responsible for any increased phenotypic similarity among MZ twin-pairs relative to DZ twin-pairs [13].

### 9.1.7 Twin Studies on PE

In 2007, Jern et al. [15] published the first study on the occurrence of PE in a large cohort of male twins in Finland. This study was followed by a number of publications on different items that have been found in the same large cohort of Finnish twins, in which the ejaculation time and other variables were measured in a 10-item questionnaire [16–18]. Jern et al. found that in the twin population there was a moderate (28 %) genetic effect on PE [15]. The strength of the Finnish twin study is that it investigates a large cohort of twins in the general male population with an IELT of more than 1 min, which enables the investigators to analyze the experience of PE in men in the general male population who do not fit the ISSM definition of lifelong PE. A limitation of this design is the relatively small number of men that is thought to suffer from lifelong PE based on the mere use of a questionnaire. If the number of men with an estimated IELT of less than 1 min in the Finnish twin study became larger, it would become easier to investigate the cause of differences between the two groups of twins with an IELTs of more or less than 1 min. Nevertheless, the studies in this large twin cohort have contributed to a deeper understanding of the genetic involvement in the ejaculation time in the general Finnish male twin population.

### 9.1.8 Rationale and Method of DNA Research

If a compelling reason exists to suspect that a gene influences a risk for a given disorder (i.e. a functional candidate gene), genetic association analysis is the appropriate method for determining if a particular gene variant has a direct effect on risk for a particular disorder [13]. The possible association of candidate genes can be evaluated in an independent sample of cases with the disorder and matched control subjects (i.e., in a case-control study).

In case-control association studies, one simply counts the number of each type of allele of a gene that is found in case subjects and compare these counts with the allele distribution seen in the control group. This process can also be performed for genotypes. A Chi-square test is then used to determine if the distribution of alleles observed in the group of cases is different from that seen in the control group. A difference in distribution of alleles is evidence for a genetic association with the disorder, where the allele that is overrepresented in the group of cases is considered the risk allele. The degree of overrepresentation of the risk allele in case

subjects relative to control subjects can be used to derive an odds ratio, which gives a numerical indication of the probability that an affected individual possesses the allele, in comparison to the probability that an unaffected individual possesses the allele. Association studies of this type can be performed for alleles or genotypes [13]. In order to understand a recent case-control association study in Dutch men with lifelong PE, it is important to have some basic knowledge of the central serotonergic system.

### **9.1.9 Serotonin, 5-HT Receptors, and Ejaculation**

The strong ejaculation-delaying effects of selective serotonin reuptake inhibitors (SSRIs) and particularly that of paroxetine [19], suggests that serotonin and 5-HT receptors play an important role in the ejaculation process, as was already demonstrated in rodents in the 1980s [20].

### **9.1.10 Central Serotonergic Modulation of the IELT**

Serotonin (5-hydroxytryptamine, or 5-HT) plays a very important role in ejaculatory activity [21–24]. Animal studies, mainly performed in laboratory rodents, have shown that various brain areas are specifically involved in ejaculatory behavior [25]. Overall, these brain areas are a complex interconnected network that regulates ejaculation. There is also a very important spinal ejaculation generator located lateral to the central canal in lamina X and in the medial portion of lamina VII of L3 and L4 of the lumbar spinal cord. These lumbar spinothalamic (LSt) neurons project to the medial parvocellular subparafascicular nucleus of the posterior thalamus (SPFp) and are specifically activated during ejaculation but not with other components of male rat sexual behavior [26]. Lesions of these neurons cause dramatic disruptions in ejaculatory behavior [26]. Serotonergic fibers have been found in all spinal cord areas containing sensory axons and motor neurons involved in ejaculation. They are present in the dorsal and ventral horns, dorsal commissural gray and thoracolumbar intermediolateral cell column (IML), and sacral parasympathetic nucleus (SPN) of the lumbosacral spinal cord [27]. In addition, serotonergic postsynaptic receptors have been found in the area where LSt cells are located [28]. This suggests a role of serotonin in ejaculation via these possible connections in the spinal cord. However, these serotonergic connections are also found in supraspinal areas. In the nucleus paragigantocellularis (nPGI), an area in the ventrolateral medulla of the brainstem, serotonergic neurons are found to innervate the bulbospongiosus muscles involved in the inhibition of ejaculation [28]. The medial preoptic area (MPOA) might lower the ejaculatory threshold by removing the tonic serotonergic inhibition exerted by the nPGI [29]. Another serotonergic innervation exists in the anterior lateral hypothalamic area (LHA). Lesions of the LHA in male rats strongly affect the occurrence of ejaculations, showing the excitatory role of this brain region in the regulation of ejaculation

[30]. This effect is caused by serotonin, because it is released in the LHA at the time of ejaculation [31] and injections of SSRIs into the LHA were shown to increase ejaculation latencies [31].

The ejaculatory reflex is complex and involves multiple afferent and efferent systems. The afferent stimuli may involve sensory, visceral, proprioceptive, and somatic inputs. It is possible that LSt cells receive stimuli related to the onset of ejaculation and, in turn, trigger the ejaculation reflex. The efferent site of the reflex involves the complex control of sympathetic and parasympathetic systems [26]. Briefly, ejaculation is a spinal reflex controlled by the spinal ejaculation generator that is “modulated” by sensory input from the pelvis and descending input from inhibitory and excitatory centers in the brainstem and the hypothalamus. Allard et al. suggested that these supraspinal centers are controlled by cortico-limbic centers, which are responsible for switching on a state of sexual excitement [32]. During sexual intercourse, the cortico-limbic centers inhibit and activate the inhibitory and excitatory centers, respectively, shifting the supraspinal tone to the spinal ejaculation generator from overall inhibitory to excitatory.

### 9.1.11 Serotonergic Modulation of the Spinal Ejaculatory Reflex

All together, the data derived from animal research suggest a major role of the central serotonergic system in modulating the spinal ejaculatory reflex. This serotonergic modulation of ejaculation may result in a faster or more delayed ejaculation, whereas the ejaculation itself is probably not only under direct influence of the serotonergic system, but rather under the influence of other neurotransmitter systems in the spinal cord [26]. I would like to underline that the consequences of the central “modulation” of ejaculation have hardly been discussed in the literature but may be pivotal for genetic research of PE. For example, it may be assumed that the modulation of ejaculation among men is variable; it can be strong, moderate, weak, or even absent. In the last case, the serotonergic system in the brainstem is unable to modulate the ejaculation reflex in the lower spinal cord. In that case, a male is not able to or hardly able to change the duration of his ejaculation time. Even by using SSRIs, this subject may still not be able to change the duration of his ejaculation time. Although never systematically investigated, it is clinically well known that a subgroup of men with lifelong PE do not respond with ejaculation delay to any SSRI treatment. I therefore suggest that in these men, the serotonergic system is unable to modulate the ejaculation reflex.

The view that serotonin modulates ejaculation may have important implications for genetic research, because it may imply that in a certain cohort of men, an unknown number have no or hardly any ability to modulate ejaculation irrespective of the presence of functional serotonergic polymorphisms. Consequently, irrespective of the presence of these polymorphisms, these men will not show any change in IELT duration when modulation of the IELT is not 100 % associated with such serotonergic polymorphisms.

### 9.1.12 Case-Control Association Study of Lifelong PE

In 2009, Janssen et al. [33] published the first (quantitative) case-control association study in men with lifelong PE, defined in terms of an IELT of less than 1 min. Janssen et al. [33], investigated 89 men who actively sought medical treatment for lifelong PE. In these men, the IELT was measured with a stopwatch. It was shown that the IELT duration in men with LPE is associated with 5-HTLPR polymorphism, indicating the presence of a disturbance of central serotonin neurotransmission, which is regulated by the activity of the 5-HT transporter. The study showed that the prevalence of LL, SL, and SS genotype in LPE is comparable with the normal Dutch population. However, subjects with LL-genotype (geometric mean IELT 13.2 s) ejaculated 100 % faster ( $p < 0.027$ ) than men with SS-genotype (geometric mean IELT 26 s) and SL-genotype (geometric mean IELT 25.3 s) [33]. The strength of this study is that by using a stopwatch, accurate measurement of the IELT was performed which made it possible to find an association between the IELT and the investigated genotypes. However, a limitation of this case-control design is that by using this method one cannot investigate the influence of genetic polymorphism on the median IELT of about 6 min in the general male population. Interestingly, this finding is in line with pharmacological knowledge, indicating that a diminished serotonergic neurotransmission facilitates ejaculation.

### 9.1.13 Three Different Methods of Genetic Research on Premature Ejaculation

As there is a gradual increase of scientific articles on genetic research of PE, it has become relevant to distinguish the current state of three different methods of research in this field [34]:

1. The first method investigates the genetics of the IELT in Dutch men with lifelong PE with IELTs of less than 1 min [33]. This investigation is based on the hypothesis of Waldinger et al. that the skewed distribution of the IELT in the general male population [35, 36], in men with lifelong PE [37], and in any cohort of male Wistar rats [23] is based on genetic factors influencing the central serotonergic system in modulating the duration of the IELT. The methodology of this genetic research consists of real-time, objective stopwatch measurement of the IELT in cohorts of men who actively seek medical treatment for their complaints associated with lifelong PE in terms of lifelong, persistent IELTs of about 1 min.
2. The second method investigates the genetics of men who complain of PE in the general Finnish male twin population [15–18]. This investigation is based on the view of Jern et al. that PE consists of various parameters (such as anteportal ejaculation, number of thrusts, ejaculation latency time, and feelings of control) that are potentially genetically interrelated [15–18]. Their methodology of genetic research consists of sending questionnaires to a large cohort of male

homosexual and heterosexual twins irrespective of their wish to seek medical treatment for complaints of PE and without objective stopwatch measurements of the IELT.

3. The third method investigates whether the prevalence of genotypes in men with lifelong PE in terms of an IELT of less than 1 min differs from the prevalence of these genotypes in the general male population [38, 39], without investigating potential associations of genetic polymorphism with the IELT (as used in the first method). This investigation is based on the view that men with lifelong PE have a different genotype profile than men without lifelong PE.

### 9.1.14 Differences Between the Three Methods

The three methods differ in (i) the investigated population (men with lifelong PE vs. general male twin population), (ii) tool of measurement (stopwatch vs. questionnaire), (iii) design (prospective real-time IELT measurement vs. retrospective IELT estimation), and (iv) variables (IELT vs. feelings of control, ejaculation prior to intercourse, number of thrusts, and ejaculation latency time) [34].

However, the major difference between the three study designs pertains to the investigated population. Whereas Janssen et al. [33] investigated a selected cohort of men with lifelong PE who ejaculate within about 1 min and who present as patients actively seeking treatment [33], Jern et al. and Santilla et al. investigated a relatively small group of respondents (40–33 %) recruited from a large general male twin population who did not present as patients seeking medical treatment [15–18]. Moreover, in the studies of Jern et al. and Santilla et al., most (98 %) of the male twins ejaculated after 1 min [15–18]. Of 1,290 twins, only 26 (2 %) twins reported an ejaculation time of less than 1 min [18]. In contrast, in the study of Janssen et al. [33], most (92 %) of the men ejaculated within 1 min, and only 8 % ejaculated between 1 and 2 min.

The third method of genetic research on PE is different from the method of Janssen et al. [33]. In this method, men with lifelong PE are selected but instead of investigating potential associations of genetic polymorphisms with the IELT, the prevalence of genotypes in these men with lifelong PE is compared with the prevalence of these genotypes in a control group. This method has been used by Ozbek et al. in Turkey [38] and Luo et al. in China [39]. The outcome of these studies points to a different genetic profile in men with lifelong PE than in men in the general male population, rather than emphasizing an association between ejaculation time and genetic polymorphism. However, such a difference in genotype profile was not found in the Dutch study of men with lifelong PE by Janssen et al. [33]. This discrepancy was explained after re-analysis of the data from Ozbek et al. [38], which disclosed that these study populations did not meet Hardy–Weinberg equilibrium, indicating potential laboratory insufficiencies or patient selection bias [40]. Further studies controlled by Hardy–Weinberg equilibrium are needed to elucidate whether men with lifelong PE indeed have a higher prevalence of certain genotypes than do males in the general male population.

### 9.1.15 Strength and Limitations Between the Three Methods

Each of the three methods has its own strength and limitation. For example, non-stopwatch assessment of the IELT in the general male population may give rise to about 30 % over- and under-estimation of the IELT compared with stopwatch assessment [36]. Therefore, it may be assumed that the non-stopwatch methodology of Jern et al. [15–17] and Santilla et al. [18] fails to precisely objectify the IELT duration both in men with an IELT of less than 1 min and in men with longer IELT durations. Notably, any questionnaire method as has been used by Jern et al. and Santilla et al. is inadequate to investigate the subtle influences of genetic polymorphisms on the IELT in men with lifelong PE who ejaculate within 1 min [15–18].

On the other hand, the methodology of Janssen et al. [33] is inadequate to provide an answer to the question of how genetic factors relating to ejaculation are distributed in the general male population. In addition, the design and method of the study of Janssen et al. do not have the precision needed to study associations between subjective feelings of control and genetic polymorphisms [33]. The small number of participants in stopwatch studies in general does not allow sufficient power to analyze subjective feelings and possible polymorphisms. Such studies would require a huge cohort of patients.

### 9.1.16 The Need for Stopwatch Measurements in Genetics

Interestingly, the current different views on how to perform genetic research on PE are strikingly similar to the different views that existed in the 1990s on how to perform drug treatment research on PE [41]. Also in that decade, a number of clinicians favored the stopwatch method to precisely assess the IELT, whereas others used questionnaires to measure control, satisfaction, and ejaculation time [41]. However, a final meta-analysis of drug treatments that were mainly performed in the 1990s confirmed that real-time, prospective stopwatch measurement of the IELT is more accurate than retrospective IELT assessments [19]. Similarly, it is my current view that real-time prospective IELT measurement is pivotal for evidence-based genetic research on lifelong PE, acknowledging that this requirement may impede large-scale genetic research of the IELT in the general male population.

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## 9.2 Conclusion

Although it remains pivotal for science to critically look at the strength and limitations of a method of investigation, both the method of Janssen et al. [33] and Jern et al. [15–18] have contributed to a new way of understanding the influence of genetic factors on the ejaculation time in the general male population and in the



rather small percentage of men with lifelong PE. Both methods add to each other, and I would like to encourage more case-control association and twin studies on PE in different countries. However, as we are only at the very beginning of genetic research on PE, and family studies on PE are currently practically impossible to perform owing to the strong taboo on PE, there is no hard evidence to answer the question whether there are genetic risk factors for PE. To answer this question, much more genetic research on PE in the next two decades is warranted.

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# Twin Studies and Quantitative Genetics in Premature Ejaculation Research

# 10

Patrick Jern

Genetic research has revealed that the vast majority of a human traits are, at least to some extent, affected by genes [1]. Genetic variation not only affects physiological characteristics, such as height, hair color, or vulnerability to disease—more abstract traits, such as personality and behavioral characteristics are also under genetic control to a varying degree [2]. Indeed, adoption studies have revealed that identical twins reared apart are more similar in most aspects, including personality and vulnerability to psychiatric disorders, than fraternal twins/biological siblings (who, on average, share half of their genetic material) reared together [1]. In summary, genetics likely play an important role in the development of any human trait, and make a convincing case that genetics should be considered when investigating the etiology of any dysfunction or disorder, including premature ejaculation (PE).

Recently, researchers have put increased effort into investigating the genetic etiology of ejaculatory disorders. The idea of a genetic component in PE, however, is decades old—in 1943; Schapiro [3] noted that PE appears to run in families. Familial resemblance for ejaculatory function has also been proven by Waldinger et al. [4], who reported increased likelihood of PE occurrence in relatives of PE patients. While familial resemblance is indeed a characteristic of a genetic trait, resemblance alone does not provide conclusive evidence for a genetic effect. Since genetically related individuals (i.e., family members) also tend to share their environment to a greater extent than non-related individuals, familial resemblance could arise from a shared environmental effect [2]. To separate such shared

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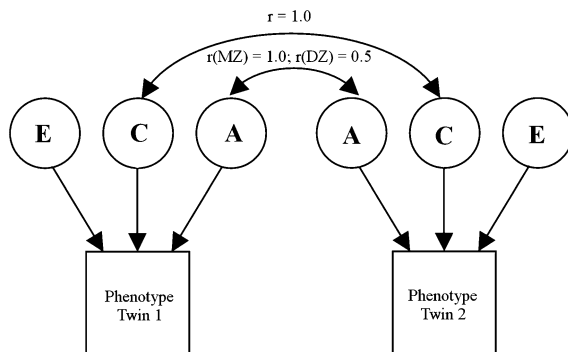
environmental effects from genetic effects, quantitative geneticists apply mathematical models that compare individuals with differing degrees of genetic relatedness, usually identical (*monozygotic*; MZ), and fraternal (*dizygotic*; DZ) twins, who on average share 100 and 50 % of their genes, respectively [1]. Variations of family designs are also possible: for example, parent–child constellations are often used in linkage studies. Usually, as has also been the case in PE research, quantitative genetic studies precede molecular genetic studies, the latter being a logical continuation of the former. In this chapter, a brief and basic introduction to quantitative genetics and twin studies will be presented, along with an overview of findings from quantitative genetic studies in PE research. Implications of results from quantitative genetic studies for molecular genetic PE research will also be discussed.

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## 10.1 Quantitative Genetics and the Twin Study

The first step to investigate if a trait is under genetic influence is usually to calculate twin correlations. This is achieved by calculating correlations within twin pairs, so that the measured trait value of one twin is compared against the trait value of his or her co-twin. Next, within-pair correlations of MZ twins are compared to the within-pair correlations of DZ twins. If the trait is heritable, the MZ correlation is expected to be considerably higher than (around twice) the DZ correlation. For example, a Mendelian trait (i.e., a trait whose total variance is explained by the effects of one gene) would result in an MZ correlation of 1.0 and a DZ correlation of 0.5. Furthermore, if the MZ correlation is more than twice the DZ correlation, there is reason to expect effects of genetic dominance. On the other hand, if the DZ correlation is more than half that of the MZ correlation (the MZ correlation still being higher) there is reason to expect that shared environmental determinants affect the trait (see [2, 6] for in-depth reviews of the methodology). An example from PE research is found in Jern et al. [5], in which 228 MZ pairs, 225 DZ pairs and 349 pairs of non-twin biological male siblings were used to calculate twin correlations using a multifactorial measure of PE. In this study, MZ twin correlations for PE were measured at 0.30, whereas DZ correlations were 0.13. Thus, one would conclude that genetics play a partial role in PE etiology, but environmental effects are expected to contribute the lion's share of the variance in PE as the correlations are considerably lower than the 1.0/0.5 ratio between MZ/DZ twins we would expect if PE was a Mendelian trait. Furthermore, DZ correlations appear to be around half the MZ correlations, hence we would not expect effects of genetic dominance or shared environment.

The next step is to apply structural equation models (SEMs) to the twin data. SEMs are powerful tools to estimate the genetic and environmental components of a trait. In the simplest case, the effects of three latent independent variables on a continuous phenotype are measured. First, we are interested in how much a trait is affected by genetic effects. This parameter includes the combined, or *additive*,



**Fig. 10.1** A simplified univariate ACE model. *A* is the additive genetic component of the trait, and is set at 1.0 for MZ twins, and 0.5 for DZ twins. *C* is the shared environmental component, and is set to 1.0 for both MZ and DZ twins. *E* is the non-shared environmental component and is by definition unique for each twin individual; hence no covariance between twins is measured for the *E* component. Latent variables are illustrated with circles (*A*, *C* and *E*); the observed variable is illustrated with a rectangle (Phenotype). Causal paths are illustrated with *single-headed arrows* and covariance paths with *double-headed arrows*

effect of all alleles that affect our phenotype, and is denoted *A*. Next, we separate between shared, or *common*, environmental effects (*C*), and non-shared environmental effects (*E*). Dominance effects (*D*) may also be calculated. By definition, *C* effects are any environmental effects that make twins or siblings more similar to one another, whereas *E* effects refer to any environmental determinants that make twins or siblings more dissimilar [6]. Measurement error is also modeled in the *E* component. Genetic and environmental parameters are then estimated taking different degrees of kinship into account: the additive genetic component *A* is expected to correlate 1.0 between MZ twins, because MZ twins share all their genetic material. However, *A* is only expected to correlate 0.5 between DZ twins or non-MZ biological siblings, whereas *C* effects are expected to affect both MZ and DZ twins similarly, and therefore correlate 1.0 in both MZ and DZ twins. A graphic illustration of a univariate (i.e., single phenotype) ACE model can be seen in Fig. 10.1. A freely available software package, Mx [6], is commonly used for the calculations.

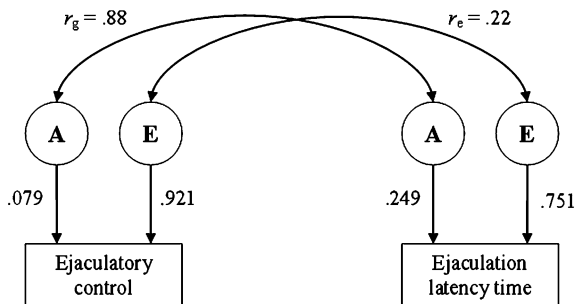
Few studies have investigated PE using twin or family data; to my knowledge, PE has only been investigated in two twin populations. The first of these studies was conducted using data from a population-based sample of nearly 4,000 twins and siblings of twins in Finland [5, 7, 8]. This research group found a significant *A* component explaining about 28 % of the variance in PE [5]. No significant effects of shared environment were found, and thus the *C* component could be omitted without significant reduction of model fit. In other words, most of the variance in PE (72 %) was explained by *E* effects. PE was estimated using a composite score based on self-report questionnaire items inquiring about, for example, ejaculation latency time, frequency of occurrence of anteportal

ejaculation, and subjective perception of ejaculatory control. Recently, a research group in Hungary [9] investigated PE using twin data, however the authors of this study noted that their estimates of concordance rates for PE between MZ and DZ twins were not trustworthy due to significant misfit of the statistical model (likely due to small sample size). PE was estimated using a dichotomous query (yes/no) and was defined as “ejaculation before introitus or as occurring when a lack of ejaculatory control interferes with sexual and emotional wellbeing in one or both partners” (p. 147). Although a valid model could not be established in the study, the concordance rates between MZ and DZ pairs suggested a heritable component.

### 10.1.1 Multivariate Models

Using bi- or multivariate models, one can calculate genetic and environmental correlations between two or more traits in addition to the heritability estimates that are calculated with a standard, univariate ACE model. A genetic correlation is an estimate of the similarity of the underlying  $A$  effects of two (or more) traits. In other words, if a genetic correlation is very high, it can be assumed that the same genes contribute to the  $A$  component in both traits. To provide an example, I computed heritability estimates as well as genetic and environmental correlations using two phenotypic variables commonly used as indicators of PE in the literature: subjective perception of ejaculatory control, and self-reported ELT. Both variables were responded to on a five-point Likert scale. The variable measuring ejaculatory control (*How often have you felt that you could decide when to ejaculate?*) had the following response options: (1) never or rarely; (2) less than 50 % of the time; (3) about 50 % of the time; (4) more than 50 % of the time; (5) almost always or always. The variable measuring ELT (*On average, during vaginal or anal intercourse, how much time elapses between when you first enter your partner with your penis and when you first ejaculate?*) had these response options: (1) less than one minute; (2) 1–5 min; (3) 5–10 min; (4) more than 10 min; (5) I usually do not ejaculate. The questionnaire is more thoroughly elaborated elsewhere [5, 7, 8]. The analysis was conducted using responses from 225 MZ and 213 DZ pairs (876 individuals in total), and its results can be seen in Fig. 10.2. A bivariate Mx script for ordinal data was fitted to the data set.

In the parameter estimation procedure, the shared environmental component  $C$  was estimated to  $1.16 \times 10^{-11}$  for ejaculatory control and  $1.25 \times 10^{-11}$  for ELT (i.e., virtually zero). In other words,  $C$  had virtually no influence on either phenotype, thus  $C$  could be dropped without reducing model fit, leaving us with a more parsimonious AE model. As seen in Fig. 10.2, about 8 % of the variance in ejaculatory control, and 25 % of the variance in ELT, were under genetic control (the remaining 92 and 75 % of the total phenotypic variance, respectively, accounted for by non-shared environment). The genetic correlation between the  $A$  components, however, was quite high at  $r_g = 0.88$ , indicating that largely the same genes influence both ejaculatory control and ELT. The non-shared environmental correlation, on the other



**Fig. 10.2** A bivariate AE model illustrating genetic ( $A$ ) and non-shared environmental ( $E$ ) effects on ejaculatory control and ejaculation latency time, as well as genetic ( $r_g$ ) and non-shared environmental ( $r_e$ ) correlations. The shared environmental component  $C$  has been dropped due to insignificant impact on either phenotype.  $A$  and  $E$  effects are indicated with *single-headed arrows*, whereas genetic and non-shared environmental correlations are indicated with *double-headed arrows*

hand, was rather modest ( $r_e = 0.22$ ) indicating that quite different environmental factors contribute to ejaculatory control and ELT. In short, both ejaculatory control and ELT are under quite modest genetic influence. However, the minority share of the phenotypic variance in both traits that is under genetic control is likely affected by largely the same genes.

## 10.2 Implications for Molecular Genetic Research

Genetic association studies focus on identification of specific genetic variants that contribute to a trait, and do not require samples that consist of genetically related individuals. Indeed, in molecular genetic studies, within-sample genetic relatedness must be controlled for in statistical analyses, since genetic similarity might otherwise lead to spurious findings. Using quantitative genetic methods alone, one cannot investigate the particular genes or genetic polymorphisms that affect a trait, but quantitative genetics nevertheless play an important role in the pursuit of mapping the genetic etiology of diseases and traits. Quantitative genetic methods are powerful tools to refine phenotypes and identify endophenotypes with higher heritability, acting at earlier stages of the pathway between genes to behavior or disease [10]. There are other advantages to quantitative genetics as well: without quantitative genetic studies, we would know virtually nothing about the heritability for most human traits. This is because association studies more often than not generate conflicting or nonreplicable results and genotype associations that are validly replicated are often of very small effect size. These problems are certainly familiar in the case of PE: the first ever molecular genetic study [11] found an association between the “long” allele of the serotonergic *5-HTTLPR* polymorphism and shorter IELT within a group of PE patients (however, no difference in allele



frequencies between patients and controls), whereas two subsequent replication studies [12, 13] found significant differences in IELT between patients and controls (although the latter studies have been criticized for methodological fallacies; [14]). In the latter two studies, however, the same allele was associated with *increased* IELT. Another example is two studies regarding a dopamine transporter gene-linked repeat polymorphism. In the first of these [15], individuals carrying two copies of the ten-repeat allele were more likely to display symptoms of PE, whereas a replication study conducted by Safarinejad [16] found instead that the nine-repeat allele was more prevalent in PE patients than controls. In summary, no molecular genetic PE study has been successfully replicated (and to my knowledge, there have been no other published attempts to replicate a molecular genetic PE study). While this difficulty to identify alleles that contribute to PE etiology—given the evident heritability of the trait—is puzzling, failure to associate genetic variants with disease phenotypes is in fact very common and not limited to PE research. Indeed, even for traits that are highly heritable (some studies estimate the heritability of autism and schizophrenia in the range of 70–90 % [1]), molecular genetic studies have mostly failed to find any replicable, convincing evidence for any particular genetic variants that contribute significantly to the etiology of psychiatric diseases [17]. There are several plausible explanations for this: poorly defined phenotypes, ethnic stratifications and lack of correction for multiple testing are but a few of the factors that can lead to false positives. Publication bias (reports demonstrating positive associations having a greater likelihood of being published than negative reports) has also been identified as a major contributor to these problems; indeed, there are entire journals devoted to publication of negative results (e.g., *Journal of Negative Results in Biomedicine*). Even if all aspects of a study are conducted appropriately, there are still several factors that make life difficult for the molecular geneticist: for example, polygenetic traits, one that PE almost certainly is, may require extraordinarily large samples to detect significant genetic effects if the effect of each contributing allele is very small. Gene-environment interactions (individuals responding differently to environmental stimuli depending on their genotype) may mask the effects of a gene if the environmental factor is not simultaneously modeled. Furthermore, it has been suggested that sequencing of rare genetic variants may be necessary to identify causal alleles for disease [18]. Nevertheless, this should not discourage any attempts to locate genetic polymorphisms that are associated with PE—and this is by no means impossible even using the tools that are available today—but it could be somewhat more challenging than we would first have expected.

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# Risks Factors in Premature Ejaculation: The Relational Risk Factor

# 11

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## 11.1 Introduction

Relational quality of life (QoL) is generally negatively impacted by premature ejaculation (PE) [1]. These negative effects are experienced by men who are single, men in committed relationships, and their partners. Depending on whether the effected person is the partner, a single man, or a man in a committed relationship, the manner in which PE affects them is different.

This chapter will examine the relational impact of PE from my personal perspective as a sexual health clinician, as well as from the evidence-based literature. PE research has primarily focused on the efficacy and safety of pharmaceutical interventions or the efficacy of psychologically based interventions [2, 3]. The psychosocial effects of the dysfunction have lagged behind efficacy/safety outcome research.

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## 11.2 The Impact on the Single Man

Imagine being a 27-year-old single male who has lifelong PE. You have been involved in three serious relationships, all of which have ended badly. Your first partner believed that in time sex would improve; unfortunately it only got

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worse. The relationship ended because she became involved with another man. Your second relationship was to a woman who was far more sexually experienced than you. She became increasingly angry that you wouldn't, or couldn't, do anything to improve the quality of lovemaking. In fact, you were getting increasingly anxious and avoided sexual contact with her. That relationship also ended badly. The third relationship was with a woman who "was the love of your life". You deeply cared for each other but sex was never satisfying for either of you. You thought she could accept your PE because you tried to please her in other ways and because she seemed to love you in spite of the sexual issues. Over time the inability to improve sexual life eroded the relationship and it too ended. Now, you are reluctant to date again because you wish to avoid a repetition of those previous failed relationships as well as the humiliation and embarrassment from the sexual symptom. You feel hopeless that you will be able to either fix the problem or find a partner who is accepting of your dysfunction. You have lost your sexual self-confidence, are worried that women are talking about your sexual dysfunction to their friends, and you find yourself distressed, anxious, and pre-occupied with sexual performance.

Unfortunately, this scenario is typical of single men with lifelong PE. Symonds et al. [4] conducted qualitative research with 28 men, ages 25–70, with self-reported PE. Subjects were asked what impact the PE had on their self-image, sex life, relationship with their partner, and everyday life. Avoidance of relationships or reluctance to establish new relationships was described by over half of the single men. Those men who were presently in a relationship characterized themselves as distressed at not satisfying their partner. Others were worrying that their partner would be unfaithful to them because of their PE. Additionally, the majority of men (68 %) reported a decrease in sexual self-confidence.

Embarrassment regarding discussing PE was the primary reason for not consulting a physician, cited by 67 % of respondents. Interestingly, almost half thought no treatment existed (47 %).

Preoccupation with thoughts about controlling their orgasm, anxious anticipation of a possible failure, thoughts about embarrassment, and keeping their erection are part of the subjective experience of men with PE according to Hartmann, Schedlowski, and Kruger [5]. In contrast, the authors found that men without sexual dysfunction tended to focus on sexual arousal and sexual satisfaction rather than negative thoughts.

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### **11.3 What is Sex Like for Men and Women in Committed Relationships?**

Imagine you are a 38-year-old married male and father of two children. For your entire sexual life you have struggled with ejaculating too quickly. You are married for 12 years to a woman that you met in graduate school. You both share similar

family and religious values and were especially close and affectionate at the beginning of the relationship.

Ejaculation consistently occurs in approximately 30 s after penetration except for the occasions where you have too much to drink. Initially you and your wife enjoyed lingering in foreplay but you thought it was too exciting and contributed to your rapid ejaculation. Also in the beginning of the relationship even if you ejaculated quickly you could almost immediately make a second attempt at intercourse with mildly extended ejaculation latency. Over the years you began to avoid foreplay so as not to get too excited and the repeated episodes of intercourse vanished. Intercourse became the “main event,” but even without foreplay you still ejaculated quickly.

Your wife has been very patient and does not often raise her concerns about the quality of your sexual life. Her sexual desire appears to have lessened; maybe because of the demands of children and her job and maybe because sex offers her very little satisfaction either in terms of intimacy or sexual pleasure.

You feel very badly about your PE. You try to control the timing of your ejaculation but can't seem to extend your latency. When you ejaculate you curse under your breath, apologize to your wife, and roll over to your side of the bed with your back toward her. She can't tell whether you are angry or embarrassed. She however, is angry at the abrupt cessation of physical intimacy. She would prefer to be held, stroked, or cuddled. She doesn't want to make you feel worse but she is getting increasingly frustrated and angry —more about the abrupt cessation of intimacy and your constant apologies. She used to experience orgasm easily but now is not even interested in one. Every once in a while she lets her anger out and demands that you do something, anything, to resolve the problem. She is getting older and tired of not having a good sexual relationship. She loves you but her frustration and anger result in an increasing emotional distance.

You don't know what to do. You have gone online and read about the anti-depressant medications and stop/start techniques but don't believe they will work for you. You have lost your sexual self-confidence, the marriage seems less than it was, you are preoccupied with sexual performance and very bothered by this not getting better.

This scenario is typical for a committed couple who struggle with PE. The emotional experience for the man and woman takes very different pathways. Initially the man is in denial that there is a problem. He may even blame the partner for being too sexy or exciting. Slowly he becomes aware that he cannot control the timing of his ejaculation and attempts to remedy the problem by limiting foreplay and or trying to please his partner by hand or mouth stimulation. Sex becomes something he tries to avoid so as not to be embarrassed, or humiliated. The man is afraid to discuss the problem with his partner fearing accusations of selfishness. He does not want to be the target of her anger, be demeaned, embarrassed or humiliated. He does not realize how he is limiting intimacy by not discussing the issue, limiting sexual contact, and not engaging in fore- or after-play.

Initially women are reluctant to raise the issue with the man for fear of hurting his feelings or adding to his sense of inadequacy. They hope that their sexual quality of life (SQoL) will improve and tend to collude with the man's silence. When they are brave or angry enough to raise the issue with their partner, he likely limits discussion and may even blame her. Over time the women feel increasingly angry and frustrated because she does not feel heard or believes that her partner is too selfish to fix the problem. The women are dissatisfied with the decreased emotional and sexual intimacy of the relationship, the repeated apologies with no attempt to fix the problem, and the routinized, mechanical and poor quality sex. Some women begin to feel contemptuous towards their partners. Ultimately they may find themselves increasingly irritable and unhappy in the relationship.

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## **11.4 Evidence-Based Data on Men with PE and the Impact on the Relationship**

In a review of 11 observational studies focused on men with PE and their partners, the authors found a consistent association between PE and adverse psychosocial and QoL consequences, including detrimental effects on the partner relationship [1]. In one study, men with PE and their partners were compared to men without PE and their partners [6]. The PE group of men and partners had lower levels of sexual functioning, sexual satisfaction, higher levels of personal distress, and greater interpersonal difficulty than men without PE and their partners. In addition, men with PE rate their overall QoL lower than that of men without PE. The authors concluded that PE places a significant psychological burden on men, their partners, and the relationship.

Contrasting men with and without PE, Shabsigh and Perelman report that 55 % of 'normal' (no erectile dysfunction (ED) or PE) subjects said that they were 'very' or 'extremely' satisfied with their QoL, while only 38 % of PE subjects felt the same [7]. A similar pattern is apparent when individuals were asked whether recent sexual activity was pleasurable. Seventy-eight percent of 'normal' subjects stated that recent sexual experiences were 'very' or 'extremely' pleasurable while only 54 % of PE subjects felt the same.

McCabe et al. in studying male and female sexual dysfunction reported that the "greatest deficits in QoL were experienced by men with PE" [8]. Employing validated scales to assess different aspects of intimacy (emotional, social, sexual, recreational, and intellectual) and satisfaction, she found that PE men score lower than non-PE men. Similarly, Porst et al. asked men to respond to two questions: (1) climaxing too soon causes me to lose confidence in my sexual abilities and (2) climaxing too soon makes me less confident even outside the bedroom [9]. Fifty percent of men with PE agreed 'completely' or 'somewhat' that climaxing too soon make them less confident outside the bedroom compared to 25 % of men without PE. Similarly, 22 % of men with PE vs. 10 % of non-PE men agreed completely or somewhat that they felt less confident outside the bedroom. These

studies highlight that the negative impact of PE extends beyond the bedroom into the lives of couples who struggle with this problem.

PE men consistently acknowledge substantially greater levels of distress than non-PE men. Extreme or quite a bit of distress was reported by PE vs. 4 % of men with PE compared to a non-PE group. Similarly, 44 % of the partners of men with PE vs. 3 % of partners of non-PE men report being distressed [10].

PE also affects the manner in which men think of themselves. Comparing PE and non-PE men on the validated Self Esteem and Relationship Scale for Men (SEAR) questionnaire demonstrated that PE men scored lower in self-esteem, self-confidence, and relationship satisfaction than non-PE men [6]. Bancroft notes that “our ability to feel safe and comfortable when relating to a sexual partner is lessened if we are feeling bad about ourselves [11].”

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## 11.5 Research on Partners of Men with PE

Research on partners of men with sexual dysfunction has focused on the female partners of men with ED [12]; the research on partners of men with PE has lagged behind. One study utilizing a chart review methodology found a high occurrence of sexual dysfunction in the female partners of men with PE [13]. Twenty-two percent of women presenting with sexual desire disorder, 29 % of women acknowledging arousal lubrication problems, 43 % of women with anorgasmia, and 48 % of women not enjoying sex had partners with PE. Treating PE by giving men clomipramine resulted not only in an extended ejaculatory latency time but also improved sexual satisfaction in both partners and coital orgasm attainment in the woman [14].

Hobbs et al. studied the partners of men with and without PE. They administered the Abbreviated Sexual Function Questionnaire (ASFAQ), PE Partners Sexual Inventory, Sexual Quality of Life Female Version (SQoL-F), and the Sexual Relationship Scale (SRS) to 138 women partners of men with PE and 89 women whose partners did not have PE [15]. Seventy eight percent of the PE partners had at least one sexual dysfunction compared to 42 % of the non-PE partners. Fifty five percent of the PE partners reported problems with arousal-sensation while 52 % reported problem with orgasm. PE partners scored significantly lower than the controls on all measures indicating that they had a poorer SQoL, sexual relationship with their partners, less sexual satisfaction and, experienced more problems with desire, arousal, and orgasm than the controls did. When asked if they had a sexual problem of their own, 30 % of the PE partners answered “yes” compared to 15 % of the non-PE partners.

While this data is interesting and suggestive of the negative impact of PE on the female partners’ sexual function, the results of the PE partner group it is not clear if the results are solely due to the man’s PE. Female sexual dysfunction is often multifactorial in etiology and more study is required before a clear cause-and-effect link is firmly established.

Reporting on a series of eight patients, Levine sets forth the hypothesis that in some cases the etiology of PE may result from hidden female sexual difficulties [16]. He describes cases where the women aggressively berate the men for their rapid ejaculation but initially hide their own problems with arousal or orgasm. The PE becomes the focus of therapy rather than focusing on the reciprocal sexual problems of both partners. The author believes that these women fail to provide the man with a patient nondestructive incentive to develop control and employ the defense of displacement to defend against recognition of their own sexual anxieties. Classical psychoanalytic writing also describes cases of PE where the basic pathogenesis is the man's lack of love for the partner or his intense moral conflict about the relationship [17].

While these psychodynamic speculations are intriguing and may accurately describe the dynamics in some couple's relationships, they likely do not characterize the majority of men or women partners who struggle with PE. More relational data needs to be collected, analyzed, and confirmed in independent samples.

Graziottin and Althof describe how female partners of men with ED differ from the female partners of men with PE [18]. Women whose partners have ED tend to primarily blame themselves whereas women partners of men with PE tend to blame the men. Specifically, the authors describe women partners of men with ED as thinking that there is something wrong with them, maybe they are not attractive enough, or sexy enough, or wondering if he is off having an affair with another woman. In contrast, the women whose partners had PE thought what is wrong with him—why can't he control himself, why does he let me down every time and why doesn't he care for me. Both ED and PE may cause problems for the women both in their sexual functioning, perceptions of "blame", and the quality of the relationship.

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## 11.6 Conclusion

The negative impact of PE extends beyond the bedroom to affect the man's sense of himself, his partner's sexual and emotional life, and their relationship. It is important for clinicians to be aware how PE affects men who are single, those in committed relationships, and their partners. Only then can an effective treatment plan be designed to address the unique concerns of the man and his partner. In addition to treating the sexual symptom, the clinician should consider helping the couple with constructive communication skills and suggestions to improve sexual and nonsexual intimacy.

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## 12.1 Introduction

Ejaculation, an important step of the male sexual response, is essential for coital reproduction. Although it is well established that all the aspects of male reproduction are hormonally regulated [1], endocrine control of the ejaculatory process and its intravaginal ejaculatory latency time (IELT) is still in its infancy. It has recently been proposed that gonadal, thyroid and pituitary hormones (oxytocin (OT) and prolactin) control, at various levels, the ejaculatory process and its overall latency time, however, only a few clinical studies are currently available ([2–10], see for review [11–14]).

Ejaculation is defined as the expulsion of seminal fluid from the meatus of the urethra and consists of three separate phases: emission, ejection, and orgasm. In this chapter the endocrine control of emission and ejaculation will be treated separately, as much as it is possible to do so.

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## 12.2 Endocrine Control of the Emission

In humans, the emission phase begins as an integrated and time-coordinated activation of both parasympathetic and sympathetic nerves; the former regulates the secretion of seminal fluid from the epithelial cells of the accessory sex glands, and the latter (T10–L2) induces a strong contractility of the proximal seminal ducts (epididymis and vas deferens) and a rapid and effective transport of spermatozoa towards more distal regions. Later on, the activity of adrenergic neurons, originating in the pelvic plexus, also induces contractions of seminal vesicles and the prostate, with expulsion of sperm and seminal fluid into the posterior urethra, which is concomitant to bladder neck closure. In response to the posterior urethra filling, the urethra-muscular reflex takes place, accompanied by the feeling of an ejaculatory “inevitability”. Ejection is mediated by somatic nerves (the perineal nerve, a division of the pudendal nerve) that originate in the conus medullaris (S2–S4 segments) of the sacral spinal cord and involves clonic contractions of the bulbocavernosus (BC), ischiocavernosus, and other pelvic floor muscles, together with relaxation of the external urinary sphincter. Activation of the pudendal nerve stimulates the forceful contractions of this muscle network, expelling the seminal fluid out through the urethra. The sperm ejection may or may not be associated with an experience of a shortly forthcoming orgasm.

An increase in epididymal contractile activity characterizes therefore the first step of the emission phase during ejaculation. It is mediated not only by neuronal but also by an array of non-neuronal locally derived factors and hormones.

### 12.2.1 Oxytocin

Oxytocin is a nonapeptide synthesized in the supraoptic (SON) and paraventricular nuclei (PVN) of the hypothalamus and contained in and released by the posterior pituitary. It was originally characterized as a hormone with noteworthy functions in female reproduction, facilitating uterine contraction during parturition and milk ejection during lactation (see for review [15]). OT neurons are equally present in the PVN and SON of the hypothalamus of both females and males without any sexual dimorphism [16]. However, a clear role for OT is recognized only in the female: it is considered, in fact, the most readily available agent that mediates milk ejection reflex and uterus contractility [17, 18].

Physiological effects of OT in the male have been a matter of intense debate for a long time. Debackere and colleagues in the 1960s [19] first postulated that OT could be released in the male circulatory system during sexual activity. In fact, using a cross-circulation technique, they found that manual stimulation, per rectum, of seminal vesicles prompted a milk-ejection response in the female partner. Further studies demonstrated that a surge of OT happens during male sexual activity, peaking during [20–23] or soon after orgasm and detumescence [24, 25]. Kruger et al. [26], in a study conducted in men for about 40 min around the time of

sexual stimulation and orgasm, found an increase in plasma OT levels immediately after orgasm, followed by a rapid decline to baseline levels within 10 min. The OT increase in men during orgasm has been reported to vary considerably (between 20 % and 360 %). This evidence in humans matches data from many other species [27–30]. A specific role for OT in regulating male genital tract motility was hypothesized, because pharmacological administration of OT increases the number of ejaculated spermatozoa in different animal species (see for refs [15, 31]), including humans [32], stimulating in-vivo [33, 34] and in-vitro [31–33, 35] epididymal motility. Maggi was the first to identify and characterize specific OTR in the pig male genital tract [36]; OTR was highly expressed in epididymis and tunica albuginea with a lower abundance in vas deferens [37] and seminal vesicles [36]. The presence of specific receptors for OT in epididymis was later confirmed in several other animal species including monkeys [38, 39], rabbits [32, 40], bulls [41], sheep [42] and humans [32, 39]. In the epididymis of several animal species, including humans, OTR is localized in both the epithelial and muscular layers [32, 38–42]. However, OTR seems to be predominantly concentrated in the muscular compartment of the epididymal cauda, where the smooth muscle cells are organized in three thick layers [32, 39]. Conversely, OT is abundant in the epithelial cells of the epididymal caput [32]. Interestingly, our group has demonstrated that the epithelial cells of the epididymis produce and secrete both OT and ET-1 [32, 43–45]. In particular, in rabbit epididymal epithelial cell cultures, we demonstrated that OTR mediated a sustained release of another potent contractile factor for the epididymal muscular wall: ET-1 [38]. ET-1 was originally characterized as an endothelium-derived constrictor factor, which is synthesized through the cleavage of a bigger precursor (big-ET) by a specific ET-1 converting peptidase (ECE-1) and acts through two distinct receptor subtypes: ETA and ETB. Both ET-1 and ECE-1 are localized in the basal epididymal epithelial cells, facing the smooth muscle layers, where ETA receptors are expressed and mediate contractility [38, 43, 45]. In human [43] and rabbit [45] epididymis, ETA receptors are present not only in the smooth muscle but also in the epithelial cells. Interestingly, rabbit and human epididymal epithelial cells are immuno-positive for OT, and release OT under ET-1 stimulation [45]. The presence of neurophysin 1, an OT synthesis-associated protein, and elevated concentration of OT mRNA indicated that human epididymis produces its own OT, along with ET-1 [45]. Mutual, feed-forward interactions between these contractile agents are assumed to support the autonomous peristaltic movements of the epididymis that favor sperm progression throughout the duct. Studdard et al. [46] studied the effects of various concentrations of OT on the frequency and extent of contractions of the caput epididymis and on the resting tone of the epididymis as measured by a change in the resting diameter of the epididymis in the rat. By using videomicrography, they observed that contractions in the caput epididymis are peristaltic in nature and always progress in one direction from the caput to the cauda. Movement of the luminal contents was bidirectional, but the net effect was always towards the distal end [46]. OT (10 and 100 µg) significantly increased both fluid output and the number of spermatozoa in the luminal fluid of the cauda epididymis within 10 min of

treatment, and the effect was dose dependent [47]. Treatment with an OT antagonist significantly reduced the fluid output and spermatozoal numbers whilst pretreatment with the same antagonist inhibited the stimulatory effects of OT indicating that OT acts on epididymal contractility through its own receptor [47]. This stimulatory effect suggests that OT affects epididymal contractility directly leading to a significant increase in the transport of spermatozoa into the vas deferens and the ejaculate.

We hypothesized that the clear-cut surge of OT plasma level which has been described during male sexual orgasm might have the double physiological significance of promoting semen emission during ejaculation and favoring penile detumescence [48].

Several studies in experimental animals indicate that the systemic release of OT at ejaculation might be accompanied by a central, extra-hypothalamic release of OT by PVN, which, in turn, has an effect on sexual behavior. OT neurons in fact project to several extra-hypothalamic areas within the central nervous system and the spinal cord [49]. In the rat, OT concentration increases in the cerebrospinal fluid 5 min after ejaculation by a factor of three, returning at the basal level after 20 min [50]. Infused into the cerebral ventricle of male rats free to copulate with a receptive female, OT facilitates ejaculatory behavior by shortening ejaculation latency and post-ejaculatory refractory period [51]. Administered via intracerebroventricular (i.c.v.) route, OT was also found to significantly increase latencies of mount and intromission [29]. A selective OTR antagonist delivered via i.c.v. route to sexually vigorous male rats was reported to inhibit sexual behavior, including ejaculation, and to reverse the pro-sexual effects of the nonselective dopamine-receptor agonist, apomorphine [52]. In an experimental rat model of PE, it has been found that in rapid ejaculators more OT-containing neurons were activated (as revealed by Fos immunoreactivity) in the SON [53]. Selective lesions of the parvocellular neurons in the PVN, which reduced the number of OT-immunoreactive fibers in the lumbosacral spinal cord and abolished the ejaculation-induced increase of OT levels in the cerebrospinal fluid, prolong mount and intromission latencies and reduce the post-ejaculatory interval [50].

The spinal nucleus of the bulbocavernosus (SNB) is a sexually dimorphic motor nucleus in the lower lumbar spinal cord that innervates the striated BC muscle. This muscle, and its associated levator ani, robustly participate in the ejaculatory reflex, are androgen-dependent and receive spinal oxytocinergic projection from PVN [54]. OT-immunoreactive fibers were reduced in the lower lumbar spinal cord (L5-L6) following N-methyl-D-aspartic acid lesions in the PVN. This reduction was associated with a significant decrease in seminal emission at the time of ejaculation, but mount, intromission and ejaculatory latencies were unaffected [55].

The effect of different doses of a peptide OT antagonist  $(\text{CH}_2)_5^1$ ,  $\text{Tyr}(\text{Me})^2$ ,  $\text{Orn}^8$ -oxytocin was recently studied in anesthetized male rats [56]. Seminal vesicle pressure (SVP) and bulbospongiosus muscle (BS) electromyograms were recorded as physiological markers of emission and expulsion phases of ejaculation respectively and intracavernosal pressure (ICP) was monitored as a physiological

marker of erection. The dopamine D<sub>3</sub> receptor-preferring agonist, 7-hydroxy-2-(di-*N*-propylamino) tetralin (7-OH-DPAT) was injected i.c.v. to induce ejaculation, which was successful in 63 % of the experiments. Intravenous injection of the OT antagonist did not impair 7-OH-DPAT-induced SVP and ICP responses while BS burst frequency was diminished ( $p < 0.05$ ). When delivered i.c.v., the OT antagonist dose-dependently inhibited occurrence of 7-OH-DPAT-induced sexual responses, including number of ejaculations, latency time, SVP and BS responses and latencies. When delivered intrathecally (i.t.) at the level of the sixth lumbar (L6) segment, but not the 13th thoracic (T13) segment, the OT antagonist reduced the duration of BS responses and the occurrence of ejaculation without impairing ICP responses [56]. The authors concluded that brain OT receptors mediate male sexual responses elicited by i.c.v. 7-OH-DPAT in anesthetized rats, whereas L6 spinal OT receptors only impair the occurrence of ejaculation. Peripheral OT receptors are marginally involved in 7-OH-DPAT-induced sexual responses [56].

From all the aforementioned studies it can be concluded that OT is actively involved in regulating orgasm and ejaculation via peripheral (see for review [48]), central or even spinal mechanisms (see for review [57]). However, in a double-blind, placebo-controlled study, a specific effect of intranasal OT on appetitive, consummatory and refractory sexual behavior was not found [58], even though an anecdotal report indicates that intranasal OT can facilitate orgasm in an otherwise anorgasmic male [59]. It is interesting to note that also in the Burri's study when subjects were asked about the subjective perception of whether OT or placebo had been applied in the experimental session, eight out of ten participants who received OT named the correct group due to increased sexual arousability [59]. The poor crossing of the peptide OT of the blood-brain barrier and its short half-life might justify the negative results of Burri et al. [59].

### 12.2.2 Estrogens

An important estrogenic modulation of epididymal function can be envisaged since estrogen level is high in the rete testis fluid [60]. Indeed a P450 aromatase (P450Ar) activity, which is involved in the irreversible transformation of androgens into estrogen, has been demonstrated to be diffusely localized both in the testis of several animal species [61] and the rabbit [40], monkey [62], rat [63], and human [64] epididymis. Epididymis not only synthesizes, but also responds to estrogens; in fact, both isoforms ( $\alpha$  and  $\beta$ ) of estrogen receptors (ER) have been characterized in the epididymis of several animal species [61], including in the rabbit [40]. However, conflicting data on the immunolocalization of ER $\alpha$  and ER $\beta$  in the epididymis are present in the literature, mainly because of the diversity of the immunohistochemical procedures (see for review [60]). Recently, an accurate study revealed that both ER $\alpha$  and ER $\beta$  are abundantly localized in the peritubular smooth muscle compartment of the epididymal cauda, while they are diffusely

distributed in the epithelial cells of the epididymal corpus in the mouse [65]. This regional localization of ERs, probably accounts for the two main functions hypothesized for estrogens in the epididymis: (1) regulation of luminal fluid re-absorption and sperm concentration, typical of the proximal regions, most probably mediated by ERs present in the epithelium of epididymal caput; (2) regulation of epididymal contractility, typical of distal regions, most probably mediated by the ERs localized in the thick muscular compartment of epididymal cauda.

The estrogenic regulation of fluid re-absorption and sperm concentration has been well-reviewed elsewhere [66]. For many years it has been known that estrogens increase epididymal motility and sperm transport through the epididymis in the mouse [67]. More recently, estradiol has been demonstrated to up-regulate the epididymal sensitivity to OT and ET-1 by using two distinct animal models of estrogen deprivation: (a) inducing a hypogonadotropic hypogonadism by the administration in the adult male rabbit of a long-acting gonadotrophin releasing hormone, GnRH, agonist and (b) inducing a blocking of aromatase activity, by treating the adult male rabbit with letrozole.

In the rabbit experimental model of hypogonadotropic hypogonadism the *in-vitro* epididymal contractile response to OT [40] as well as to ET-1 [45], was almost abolished. Interestingly, estradiol valerate, but not testosterone enanthate, supplementation fully restored the hypogonadism-induced epididymal hyporesponsiveness both to OT [40] and to ET-1 [45]. Interestingly, the reduced OT responsiveness of epididymis in hypogonadal rabbits was also restored by tamoxifen [40], a selective estrogen receptor modulator (SERM), which acts as an estrogen agonist in the epididymis [68].

Tamoxifen citrate was introduced three decades ago as an empiric treatment for idiopathic oligospermia [69] and it has been recently proposed by a World Health Organization working committee as the first line of treatment for idiopathic oligospermia [70]. Along with its supposed central effect in stimulating gonadotrophin release, tamoxifen also may act at peripheral levels, stimulating epididymal sensitivity to OT, thus promoting the contractile paracrine loop between OT and ET-1 [32, 40, 45]. This hypothesis supports the beneficial effect of tamoxifen in normogonadotropic idiopathic oligospermia [71].

In intact rabbits, blocking endogenous estrogen synthesis by letrozole, an inhibitor of P450Ar, substantially reduced ET-1- [45] and OT-induced [42] epididymal contractility up to hypogonadal levels, suggesting a physiological role for endogenous estrogens in epididymal contractility. In several animal tissues, including the uterus [72–75], cervix [76], hypothalamus [77], kidney [78], and also the epididymis [40], OTR gene and protein expression are positively regulated by estrogens, through a still unidentified mechanism [79]. In fact, although in the mouse the OTR gene promoter contains a classical estrogen responsive element (ERE), in other animal species, including humans, only a nonfunctional half-palindromic ERE sequence has been detected [80].

Recent data demonstrated that estrogens could positively regulate both ET-1- and OT-mediated contractility also by activating their common downstream effector: the calcium-sensitizing RhoA/Rho-kinase system [35]. In fact in ET-1

pre-contracted epididymal strips from hypogonadal rabbits, obtained with a single administration of a long-acting GnRH analog as previously described [35, 45], the relaxant effect of a specific Rho-kinase inhibitor Y27632 was completely abolished [35]. Estradiol valerate, but not testosterone enanthate, supplementation in hypogonadal animals was able to completely restore Y27632 sensitivity in epididymal strips, indicating that the RhoA/Rho-kinase calcium-sensitizing pathway is under positive estrogenic control. Accordingly, blocking aromatase activity, by treating intact rabbits with letrozole as previously described [40], we observed that the epididymal responsiveness to Y27632 was abolished. Moreover, we found that both Rho-kinase gene and protein expression are induced by estradiol in epididymis [35].

Overall, these studies support the hypothesis that epididymis is a male target for estrogens which regulate epididymal motility tuning up contractile hormones and local peptide responsiveness by increasing RhoA/Rho-kinase signalling and therefore calcium sensitivity.

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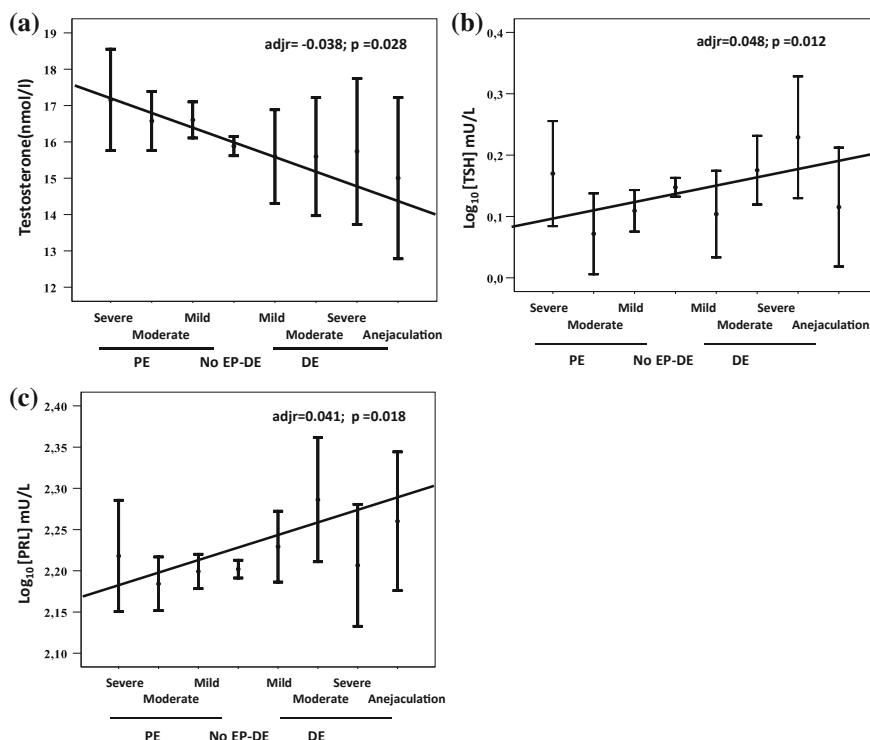
## 12.3 Endocrine Control of Ejaculation

### 12.3.1 Testosterone

Testosterone plays a crucial role in male sexual response acting both at the central and peripheral level (see for review [81]). In particular, T is a clear determinant of motivation to seek sexual contact and several studies in hypogonadal men demonstrated an unequivocal role for T substitution in restoring sexual desire, spontaneous sexual thoughts, and attractiveness to erotic stimuli [81]. In addition, androgens act also at the penile level regulating the formation and degradation of cyclic guanosine monophosphate (cGMP), the main determinant of penile erection. In fact, both nitric oxide (NO) synthase activity and type-5 phosphodiesterase (PDE5) expression and activity are T dependent ([82], see for review [81]). A T dependency of PDE5 expression and activity also has been demonstrated in other portions of the male genital tract (MGT) such as vas deferens, a critical effector for semen emission and ejaculation [83].

Low T levels and the presence of hypogonadal symptoms are associated with an overall lower propensity to ejaculate ([3, 4, 9]; see also Fig. 12.1). Testosterone might have both a central and peripheral action on the ejaculatory process. Androgens profoundly influence male sexual behavior, acting on several areas within the central and peripheral nervous system, most of them related to the ejaculatory reflex. Androgen receptors are expressed in the medial preoptic area, the bed nucleus of the stria terminalis, the median amygdala, and the posterior thalamus; all regions deeply involved in the supraspinal control of ejaculation (see for review [84]). Even at the spinal-cord level, crucial nuclei controlling ejaculation, such as the spinal nucleus of the bulbocavernosus (SNB), are androgen-dependent [85]. Circulating androgens, in adult rats, can profoundly alter the





**Fig. 12.1** Testosterone (a), TSH (b) and PRL (c) levels as a function of ejaculatory difficulties. In particular, 0 = severe premature ejaculation (PE), 1 = moderate PE, 2 = mild PE, 3 = no ejaculatory difficulties, 4 = mild delayed ejaculation (DE), 5 = moderate DE, 6 = severe DE and 7 = anejaculation. From 0 (severe PE) to 7 (anejaculation). Data are derived from a consecutive series of 3,202 unselected patients attending our unit seeking medical care for sexual dysfunction

expression of gastrin-releasing peptide in the lower spinal cord [86] that, by innervating the SNB, mediates the ejaculatory reflex [87]. Interestingly, bulbo-cavernosus muscles, like other muscles of the pelvic floor involved in the ejaculatory ejection of the seminal bolus (ischiocavernosus and levator ani muscle), is specifically androgen-dependent. In fact, hypertrophic action on the levator ani is a good predictor of effective anabolic androgens [88]. Testosterone can also positively affect the emission phase of the ejaculatory reflex. The integrated system NO-PDE5, one of the most important factors involved in the contractility of the male genital tract (MGT) is under T control. In an experimental model of hypogonadotropic hypogonadism, we found that in vas deferens of T-deficient rabbits cGMP degradation was reduced and PDE5 less expressed and biologically active [83]. T administration completely reverted these alterations [83]. Hence, it is possible that hypogonadism-associated DE is a result of an increased inhibitory nitric tone on smooth muscle cells of MGT. Testosterone can be aromatized by

cytochrome P450 aromatase to an active estrogen,  $17\beta$ -estradiol, and the aromatase enzyme is widely expressed in MGT, in particular in epididymis [48]. In epididymis, testosterone, but more efficiently its metabolite estradiol, can revert hypogonadism-induced down-regulation of the RhoA/ROCK pathway (a calcium-sensitizing pathway) and restore contractility [35]. Hence, in our view, low testosterone should be suspected and analyzed in all subjects with delayed ejaculation. To better increase the strength of this recommendation, interventional studies showing that treating hypogonadism ameliorates ejaculatory difficulties are currently being performed.

### 12.3.2 Thyroid Hormones

Associations between DE and PE and hypo- [10] and hyperthyroidism [2, 6, 10], respectively, have been extensively documented, even in animal models [7, 8]. L-Thyroxin-induced hyperthyroidism in rats leads to enhanced seminal vesicle contraction frequency and BS muscle contractile activity, suggesting that hyperthyroidism affects both the emission and expulsion phases of the ejaculation process. In that study, after a 28-day washout period (to determine spontaneous recovery from hyperthyroidism) all the previously described alterations were reversed [8]. Similar results have been obtained by several clinical studies (Fig. 12.1). In a consecutive series of 755 men presenting with SD, a two-fold greater prevalence of hyperthyroidism was evident among the men with PE [2]. Carani et al. [10] in a small multicenter, prospective study demonstrated that 50 % of hyperthyroid patients have PE, a prevalence that was substantially reduced (15 %) by treating the underlying disease, with a consequent doubling of ejaculatory latency. Cihan and coworkers [6] studied the prevalence and characteristics of premature ejaculation (PE) in a single-center prospective study in a small Turkish population of hyperthyroid subjects ( $n = 43$ ; 40 % with Graves-Basedow disease, the rest of the sample with toxic nodules). PE was defined according to *the Diagnostic and Statistical Manual of Mental Disorders, (4th Edn. Revision)* criteria along with patient-reported outcome and stopwatch measurement of intravaginal ejaculation latency time (IELT; PE: IELT of <1 min). PE was observed in 31 (72 %) hyperthyroid subjects. There was a positive correlation between thyroid-stimulating hormone (TSH) and IELT. After 2 months of high-dose medical therapy, subjects were enrolled in continuing medical therapy ( $n = 10$ ) or had definitive treatment with surgery ( $n = 7$ ) or radioactive iodine ( $n = 7$ ). Achieving euthyroidism at follow-up (24 patients), regardless of therapeutic intervention, increased mean IELT by a factor of two in the total population or by a factor of three in the PE population. Beck anxiety scores and international index of erectile function also significantly improved in the euthyroid state. The authors concluded that hyperthyroidism should be considered a novel and reversible etiological risk factor for PE. However, it should be recognized that Waldinger et al. [89] did not find any association between TSH levels and IELT in a cohort of

Dutch subjects with lifelong PE, without erectile dysfunction. Since thyroid diseases represent a risk factor for ED [10], it cannot be excluded that our population was abundant in thyroid diseases, explaining, at least partially, this difference. Overall, the majority of studies suggest a direct role for thyroid hormones in decreasing ejaculation latency that is independent from hyperthyroidism-induced anxiety. Furthermore, Carani et al. [10] showed that medical treatment of the opposite state, hypothyroidism, resulted in a two-fold decrease in ejaculatory latency and a reduction in delayed ejaculation. Hence, the view that thyroid hormones regulate not only the ankle reflex but also the ejaculatory reflex is consistently emerging. Accordingly, in a recent study [9], after excluding subjects with low TSH due to pituitary diseases, we found that TSH levels were positively related to reported ejaculatory latencies. Because TSH levels are tightly related, by a negative feedback, to thyroid function, it can be assumed that thyroid hormones negatively affect ejaculatory latency (Fig. 12.1). Since hyperthyroidism, even in its subclinical form, is associated with 41 % increase in all-cause mortality, especially in men [90], and hyperthyroidism-associated PE is a treatable condition, clinical screening with eventual laboratory confirmation for thyroid diseases in men with ejaculatory dysfunction is strongly advised.

### 12.3.3 Prolactin

Human prolactin (PRL) is a non-glycosylated protein, which contains a simple polypeptide chain of 198 aminoacids. Circulating forms of prolactin include, besides the usually predominant monomer, high-molecular forms, such as macroprolactin (>100 kDa), a biologically inactive complex of PRL and IgG [91, 92]. In women, the main biological function of PRL is to control breast development and lactation, while the role of PRL in men is unclear. Gene deletion of PRL, or of its receptor (PRLR), does not alter male reproductive fitness [93–95], although PRLRs are expressed in the male brain, testis, and accessory glands [93] and even in the penis [96]. Hence, up to now, the physiological effect of PRL on male reproductive fitness is unknown. Conversely, the association between PRL pathological elevation and derangements in both reproductive and sexual behavior is well defined [97–99]. A wealth of data demonstrate a marked inhibitory effect of hyperprolactinemia on sexual desire [97, 99–101], most probably acting on hypothalamic GnRH (and therefore on T production) and/or dopamine production and turnover. Several studies have shown that PRL increases following male orgasm ([26, 102, 103], see for review [104]), hypothesizing a negative feedback control of this PRL surge on sexual motivation, contributing, therefore, to the post-orgasmic refractory period. However, it is noteworthy that the post-orgasmic rise in PRL is relatively modest and similar in men and women, which are less prone to post-orgasmic refractoriness and satiety. In addition, PRL increases during other emotionally stressful or disturbing conditions (including venipuncture) or following stimulation of the nipple or areola [105]. The prevalence of mild

hyperprolactinemia (PRL > 420 mU/l or 20 ng/ml) in male subjects with sexual dysfunction is quite variable, ranging from more than 13 % [106] to less than 2 % [97]. In these subjects, severe hyperprolactinemia (SHPR, PRL > 735 mU/l or 35 ng/ml) is a relatively rare event (less than 1 %; [97, 99]). Milder forms of hyperprolactinemia do not play a significant role in the pathogenesis of male sexual dysfunction [97, 99], while severe hyperprolactinemia has a negative impact on sexual function, impairing sexual desire as well as erectile function, and testosterone production [97–101].

PRL secretion from the pituitary is influenced negatively by hypothalamic dopaminergic neurons and positively by central serotonergic pathways. A low PRL response to a serotonergic challenge, which could be considered a mirror of a blunted central serotonergic function [107, 108], is associated with carotid artery thickening, suggesting that individual differences in central serotonergic responsiveness are inversely related to preclinical vascular disease [109]. We previously demonstrated that even basal PRL determination could be used as a marker of blunted central serotonergic function [5]. In the brain, serotonin modulates neuronal activity and is actively involved in mediating many cognitive functions and behaviors, including eating and locomotion. Different abnormalities in serotonin function have been detected in patients with anxious symptoms and disorders [110], and the serotonin system is a primary target for drugs used in the treatment of these conditions [10]. The classical view that anxiety is secondary to excessive serotonin activity has been challenged by more sophisticated models, which place less emphasis on global levels, but consider different serotonergic neural circuitry and receptors, mediating different aspects of anxiety [111]. In particular, the discovery of genetic variation in a crucial regulatory molecule within the serotonin system, the serotonin transporter, and its influence on emotional traits [112] provided a new foundation for understanding the neurobiological and genetic basis of emotional regulation and anxiety disorders [113].

We originally reported that hypoprolactinemia (i.e., prolactin levels in the lowest quartile) is associated to men with sexual dysfunction with peculiar psychobiological features, including a higher prevalence of MetS and arteriogenic ED, as well as anxiety symptoms and PE. According to the *Waldinger's neurobiological hypothesis*, a disturbance in the central serotonin pathway (serotonin-2C receptor hyposensitivity and/or serotonin-1A receptor hypersensitivity; [114]) has been advocated—but never demonstrated in humans—as a possible cause of lifelong PE. In experimental animal models, the serotonergic system acts, at the hypothalamic level, as a suppressor of the ejaculatory reflex [114]. Accordingly, both selective serotonin reuptake inhibitors (SSRIs) and serotonin agonists determine the extension of ejaculatory latency [114]. Our data provide the first clinical finding apparently in keeping with the *Waldinger's hypothesis*. In our cohort of patients, the relatively low prolactin levels were in fact associated with a higher risk of PE, even after adjustment for confounders. However, no differences were observed when lifelong or acquired PE were considered. Hence, it could be speculated that even secondary causes of PE would act mainly influencing the brain serotonergic system [2–6]. On the other hand, this may be true also for

lifelong PE: it can, in fact, be speculated that the serotonergic central changes, mirrored by low prolactin levels both in lifelong and acquired PE, are a consequence, and not a cause, of the absence of ejaculatory control. In fact, many psychological disturbances (such as stress and frustration for chronic or acquired inability to enjoy sex) are capable of provoking a neuroendocrine imbalance. Furthermore, the effectiveness of serotonergic antidepressants has been demonstrated in both lifelong and acquired PE. The ejaculation-delaying effects of some long-acting or specifically designed short-acting SSRIs are currently used therapeutically to treat PE [11–14]. Our results cannot clarify the cause-effect relationship between serotonergic imbalance and PE, but they demonstrate that lower levels of PRL characterize patients with PE with respect to others with different sexual dysfunctions. We recently found that PRL levels are positively correlated to the reported ejaculatory latency (starting with severe PE *ante portas* and ending with anejaculation), after excluding from the analysis subjects with pathological hyperprolactinemia (PRL > 735 mU/l or 35 ng/ml) and adjusting for SSRI use ([9], see also Fig. 12.1). Interestingly, in this study, the MHQ-A score, which is an index of symptoms of free-floating anxiety, decreased across PRL quartiles. These data suggest that low PRL levels should be considered in the evaluation of subjects with sexual dysfunction, since it can give insights into ejaculatory behavior and might reflect central serotonergic tone.

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## 12.4 Conclusions

We recently confirmed experimentally [9] the view that PE and DE could be considered two ends of a single continuum, spanning from severe PE to extreme DE [114]. We, in fact, demonstrated that the endocrine milieu (testosterone, TSH, and PRL) influences the ejaculatory process, by affecting its overall latency. In a population of more than 2,000 subjects complaining of sexual dysfunction, when all hormonal parameters (testosterone, TSH, and PRL) were introduced in the same mathematical model, we found that, after adjusting for age,  $\Sigma$ MHQ (an index of general psychopathology) and use of SSRIs, they were independently associated with ejaculatory problems [9] which is tantamount to say that they significantly and independently contribute to reported IELT variation. Hence, although endocrine regulation of the ejaculatory reflex is still in its infancy, recent data indicate that it is growing rapidly, shedding light on frequently occurring and seldom-studied conditions such as ejaculatory disturbances. Endocrine therapies are widely available and very effective in treating the cognate underlying conditions. It is possible that endocrine therapy of ejaculatory disorders, whenever indicated, not only ameliorates sexual life but also the overall health of our patients, as could be the case for thyroid or testis disorders.

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## 13.1 Introduction

Premature ejaculation (PE) is accepted as the most common form of male sexual dysfunction and a major source of male sexual distress [1]. Based on various definitions, the prevalence of PE complaints can range from 20 to 40 % among sexually active men [1–3] and PE is a more common sexual problem than erectile dysfunction (ED) among males younger than 50 [3, 4]. In spite of these high prevalence rates, there is still a paucity of evidence-based research on PE. Although the International Society of Sexual Medicine (ISSM) recently introduced an evidence-based definition for lifelong PE [5], the published objective data was found to be insufficient to develop such a definition for acquired PE, which occurs at some point in a man's life due to an underlying organic or psychological cause [6, 7]. However, recent guidelines suggested that the criteria for lifelong PE may also be used to define acquired PE with a very low level of evidence (LOE 5d) [8] and its prevalence is found to be 3.9 % among sexually active men [3].

The etiology for acquired PE may be an identifiable, and possibly treatable organic cause. Recent evidence has elucidated certain medical conditions (e.g. hyperthyroidism) that may represent treatable etiologies of PE [9–11]. In addition to endocrinopathies, the literature has also revealed several urologic risk factors

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that may predispose a man to acquired PE; including (ED) [12–15], prostatic diseases and chronic pelvic pain syndrome (CPPS) [4, 16–22], varicocele [23, 24], monosymptomatic enuresis [25], and circumcision [26, 27]. Although much of the literature has been geared towards prevalence and treatment studies of these risk factors, most of them are not strongly supported by evidence-based data. This chapter aims to provide a review and systematic analysis of the literature regarding these urological risk factors of PE.

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## 13.2 ED and PE

Well-known epidemiological studies consistently demonstrated that almost half of the patients who report ED also experience PE [11, 13, 14]. However, it is not clear whether this coexistent ED is a cause (men with PE can reduce their level of excitation while trying to control their ejaculation) or result of PE (men with ED may rush to ejaculate before losing their erection) [15]. Moreover, negative personal consequences such as distress, bother, frustration and anxiety due to PE may result in ED. Regardless of being the cause or the result of PE, the beneficial effect of phosphodiesterase-5 (PDE5) inhibitors used for treating comorbid ED in acquired PE patients has been documented in several clinical studies [12, 28, 29]. Since the improved erectile function was correlated with an increase in intravaginal ejaculation latency time (IELT) among acquired PE patients in those studies, PE severity may be correlated to the severity of ED [28, 29]. Therefore recent guidelines recommend treatment of PE and co-morbid ED with PDE5 inhibitors [8].

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## 13.3 Prostatic Diseases and PE

Chronic prostatitis (CP) or chronic pelvic pain syndrome (CPPS) is a common urogenital condition that affects a man's quality of life, yet this condition is still poorly understood [30, 31]. This syndrome includes urogenital pain, ejaculatory pain, urinary dysfunction, and sexual dysfunction. In the literature, CP has been closely linked with PE [4, 16, 17]. While the co-existence of these conditions is common, a true causal relationship or mechanism has not been established. Prevalence and treatment studies are the cornerstone of this relationship and this data has given researchers insight into potential diagnostic and treatment options for men with PE.

Screponi et al. were one of the first groups to systematically determine the prevalence of CP in men with PE [16]. A cohort of 46 men with PE was compared against 30 healthy age-matched controls in their study. The incidence of CP in the patient group was significantly greater than the control group. In a similar study, Shamloul et al. sought to confirm these results with a larger cohort of 153 men with PE (94 with lifelong PE and 59 with acquired PE) and found that 63.3 % had prostatic inflammation on urine and expressed prostatic secretion (EPS) analysis [17]. Interestingly, prostatitis symptoms were present only in 12.4 % of the PE patients. They also showed that there

**Table 13.1** National Institutes of Health (NIH) prostatitis syndrome classifications [41]

Category	Characteristic clinical features	Bacteriuria	Inflammation
I. Acute Bacterial	Acute UTI	+	+
II. Chronic Bacterial	Recurrent UTI caused by the same organism	NR	+
III. CP/CPPS	Primarily pain complains: also voiding complaints and sexual dysfunction	–	NR
Type A: Inflammatory subtype (formerly: non-bacterial prostatitis)		–	+
Type B: Non inflammatory subtype (formerly: prostatodynia)		–	–
IV. Asymptomatic	Diagnosed during evaluation of other genitourinary complaints	–	+

*CP/CPPS* Chronic prostatitis/chronic pelvic pain syndrome, NR—not reported

was a significantly higher difference in prevalence of CP in men with acquired PE (91.5 %) compared to lifelong PE (45.7 %).

Liang et al. continued to evaluate this association with a study of 1768 Chinese men with CP and observed that overall sexual dysfunction was present in 49 % of this cohort whereas PE, in particular, was present in 26.2 % of these patients [4]. Duration of CP was shown to be a contributing factor in sexual dysfunctions (PE and ED), where stratification of duration of CP revealed that individuals with  $\geq 19$  months of CP-like symptoms have a greater prevalence of PE (44.2 %) than those with less than 19 months (24.4 %).

In a follow-up study, 7,372 Chinese men were evaluated via cross-sectional survey to determine the correlation between PE and CP and study results demonstrated that 15.3 % of randomly recruited Chinese men self-reported PE [32]. In addition, to those that reported PE, 64.1 % reported prostatitis-like symptoms determined by criteria developed by Nickel et al. [33]. Men with clinical symptoms of CP suffered from PE at a rate of 36.9 %, higher than the general population.

In comparison, a study by Gonen et al. evaluated 66 CP patients and found a PE rate of 77.3 %. In comparison, ED was only associated with PE in 15.2 % of these patients [18]. A similar study evaluated 43 patients with type-III prostatitis (see Table 13.1) and found a significant difference between PE prevalence in these patients (67.44 %) versus their control group (40 %) [19]. An Italian study also evaluated 399 patients with symptoms that were suggestive of CP to determine prevalence of sexual dysfunction within this cohort [20]. The authors demonstrated that 220 (55 %) of the patients had ejaculatory dysfunctions, with 110 (28 %) of these patients reporting PE. The authors also showed that PE was more frequently

associated in patients with high to medium levels of inflammation compared to patients with lower levels of inflammation. This analysis was consistent with Shamloul's study as noted previously [17]. In addition, these researchers stratified prevalence of PE by NIDDK/NIH classification of prostatitis (see Table 13.1). PE was evenly associated throughout category II (33 %), IIIa (29 %), and IIIb (21 %), respectively ( $p = 0.125$ ).

Several studies have also shown that antibiotic treatment of patients with CP may help to delay ejaculation. Treatment for CP is usually targeted towards gram-negative rods, but other common species may arise, such as *Enterococci*, *Ureaplasma urealyticum*, and *Pseudomonas* species [17, 34]. The initial account that showed improvement in ejaculatory function through treatment of CP was a study by Boneff [35]. Patients were treated with a topical hydrocortisone antibiotic mixture introduced into the posterior urethra via catheterization after prostate massage. The men who underwent this treatment ( $n = 42$ ) experienced a 52 % improvement in ejaculation status, defined by prolongation of copulation for up to 5 min. There was a greater benefit from this treatment in patients with co-existing CP (15/22, 68.2 %) than just PE alone (7/20, 35 %). In a follow-up to their previous prevalence study, El-Nashaar and Shamloul studied a cohort of 145 men who complained of PE for at least 6 months prior to the study [21]. EPS-positive prostatitis was found in 94 (64.8 %) of these men, all of whom were asymptomatic. Antibiotic treatment was given for 1 month and 62 (83.9 % of those treated) showed a significant increase in their IELT and no recurrence of PE or CP after 4 months. Zohdy et al. performed a similar study of 210 men with CP symptoms and concomitant PE [22]. The goal was to determine clinical parameters that may predict successful outcomes in treatment of CP. They found that 59.0 % of the men treated with antimicrobial therapy had a significantly greater increase in IELT, in comparison to an untreated cohort. In addition, there was a difference in outcome between men with acquired PE and lifelong PE, where men with acquired PE responded more effectively to the antibiotic treatment. They also found that men with higher levels of inflammation experienced greater benefits (70.0 %) to antibiotic treatment in their IELTs compared to individuals with lower levels (31.4 %).

In summary, the urologic literature has shown a higher prevalence of CP or CPPS among PE patients and vice versa. There is also an association between the qualities of the patient's CP, i.e., duration of symptoms and levels of inflammation, and the possibility of having PE. Lastly, the beneficial effect of treatment with antibiotics on the improvement of ejaculatory function has been strongly supported.

Together, this evidence strongly supports the idea that CP may be a common cause of acquired PE, thus it should be ruled out, especially in men with associated pelvic pain and/or urinary symptoms. EPS analysis, such as the Meares–Stamey test, is a cheap and easy tool that can delineate such an etiology of the patients with PE [36]. Culture of the EPS with speciation of the organism may be beneficial in cases refractory to empiric antibiotic use. Although the connection between prostatic inflammation and pathology of the ejaculatory reflex has been proposed to occur through modulation of the neurophysiologic pathway [37], further studies are required to elucidate the exact mechanism.

### 13.4 Varicocele and PE

Varicocele, the abnormal dilatation of veins in the pampiniform plexus due to retrograde venous flow, has been shown to impact sexual function. Varicoceles are a common urological condition, with the estimated incidence ranging from 15 % of the general population to 35 % of men with primary fertility issues depending on the screening method [23].

The impact of varicocele on ejaculation has recently been hypothesized as a possible etiology of acquired PE. In an Italian cross-sectional study, Lotti et al. evaluated 2,448 sexual dysfunction patients for the presence of varicocele [24]. Their comparison of groups, varicocele versus no varicocele, showed a significant difference in PE status (29.2 vs. 24.9 % in subjects with or without varicocele, respectively) when adjusted for factors such as age, anxiety levels, and prolactin levels. The researchers showed an association between severity of varicocele on Doppler ultrasound analysis and seminal levels of interleukin-8, a surrogate marker for non-bacterial prostatitis. These findings were extrapolated to hypothesize that PE may be a clinical symptom of an underlying inflammatory state caused by varicocele and/or prostatitis. The authors also note that venous congestion through a connection between the testicular and prostatic venous systems may predispose a varicocele patient to prostatitis.

In conclusion, the presence of varicocele has been shown to be associated with high levels of inflammation in the pelvic area. In the large study conducted by Lotti et al., biological support was given to show the association between the PE and varicocele, yet it is uncertain which of these states may predispose a man to the other pathology. More research should be conducted to understand the underlying mechanism that connects these two pathologies.

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### 13.5 Monosymptomatic Enuresis and PE

Gokce et al. recently hypothesized an underlying neurological mechanism between lifelong PE and monosymptomatic enuresis (ME). In a randomized prospective study, the researchers found that 37.2 % of a cohort of men with lifelong PE had a history of primary ME compared with 15.1 % of the control population ( $p < 0.005$ ) [25]. Although the authors proposed a mechanism of a deficiency in the central nervous system inhibition of both ejaculation and micturition, further studies are required to confirm this association and clarify the underlying mechanism.

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### 13.6 Circumcision and PE

Circumcision, removal of the penile foreskin, is a routine practice among Islamic and Jewish communities. Considering the loss of high amounts of specialized sensory mucosa during this surgery, some authors claimed that circumcision has a

negative impact on the overall sensory mechanism of the human penis [38]. Some international epidemiological studies demonstrated lower prevalence for PE in the Middle East, confirming this presumption [13]. However, clinical studies regarding the penile sensitivity, PE status, and sexual satisfaction are not conclusive [26, 27, 39]. Adult circumcision was found to be associated with worsened erectile function, decreased penile sensitivity, and improved satisfaction without causing any changes in sexual activity [26]. Senkul et al. also evaluated the sexual performance of 42 adults before and 12 weeks after circumcision by using brief male sexual function inventory (BMSFI) questionnaire and they could not demonstrate any difference in sexual function [39]. It is of note that these authors also observed significantly longer mean IELTs after circumcision and considered this as an advantage of this procedure.

On the other hand, Waldinger et al. measured the IELTs of 500 men in the Netherlands, United Kingdom, Spain, the United States, and Turkey. They observed that Turkish men, all but two being circumcised (122/124), had significantly lower median IELT (3.7 min) compared to the median IELT value of each of the other countries [7]. Interestingly, the authors also compared circumcised men with non-circumcised men in countries excluding Turkey and observed that IELT values were independent of circumcision status, which also has been confirmed with a later study [40]. Similarly, a recent study investigated the role of postcircumcision mucosal cuff length in PE by measuring it in men with and without PE [31]. These authors concluded that neither postcircumcision mucosal cuff length nor circumcision timing is a risk factor for PE. Considering the above mentioned, circumcision does not seem to be a risk factor for development of PE, however further studies focusing on the genetic background of the societies performing this surgery or the psychological burden of this procedure may be necessary.

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## 13.7 Conclusion

PE is a common problem among men of all ages. The clinical relevance of PE cannot be ignored and may signify underlying perturbations to a man's normal physiologic state. An underlying urologic inflammatory process may predispose individuals to sexual dysfunction, especially acquired PE. Evidence is available in the literature that shows that diagnosis and treatment of prostatitis with antibiotics may be useful in patients with PE and prostatitis-like symptoms. Other associations, such as varicocele, enuresis, and circumcision may predispose individuals to PE, but the clinical evidence is lacking.

It is important for all clinicians to recognize that urologic risk factors may predispose individuals to acquired PE. An organic etiology needs to be ruled out when evaluating any patient with complaints of PE.



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# Risks Factors in Premature Ejaculation: The Neurological Risk Factor and the Local Hypersensitivity

# 14

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and Tarek Anis

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## 14.1 Introduction

Premature ejaculation (PE, sometimes referred to as rapid or early ejaculation) is the most common male sexual complaint [1]. Historically, attempts to explain the etiology of PE have included a diverse range of organic and psychological factors. Organic causes of PE are often categorized into genetic, neurological, endocrinal and metabolic, urological, and drug-induced subsets [2]. The past two decades have seen advances in awareness of PE in neurological disorders, tools for the assessment of PE, and treatment options. Despite these advances, there remains a dearth of clear, evidence-based research as to its etiology. The condition may be a complication of many neurological risk factors that significantly impacts quality of life, and as such must be addressed and treated. In addition, prevention of PE begins with awareness of risk factors by patients and clinicians. This chapter provides an overview of the neurological risk factors and local penile hypersensitivity that appear to be involved in the pathogenesis of PE.

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## 14.2 Neuroanatomical and Physiological Considerations

A basic understanding of the neuroanatomy and neurophysiology of ejaculation is critical if one is to understand and manage the neurologic risk factors of PE.

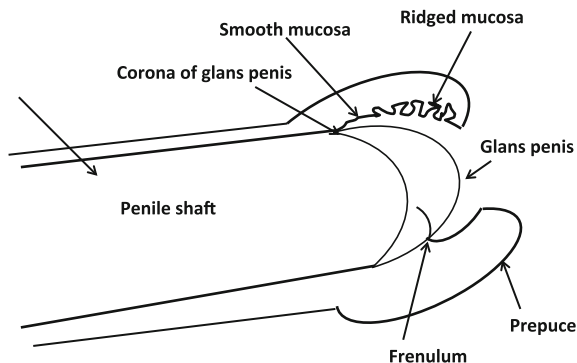
### 14.2.1 Local Sensations

#### 14.2.1.1 Anatomy and Histology

The penis is divided into a distal portion (Fig. 14.1), which includes the glans, the coronal sulcus and the foreskin (prepuce), and a proximal portion, named the penile shaft. Hidden in the pubic area is the root of the penis. The glans, coronal sulcus and inner surface of the foreskin are covered by stratified squamous epithelium and a dense layer of connective tissue equivalent to the dermis of typical skin. Rete ridges of the epidermis are irregular and vary in height depending on location, age, and presence or absence of a foreskin [3]. The mucosa of the inner prepuce is comprised of two distinct zones: the ridged mucosa, and the smooth mucosa. The ridged mucosa is a pleated band that occurs near the mucocutaneous junction. It contains 10–12 transverse ridges [4]. The smooth mucosa constitutes the remainder of the inner prepuce, from the ridged band to the coronal sulcus. On the ventral aspect of the glans, the point of attachment of the prepuce is advanced towards the meatus and forms the frenulum, a bridge-like structure that is continuous with the ridged band. The preputial frenulum restricts proximal movement of the ridged band and assists in returning the prepuce to its distal position over the glans.

#### 14.2.1.2 Receptors and Nerve Endings

Numerous specialized nerve endings have been identified in the penis and prepuce (Table 14.1). The most numerous nerve terminals are free nerve endings (FNEs) present in almost every dermal papilla, as well as scattered throughout the deeper dermis [3]. They penetrate the epidermis and end in the stratum granulosum. FNEs are characterized by an incomplete Schwann cell investment. A typical FNE was derived from a thin myelinated axon measuring 1–3  $\mu\text{m}$  in diameter or from unmyelinated C fibers. Other receptors such as Pacinian corpuscles, Ruffini's corpuscles, and so-called genital end bulbs are also observed [3, 5]. The ratio of FNEs to corpuscular receptors is approx. 10:1 and a similar ratio of small to large axons is seen in dermal nerves. The abundance of FNEs in isolated as well as corpuscular form can be correlated with embryogenesis and with the known neurophysiologic functions. In addition, it can be considered as an example of dissociated sensibility. The glans penis primarily has free nerve endings that can sense deep pressure and pain [3]. The ridged band of the prepuce has a high density of fine-touch neuroreceptors, such as Meissner's corpuscles [6, 7]. The most sensitive location on the circumcised penis is the circumcision scar on the ventral surface. The transitional region from the external to the internal prepuce is the most sensitive region of the uncircumcised penis and



**Fig. 14.1** Anatomy of the penis and prepuce

**Table 14.1** Nerve endings of the penis

Nerve endings	Proposed main function	Distribution
Free nerve endings	Pain and deep pressure receptors	Dense and present in whole penile skin, glans and prepuce
Paccinian corpuscles	Pressure receptors	Penile skin, glans and prepuce
Ruffini's corpuscles	Mechanoreceptors	Penile skin, glans and prepuce
End-bulbs of krause	Cold receptors	Penile skin, glans and prepuce
Meissner's corpuscles	Light touch receptors	Penile skin, glans and prepuce Ridged band of the prepuce has a high density

more sensitive than the most sensitive region of the circumcised penis [8]. There is some evidence indicating that circumcision adversely affects penile sensitivity and it ablates the most sensitive parts of the penis suggesting that circumcised men have difficulty reaching orgasm [8]. Although, other studies failed to confirm these findings [9, 10], Waskett and Morris found the claim that circumcision adversely affects penile sensitivity to be poorly supported due to poorly representative sampling and methods prone to exaggerating the sensitivity of the prepuce [11]. Moreover, Krieger et al. noted increased penile sensitivity and enhanced ease of reaching orgasm in circumcised Kenyan men [12].

### 14.2.1.3 Sensory Nerve Supply

The dorsal nerve of the penis (DNP) originates as one of the three branches of the pudendal nerve. The pudendal nerve primarily originates from S2–S4 spinal nerves. The nerve divides in the pudendal canal into three branches; the dorsal

nerve of the penis, the perineal nerve and the inferior rectal nerve [13]. It runs anteriorly into the deep perineal space, through the suspensory ligament of the penis and continues on the dorsal surface through Buck's fascia, where it passes lateral to the penile arteries and terminates in the glans penis [14]. The skin covering the root of the penis and the ventral aspect of the penis is supplied by the ilio-inguinal nerve, the perineal branch of the posterior cutaneous nerve of the thigh, and the posterior scrotal branches of the perineal nerve [15, 16]. The dorsal and lateral aspects of the prepuce are innervated by the DNP. The ventral prepuce and frenulum are innervated by the perineal nerve [17]. The main nerve supply of the scrotum arises from the scrotal branches of the perineal nerve, a branch of the pudendal nerve. A small contribution also arises from the inferior pudendal branch of the femoral cutaneous nerve. Finally, the anterior and lateral aspects of the scrotum receive contributions mainly from the genital branch of the genitofemoral nerve and the anterior cutaneous branches of the iliohypogastric and the ilioinguinal nerves [18, 19]. The brain and spinal cord also receive sensory information from mechanoreceptors located in the urethra, muscle spindles/golgi tendons of ischiocavernosus (ICM), bulbospongiosus (BCM) and external urethral sphincter (EUS) muscles, tunica albuginea (TA), and corpora [5]. This sensory input may be crucial in the central regulation of ejaculation [20].

### 14.2.2 Ejaculation Reflex

Ejaculation is a complex reflex consisting of two stages—seminal emission and propulsive ejaculation proper—and is mediated through the T10-S4 segments of the spinal cord [21]. The emission phase is characterized by the secretion of seminal fluids from the accessory sex glands, as well as closure of the bladder neck to ensure expulsion of semen from the urethral meatus as opposed to retrograde transport into the bladder. During the ejaculation proper, stereotypic rhythmic contractions of the smooth muscle of the urethra, as well as striated perineal muscles such as the ischiocavernosus and bulbocavernosus muscles (BMs), result in the forceful expulsion of semen [22]. Ejaculation reflex critically depends on a network of neurons referred to as the spinal generator for ejaculation, or SGE. The SGE is defined as a circuit capable of producing self-sustained rhythmic output to pudendal motoneurons. The SGE was found to contain a key population of neurons (lumbar spinothalamic neurons, or LSt cells) that (1) project to the brain, (2) project to the pudendal nerve, and (3) receive input from sexual organs via the pudendal and dorsal nerves of the penis [23, 24].

### 14.2.3 Supra-Spinal Control of Ejaculation Reflex

Like erection, ejaculation reflex is under tonic inhibition from the supraspinal centers. Usually, genital stimulation in combination with central arousal acts as an afferent that removes this inhibition, allowing the natural efferent components to

**Table 14.2** Possible neurologic risk factors of premature ejaculation

Category	Disease
Cerebral disease	Traumatic brain injury
	Cerebrovascular disease
	Parkinson's disease
	Epilepsy
Multiple sclerosis	
Spinal cord lesions	Injury
	Ischemia
	Tumors
Penile hypersensitivity	

unfold. Excitatory supraspinal afferents alone can induce ejaculation as evidenced by nocturnal emissions. Alternately, if supraspinal control is lost as the case of complete SCI, the tonic inhibition is removed, allowing the undamaged spinal ejaculatory center to function as its own independent system and can be triggered by the appropriate genital afferents, which results in ejaculation [24, 25]. The regulation of the ejaculatory reflex requires neurochemically coordinated interrelationships at different levels of the neuraxis. Several neurotransmitter systems have been implicated in this process. The central serotonergic and dopaminergic neurons play a primary role; other chemical factors including acetylcholine (Ach), adrenaline, neuropeptides, oxytocin, gamma-aminobutyric acid (GABA), and nitric oxide (NO) intervene secondarily. The reflex comprises sensory receptors and areas, afferent pathways, cerebral sensory areas, cerebral motor centers, spinal motor centers and efferent pathways [(25), for more details see [Chap. 3](#)].

### 14.3 Neurological Risk Factors

It is clear from the foregoing description that neurological disorders at various levels of the nervous system may influence the ejaculation. In the following sections cerebral disease will be discussed first, followed by diseases which affect the spinal cord, and concluding with descriptions of the role of penile hypersensitivity (Table 14.2).

#### 14.3.1 Cerebral Disease

Premature ejaculation is not uncommon in the general population. In patient populations with cerebral disease, few comparative studies have been done. The condition may be associated with cerebral diseases including traumatic brain injury (TBI), cerebrovascular disease (CVD), Parkinson's disease (PD), and epilepsy.

Surveys of sexual dysfunction after TBI have identified that between 17–36 % of males report a number of different post-injury ejaculatory problems, including PE [26, 27], with Meyer reporting a 9 % incidence of PE [28]. In contrast, de Morsier and Gronck [29] found that two of the 49 male patients (4 %) reported being premature ejaculators. In general, hyposexuality has a much higher incidence in this population than hypersexuality, although the latter can be seen occasionally [especially during the early stages after coming out of coma (the so-called posttraumatic amnesic state) and with bilateral temporal lobe lesions] [30]. Various authors attribute a particular sexual dysfunction to damage of different sites of the brain, or different sexual dysfunctions are connected to the same brain localization [31, 32]. It is also difficult to be precise about the exact location and severity of the injury at that particular site and its effect on sexual function. One cannot assume that, even when injury to a critical area is proven, the sexual dysfunction is definitely a result of that injury. There are always the neuroendocrine dysregulation, erectile dysfunction (ED), emotional, and relationship parameters to be considered, rendering the situation more difficult to evaluate [31, 33]. This differentiation is especially difficult since the issue of sexual function is usually raised at a later stage of the rehabilitation process. However, Simpson et al. [34] utilized a combination of medical, behavioral, and educative interventions to treat a case of PE. Successful treatment may indicate that PE may be due to psychogenic rather than organic causes.

Cerebrovascular accidents have generally been shown to alter sexuality in several ways, including decreased libido, ED, ejaculatory dysfunction, and decreased frequency of intercourse [35–37]. Ejaculatory dysfunction after stroke is common in men. Whereas most men were able to ejaculate before a stroke, only 29 % could do so afterwards in one study [38], and similar findings have been reported by others [39]. It seems that there is no good agreement regarding the incidence of sexual dysfunction as related to dominant vs. nondominant hemispheric involvement [35, 36], however Jung et al. noted that stroke lesions affecting the right cerebellum might be associated with ejaculation disorder [37]. Sexual dysfunction appearing after a stroke is a complex reaction with both organic and psychological factors. The main subjective reasons for diminished poststroke sexual activity are hemiparesis, spasticity, decreased libido, fear of a new stroke, ED, aphasia, associated comorbidities, drug-induced sexual dysfunction, as well as sensory deficits [36, 37]. It has been reported that sexual dysfunction correlated significantly with the presence of the sensory hemisyndrome [37, 40]. It is well known that tactile stimulations are extremely important in sexual arousal and orgasm during foreplay and intercourse. Therefore, it is obvious that the sensory hemisyndrome is related to problems with erection, ejaculation, and orgasm resulting in impaired libido and quality of sexual life [37]. Theoretically, elimination of all sensation from one half of the penis and scrotum may lead to delayed ejaculation in stroke patients showing pre-stroke PE and increased penile hypersensitivity. Whether cerebrovascular disease may emerge as a negative risk factor for PE in those patients with pre-stroke increased penile hypersensitivity remains to be determined. On the other hand, stroke patients may be



susceptible to PE secondary to ED because patients with multiple brain lesions showed a significant decrease of erectile function compared with the patients with one lesion [37].

Sexual dysfunction is common even in young males with Parkinsonism. In comparison with age-matched controls, in whom the prevalence of ED was 37.5 %, the corresponding number in patients with PD was 60 % in one study [41]. Many men cannot ejaculate or reach orgasm, but PE has also been reported [42, 43]. In one study, Bronner et al. [43] diagnosed PE in 13 out of 32 patients (40.6 %). In contrast difficulties in reaching ejaculation was diagnosed in nine out of 33 patients (27.3 %) [43]. In another study, evaluation of young PD patients (<55 years of age at disease onset) revealed PE in 8 % of patients [44]. The mechanisms behind PE in PD are not well understood. In general, symptoms of PD are due to a progressive loss of nigral neurons causing striatal dopaminergic denervation. However, nigral degeneration is only a part of the underlying synucleinopathy, and clinical symptoms go far beyond motor Parkinsonism [45]. However, autonomic dysfunction, depression, and testosterone deficiency, are frequently seen [45–47]. Although antiparkinsonian dopaminergic medications such as levodopa may decrease the ejaculation latency [48, 49], previous studies found no correlation between medication regimen and sexual activity [42, 50]. The large number of possible combinations of antiparkinsonian medications makes systematic study of medication effects on sexual function difficult. The variability in the expression of symptoms such as PE and difficulty in reaching ejaculation might be explained by the specific topographical sequence of the pathology, depending on the extent and progression of the degenerative process at defined sites. A longitudinal study of the ejaculatory function from the onset of PD would be of value.

The relation between epilepsy and sexual function is more complicated. It is estimated that 38–71 % of men with epilepsy experience diverse sexual problems [51–53]. These problems include various types of sexual dysfunction (such as ED, PE, orgasmic dysfunction, and diminished sexual desire), deviant sexual behaviors, hypersexuality, and, most commonly, hyposexuality. These problems may be associated particularly with temporal lobe epilepsy [54–56]. In addition, sexual fantasies, arousal, intercourse, and orgasm can provoke an epileptic attack through several pathophysiological mechanisms [55–57]. For example, hyperventilation, commonly accompanying sexual activity, can provoke generalized epileptic seizures [57, 58]. Moreover, somatosensory auras presented as sensations in the genital organs like numbness, tingling, pain, and unpleasant feeling may be manifestations of epileptic seizure arising from a genital sensory cortical area [59–61]. These sensations involve discrete parts of the body contralateral to the ictal discharge. In one study, men with epilepsy have an approximately five-fold increase in risk of sexual dysfunction including diminished sexual interest and poor sexual performance [52]. The prevalence of the complaint of PE varies between 2 to 66.7 % [62–64]. The prevalence in the general population in the National Health and Social Life Survey study was 28.5 % for men between 18 and 59 years [65]. Although Nikoobakht et al. failed to detect a correlation between PE and seizure type, frequency of epileptic seizures, control of the disease, and the medication used

[62], Daniele et al. noted that the incidence of PE was significantly higher in the group with right-temporal lobe epilepsy, as compared to left-temporal lobe epilepsy patients and to controls [66]. These findings can be analyzed in the same way as Suffren et al. explained why hypersexuality more often results from right-hemisphere than left-hemisphere lesions [67]. The authors noted that ictal orgasm more often occurs in patients with right-sided than left-sided seizure foci, with the symptom probably resulting from right-hemisphere activation. The left hemisphere may be specialized for increasing sexual tension, whereas the right hemisphere may be specialized for release of this tension (orgasm), the former being catabolic and the latter being anabolic. The mechanisms behind PE in epileptic patients are not well understood but are likely to be multifactorial, involving neurological, endocrine, iatrogenic, cognitive, psychiatric, and psychosocial factors [68]. For example, epileptiform discharges from the temporal lobe region may be transmitted through amygdala-hypothalamic pathways, disrupting the normal pulsatile secretion of gonadotropic hormones and the basal levels of dopamine secretion, resulting in hypogonadism and hyperprolactinemia [69]. Several antiepileptic medicines increase sex hormone-binding globulin (SHBG), including carbamazepine, phenytoin, valproate, and oxcarbazepine. The increase of SHBG could alter testosterone homeostasis [70].

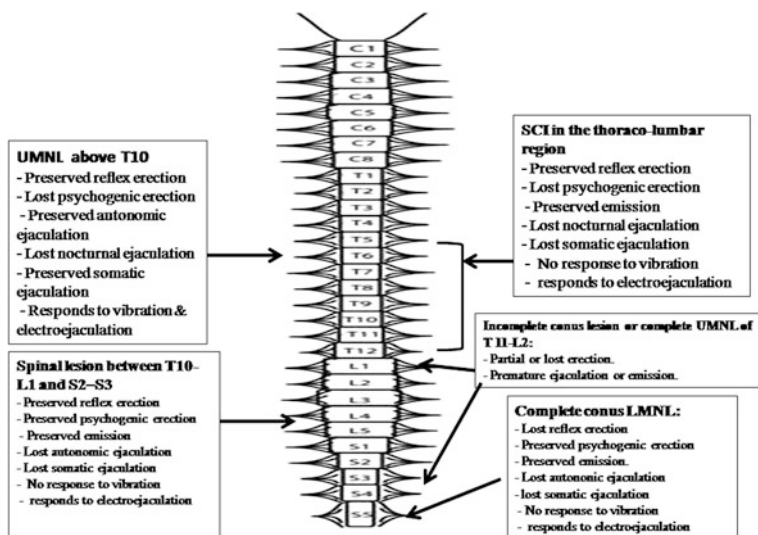
### 14.3.2 Multiple Sclerosis

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS) with a predilection for white matter tracts in the cerebral hemispheres, optic nerves, brainstem, cerebellum, and spinal cord. The disease generally affects sexually active young adults in populations of the western world. Sexual dysfunction is a common complaint in men with MS and it affects more than 75 % of patients [71–73]. Male sexual dysfunction includes difficulty in achieving and/or maintaining an erection (ED), decrease or loss in libido, painful or uncomfortable genital sensations (burning, tingling, and numbness), and orgasmic and/or ejaculatory disorders. ED appears to be the most common form of sexual dysfunction documented in MS [73, 74]. PE research and management in MS have been minimal. The topic is underrecognized and undertreated. This is a less frequent complaint than ED among male MS patients with sexual dysfunction. The incidence of PE in patients with MS has been estimated between 0–45.2 % [72–75]. In their study, Tepavcevic et al. reported a 45.2 % incidence of PE among MS patients [73]. The authors noted statistically significantly lowered scores on sexual function (SeF), and sexual function satisfaction (SFS) subscales of the health-related quality of life (HRQoL) in patients with PE. On the other hand, Barak et al. failed to detect any case of PE among nine patients with PE [75]. This may be attributed to the fact that some patients with MS could not answer the question because they did not remember or they did not know exactly if sexual dysfunction began before, simultaneously, or after the other symptoms of MS [74]. Another explanation is that genital somatosensory evoked potential abnormalities

are common in men with MS and sexual dysfunction. Decreased penile sensation has been reported in 53.8 % of cases in one study [72]. Theoretically this could explain the high incidence of delayed ejaculation and anejaculation rather than PE in patients with MS. Previous questionnaire surveys have quoted of 35–45 % of patients with MS reporting difficulty in achieving ejaculation [76, 77]. In one study [72], there were more complaints of difficulty with orgasm (53.8 %) and trouble of ejaculating (46.2 %) than of PE (7.6 %). In addition, it has been demonstrated that temperature and nociceptive (pain) signals from penile FNEs travel via small-diameter, thinly myelinated, or unmyelinated nerve fibers, whereas vibration, touch, and pressure utilize large-diameter, myelinated fibers [14]. These findings explain the low incidence of PE in MS because the nerves which are more heavily myelinated are more likely to be damaged by MS. The pudendal nerves enter the CNS at the most caudal aspect of the spinal cord. With the longest tract to the cortex, pudendal somatosensory tracts are the most likely to be damaged by MS. This has been borne out in the literature, with pudendal somatosensory evoked potential abnormalities frequently found in MS, even in early stages of the disease [78]. Sexual dysfunction may not only be due to lesions affecting the neural pathways involved in physiological function (primary dysfunction), but also results from general physical disabilities (secondary dysfunction) or psychological and emotional issues (tertiary dysfunction) [79]. The pathogenesis of PE in MS patients is not known. Explanations included: deficits in central serotonergic activity which are related to the rate of disability accumulation in relapsing-remitting MS and could be linked to the reported reduction of disease activity by serotonergic drugs [80], higher serum prolactin levels compared with healthy controls in MS [81], hypothalamo-pituitary gonadal dysfunction in some cases [82], and the increasing evidence that testosterone has a neuroprotective role and influences damage repair in the nervous system [83], secondary to ED, or psychological factors [84].

### 14.3.3 Lesions of the Spinal Cord

The annual incidence of spinal cord injury (SCI) in developed countries is estimated at 15–40 cases per million population [85]. Young adult sexually active men constitute roughly 82 % of these individuals [86]. The disruption to autonomic circuits and sensations following SCI can result in low sexual satisfaction and sexual dysfunction which are both well documented after SCI, and the resolution of these problems has been identified as a high priority [87–89]. These sexual problems include ED, decreased libido, orgasmic dysfunction and ejaculatory disorders [88, 89]. In general, the effect of SCI on sexual function is highly dependent on the site and extent of injury and the most commonly affected sexual responses are arousal and orgasm [90]. For example, individuals with upper motor neuron lesions (UMNL), and preserved S2–S5 roots, generally have preserved reflex genital arousal, as the reflexes mediating erection are located in the spinal cord. However, these individuals generally are unable to initiate genital arousal



**Fig. 14.2** Types of sexual dysfunctions after spinal cord lesions (Fig refers to spinal cord segment rather than vertebral level). In humans, the spinal cord ends at L2 vertebral level. The tip of the spinal cord is called the conus. Below the conus, there is a spray of spinal roots that is called the cauda equina. Injuries to T12 and L1 vertebrae damage the lumbar cord. Injuries to L2 frequently damage the conus. Injuries below L2 usually involve the cauda equina and represent injuries to spinal roots rather than the spinal cord proper. Upper motor neuron lesions = UMNL, lower motor neuron lesions = LMNL, complete = complete transection and no sensory or motor function is preserved below the neurological level, incomplete = incomplete damage and sensory or motor function may be preserved below the neurological level

psychogenically. On the other hand, lower-level SCI (infraconal or cauda equina) tends to disrupt reflex vasocongestion, but can leave sympathetically mediated psychogenic arousal intact [91, 92].

Although men with SCIs are less likely than controls to achieve orgasm, orgasm is seen in 40–50 % of the patients [93, 94]. In these patients, latency to orgasm is not significantly different between controls and SCI subjects [91]. Men with incomplete SCIs are more likely to achieve orgasm and ejaculation than those with complete SCIs (Fig. 14.2). In contrast, men with complete lower motor neuron lesions (LMNL) affecting their sacral segments are significantly less likely than men with any other levels and degrees of SCI to achieve orgasm [93]. Although orgasm and ejaculation are generally associated during sexual activity, this is not always the case and ejaculation can occur without orgasm and vice versa in SCI. Subjects with complete LMN injuries affecting their sacral segments would be the least likely to achieve orgasm [92]. In SCI, presumably descending inhibitory pathways controlling ejaculation (and erection) were damaged, leaving descending facilitatory pathways functionally intact and unopposed leading to PE [95]. In general, patients with hyperesthesia in the genital region and patients with incomplete lesions of the conus region of the spinal cord may suffer from PE.

**Table 14.3** Premature emission or ejaculation after spinal cord lesions

Reference	Case No	Age	Level of injury	Triggering and timing of PE or emission	Erectile function	Penile sensation	Other significant findings
Williams [96]	1	27	Severe sacral cord damage	On intromission, non-propulsive	Intact	Decreased genital sensation	Response to phenoxybenzamine
	2	24	Ischemic infarction of his spinal cord after traumatic rupture of aorta	Thoughts and spontaneously, on intromission	Intact, erection at the slightest thought	Markedly impaired sensation below the T10 dermatome	Incomplete paraplegia
Kuhr et al. [97]	1	37	L1, bursts, T10-L4	Thoughts and starting	Intact	Pressure in penis	Neurogenic bladder dysfunction
	2	24	L1, bursts	Thoughts	Lost	None	Neurogenic bladder dysfunction
	3	24	L1-2 open fracture	Before intromission	Lost	None	Neurogenic bladder dysfunction
	4	29	L1 laminectomy	Before intromission	Partial	Decreased light touch and pinprick	Neurogenic bladder dysfunction
	5	20	L1	Before intromission	Lost	Pressure only	Neurogenic bladder dysfunction
	6	41	T11-T12	Before intromission	Intact	Decreased light touch and pinprick	Neurogenic bladder dysfunction
Mossman et al. [98]	1	70	Ischaemic single lesion in anterior part of midthoracic segment	Spontaneous, touching of glans, onset of micturition with flaccid penis	Lost	Paresthesiae	Myocardial infarction, atrial fibrillation, carotid transient ischaemic attacks
Yasien and Attia [99]	1	23	T12, L1-2, fracture leading to compression	Spontaneous ejaculation without desire or erection	Lost	Hypersesthesia	Single, paraplegic

In this context, Kuhr et al. reported six cases of acquired premature emission after thoracolumbar spinal cord trauma suggesting that spinal lesions may be a cause of premature emission [96]. These patients were sexually healthy before sustaining traumatic SCI. They demonstrated neurogenic bladder dysfunction on urodynamic evaluation and five of them required intermittent catheterization. Bulbocavernosus and anal reflexes were absent in all patients while perineal sensory deficits varied. Therefore, the authors were in doubt that bulbocavernosus muscle contraction and true ejaculation occurred although there was emission. Premature emission developed after a vertebral fracture with sacral cord damage in one case and after iatrogenic ischemic injury to the thoracic spinal cord also in one case. One patient was successfully treated with phenoxybenzamine before intercourse but the other declined treatment. Earlier and recent reports (table 14.3) of this association have been anecdotal [95, 97, 98], and SCI is generally found to lead instead to impairment of ejaculation. Ejaculation may be easily provoked by touching the glans penis or if the patients have thoughts about sexual contact [95, 97]. It may be induced spontaneously at the onset of micturition, in association with symptoms of urinary urgency or the sensation of bladder fullness. Spontaneous ejaculation also occurred occasionally during midstream micturition [97]. This complaint may occur many times per week and sometimes per day without any sexual desire, sexual excitation, or any provocative factors with preserved orgasm at every time ejaculation occurs [98]. This association is in need of further studies to disclose the exact pathophysiology.

#### **14.3.4 Penile Hypersensitivity**

Among researchers, still there is a debate on the role of penile hypersensitivity as a risk factor in PE. The theory of penile hypersensitivity as a possible risk factor of PE comes from the following findings: (a) It has been demonstrated that the amplitudes of the genital somatosensory evoked potentials (SEPs) in the cortical area were significantly higher in men with PE than in 'normal' controls [99, 100], suggesting a greater cortical representation of the sensory stimuli from the penile shaft and glans and indicating that excessive excitation from the glans penis to the ejaculation center may have a role in PE, (b) The mean latency of both the dorsal nerve and the glans penis SEP was shorter in the PE group than in the control group, although both were within normal limits [100] suggesting a rapid transmission of peripheral sensation in patients with PE, (c) There was a statistically significant decrease in vibratory threshold (using penile biothesiometry) on the glans penis and penile shaft in patients with PE without age dependency indicating hypersensitivity of the glans penis and penile shaft [101], (d) One study has shown a significant correlation between self-estimated IELT and penile sensory threshold measured by biothesiometer at various locations on the flaccid penis without retraction of the foreskin [102], (e) Electrophysiological monitoring of the bulbocavernosus reflex by stimulating the penis and recording evoked potentials (the electrical potential produced as a result of the external stimulus) from the anal

sphincter revealed that men with PE showed shorter average latency in the bulbocavernosus muscle and in the anal sphincter compared with healthy males (15 vs. 45 ms) [103], (f) The use of topical desensitizing agents in patients with PE penile hypersensitivity is associated with successful improvement of IELT [104–106], and (g) Evaluation of penile biothesiometry and SEPs in men with PE showed that SS cream increased the penile sensory perception threshold, prolonged the latencies of SEPs and decreased the amplitudes of SEPs [107, 108], suggesting that SS cream has a local desensitizing effect on penile hypersensitivity and/or hyperexcitability in men with PE.

On the other hand, findings that refute the role of penile hypersensitivity as a risk factor in PE include the followings: (a) Perretti et al. [109] failed to demonstrate a faster conduction along the pudendal sensory pathway or a greater cortical representation of the sensory stimuli from the genital area in PE patients. Moreover, they did not confirm hyperexcitability of the bulbocavernosus reflex in these patients, (b) It has been shown that there was no significant statistical difference in the average vibratory thresholds in patients with PE vs. normal men at the glans penis, dorsum of the penile shaft, frenulum of the penis, the styloid process of the ulna, or medial malleolus of the tibia either in the flaccid or erect state [110], (c) Although ejaculation latency time is highest during intercourse, lower in the laboratory and lowest during masturbation, no correlation has been found between penile sensitivity at any of the penile surface areas and ejaculation latency time during these conditions, indicating that ejaculation latency time variability in normal men cannot be explained by differences in penile sensitivity [111], and (d) Salonia et al. [112] noted that primary lifelong PE patients might suffer from a peripheral hyposensitivity rather than hypersensitivity, both at the index finger and the penile shaft level, compared with healthy controls. The authors used quantitative sensory testing to assess the peripheral sensory thresholds for the modalities of vibration, warm, and cold in right-handed, healthy, fully potent European Caucasian patients. Therefore, these results objectively exclude the possibility that a penile hypersensitivity profile may be a contributing aspect of lifelong PE.

In essence, based on the previous investigations there are insufficient data to conclude that patients with PE have increased penile sensitivity and greater cortical representation of the sensory stimuli from the genital area. The role of somatosensory inputs in triggering the ejaculation and the weight of this role in relation to other visceral sensory inputs and central regulation should be fully investigated among patients with PE. However, Wyllie and Hellstrom detected that all of the studies examining the link between penile hypersensitivity and PE were completed before the new International Society of Sexual Medicine PE definition [113]. In this context, the evidence that penile hypersensitivity is the underlying cause for PE has been hindered in part by the methodology and definition of PE used in the analysis of data. In addition, two important questions must be addressed: (a) Is penile somatosensory input a major trigger of ejaculation? and (b) Is penile somatosensory input increased in PE patients?. Moreover, if the answer is yes, the subsequent question is: What are the molecules in sensory nerve endings

that could act as target for ejaculation delay? [2]. For example, it has been demonstrated that neurotrophin nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) may be more important for the sensory innervation of the penis [114].

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## 14.4 Conclusion

What is the relation among neurological lesions and PE? In virtually all studies, the strength of the associations could not be estimated and many of the studies are anecdotal reports.

Nevertheless, the possibility exists that neurological disorders are involved in the pathogenesis of PE either through direct enhancement of the normal neurophysiologic mechanisms or by producing endocrine, metabolic, or psychological changes that could induce PE. It may also be that the comorbidities (such as diabetes mellitus) that can induce neurologic disorders predispose in some way to the development of PE. These mechanisms might be operative at different times and levels during the development of PE. More research, both experimental and on humans, will be needed to sort out either the slowly emerging or the rapidly developing PE and complex picture of the pathogenesis of PE and different neurological disorders.

The varying patterns of PE, along with their types and severity, suggest that they might have differing pathogenesis. The notion was put forward earlier that PE might be a form of increased penile hypersensitivity or greater cortical representation of the sensory stimuli from the genital area. However, available research revealed that this association is still a matter of debate. Neurological disease remains an important risk factor in PE, and there is an urgent need to develop novel diagnostic and therapeutic strategies to reduce this risk.

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# Risk Factors in Premature Ejaculation: Experimental Psychology in the Evaluation of Premature Ejaculation

# 15

David L. Rowland

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## 15.1 The Approach of Experimental Psychology

Premature ejaculation has physiological, psychological, and socio-cultural elements. Over the past 20 years, substantial effort has been devoted to understanding men's psychological experience of premature ejaculation. Questions are, how it relates to their level of subjective sexual arousal, to their emotional and cognitive responses, and to their physiological response. Much of this research has been "psychophysiological" in nature, a term referring to any process that involves the interaction of psychological and physiological systems. From a traditional standpoint, however, the field of psychophysiology has referred to an approach investigating the relationship between particular psychological states or experiences (perceptive, affective, and cognitive) and concomitant or subsequent physiological responses. The range of physiological responses has been wide, including but not been limited to, electrodermal response, event-related potentials, EEG, EMG, EKG, and/or other direct or indirect measures of neurophysiological or neuromuscular response.

Psychophysiology shares much in common with other subdisciplines of psychology, including psychosomatic medicine, behavioral medicine, and health psychology. However, the "psychophysiological" approach is also defined in part by a laboratory methodology that supports the acquisition of knowledge within this setting and is characterized by the precise and (often) amplified measurement of subtle (often autonomic) physiological responses. These responses are measured during specific mental states (sensory-perceptive, affective, and/or cognitive) induced through the presentation of controlled stimuli.

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With respect to the study of human sexual response, the psychophysiological approach attempts to understand mind (subjective/psychological)/body (various physiological responses) interactions that occur during sexual arousal, studied in a controlled laboratory environment. This approach not only makes it possible to control the stimulus conditions, but enables assessment of both outcome (response) and predictor (often stimulus or contextual) variables with substantial precision and reliability. Thus, sexual response (including such measures as erection and ejaculation in men) can be investigated as a function of any number of covariates of presumed importance to this response. With respect to premature ejaculation (PE), such covariates may include the kinds of stimuli most likely to elicit the dysfunctional response (rapid ejaculation), the patient's self-reported levels of sexual arousal, the mitigating effects of anxiety and negative affect, various dyadic relationship factors, and so on [1, 2].

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## 15.2 Psychophysiology of Premature Ejaculation

Psychophysiological analysis of sexual response affords a valuable tool for testing hypotheses regarding the cause or etiology of premature ejaculation. For example, a number of cognitive-behavioral explanations have been offered to account for rapid ejaculation. These explanations have generally focused on centrally-mediated processes such as "hyperarousability" during sexual response, a lack of awareness by the man with PE of his high level of physical arousal, a lack of ejaculatory control, and elevated levels of anxiety. More specifically, such explanations have suggested that men with PE may ejaculate rapidly because they reach high levels of sexual arousal very quickly, or because they lack control over their rapidly rising levels of sexual arousal [3, 4]. Furthermore, because of these rapidly rising and high levels of arousal, PE men may be less attuned to graded levels of arousal and therefore less accurate in their ability to anticipate the moment of ejaculation. Finally, repeated sexual failure is likely to generate negative affect or anxiety [5, 6], which may in turn affect the man's response in subsequent sexual situations.

Physiologically-based explanations of PE, which typically emphasize the spinal and/or central sensorimotor pathways involved in the ejaculatory process, may also be explored using variations of psychophysiological methodology. Such studies have, for example, examined the latency and strength of event-related potentials (ERPs) measured along afferent or efferent pathways of the spinal reflex, or within specific areas of the somatosensory cortex. Several studies support the idea that differences exist between PE and sexually functional men at this level. For example, men with PE show greater, stronger cortical ERPs to stimulation of the pudendal afferent nerves and shorter latencies in the efferent processes involved in bulbocavernosal contractions eliciting seminal expulsion [7, 8].

### 15.3 Stimulus Relevance

Early psychophysiological research on men with PE was unable to differentiate their sexual response from that of sexually functional counterparts. For example, contrary to the expectation of “hyperarousal” in PE men (defined by shorter latencies to maximum arousal and higher levels of overall arousal), several researchers [9, 10] reported no differences between men with PE and controls on erectile response to visual sexual stimuli (VSS). Men with PE did not exhibit stronger or more rapid erections, nor were they more likely to ejaculate during VSS. More recent research, however, indicates that in order to simulate the conditions most likely to evoke the dysfunctional response of rapid ejaculation in men with PE, the inclusion of direct penile stimulation (e.g., vibrotactile) is critical [11].

The potential relevance of penile stimulation to rapid ejaculation in men with PE is not surprising in view of the fact that such men sometimes refer to penile “hypersensitivity” as an explanation for their condition. Research, however, does not consistently support penile “hypersensitivity” in men with PE, at least at the level of surface tactile receptors [12, 13]. In fact, men with coexisting PE and erectile dysfunction (ED) exhibit *lower*, not higher, penile sensitivity than sexually functional men, thus demonstrating that PE can occur under conditions of reduced penile sensitivity.

Even if differences in sensitivity do exist between men with PE and controls (as indicated in several studies), the functional significance of this “sensitivity” is unclear. When men are given the opportunity to select the intensity of penile vibrotactile stimulation (VIB)—based on the criterion of “most pleasant”—for later application during psychosexual stimulation, PE men do not choose intensities that are lower than functional counterparts or men with ED. Nor do they report that the intensity they do select is any “less pleasant” than other men [14].

Such findings suggest that genital receptor sensitivity may play either no or only a minor role in rapid ejaculation, and furthermore, that rapid ejaculation can occur in men with low penile sensitivity. Yet, such findings do not necessarily negate the overall relevance of penile stimulation to dysfunctional response, as penile stimulation is typically critical for manifestation of the dysfunctional response. For example, when VIB is applied to the penis in conjunction with VSS, PE men’s responses begin to diverge from those of functional counterparts in several ways. First, regarding *maximum* penile response, penile stimulation has greater impact on men with PE than controls. Specifically, comparing across different types of stimulus conditions (VSS vs. VSS + VIB), functional controls respond with about equal erectile response, whether or not penile stimulation is included. In contrast, PE men’s erectile responses increase by 15–20% when penile stimulation is included. Second, comparing across PE and functional groups, under VSS alone, PE men show lower maximum erectile response than controls, but equivalent erectile response under the stronger stimulus conditions of both VSS + VIB.



In other words, compared with controls, PE men do not show stronger maximum penile response to VSS + VIB, but rather weaker penile response to just VSS.

Actual ejaculation, as well as self-assessed measures of proximity to ejaculation, also differs across PE and control groups. In the presence of VSS only, ejaculatory rates across men with PE and controls are low and about the same. However, with the inclusion of penile stimulation, about 50–60% of men with PE ejaculate in the laboratory compared with only about 5% of controls. In addition, those men with PE who do not ejaculate during the session consistently report greater *proximity* to the ejaculatory threshold than functional counterparts. Furthermore, when subjects are asked about the *control* they felt over their ejaculatory response, the level is much lower for men with PE than for controls. Whereas functional subjects indicate no change in control between VSS alone versus VSS + VIB, PE men report a significant decrease in control during the combined visual and penile stimulation.

Interestingly, when men with PE are compared with men having both PE and ED, the latter group reports *greater* loss of control over ejaculation when VIB is introduced. This finding questions the assumption that men with coexisting PE and ED ejaculate rapidly simply because they fear losing their erection [3, 15]. Rather, it suggests that either the pathophysiological factors affecting erectile response (e.g., compromised neurovascular integrity) or psychological factors resulting from erectile dysfunction (e.g., increased anxiety/affective response) may also be affecting ejaculatory function.

Overall, these findings indicate that maximal erotic pleasure is derived from about the same penile stimulation intensity for PE and non-PE men. They also verify the long-standing supposition regarding the relevance of penile stimulation to overall sexual arousal and dysfunctional sexual response in men with PE. Such findings are consistent with reports that sensory stimulation of the penis has greater electrophysiological cortical representation, and thus perhaps subjective significance, in men with than controls [8].

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## 15.4 Self-Reported Sexual Arousal

Conceptualization of PE has often included the idea that such men become aroused very quickly—perhaps too quickly—resulting in “hyperarousal” during sexual stimulation. Kaplan [3] and others have suggested that this rapid ascent to peak arousal may lead men with PE to underestimate their level of arousal, thereby leading to ejaculation prior to expectation. Furthermore, a positive correlation between ejaculatory latency and frequency of sexual activity (more sexual activity being associated with longer latencies [10, 16]) has further implicated level of sexual arousal as a factor in PE. This correlation has been interpreted in two ways. First, sexual arousal tends to habituate to repeated stimulation [17, 18]. Specifically, habituation of arousal and/or ejaculatory inhibition due to refractory periods is *less* likely to occur in PE men because of their lower frequency of activity [19]. The second interpretation is that because of the combined effects of a short ejaculatory latency and lower sexual activity, men with PE may have had fewer

opportunities to learn adequate control over their arousal and therefore the ejaculatory process [3]. To date, however, no clear etiological course has been supported empirically.

The issue of arousal in premature ejaculation is actually threefold: first, whether men with PE report higher levels of arousal to psychosexual stimulation than controls; second, whether these men are less aware of their level of sexual arousal than others; and third, whether, men with PE reach peak arousal more rapidly than functional counterparts. Psychophysiological research has addressed all three questions.

#### **15.4.1 Levels of Sexual Arousal in Men with PE**

Overall levels of self-reported sexual arousal to VSS appear to be no greater in men with PE than controls [9, 10]. More recent analysis of self-reported arousal to sexual stimuli that include VIB confirm this pattern—men with PE report neither higher levels of arousal nor greater ease of becoming aroused to psychosexual stimulation than controls [2].

#### **15.4.2 Awareness of Level of Arousal in Men with PE**

Regarding their awareness of their level of arousal, again there is no clear distinction between men with PE and controls. Strassberg et al. [20], for example, have demonstrated that self-assessments of sexual arousal were not less accurate for men with PE than controls. Furthermore, Rowland et al. [2] reported no differences in the correlation between erectile response and self-reported arousal, or between erectile response and estimated erectile response, for PE men versus controls. Such findings tend to negate the idea that men with PE are less attuned to their level of sexual excitation, at least insofar as the erectile phase of the sexual response cycle. Interestingly, when men with PE are treated with an anti-ejaculatory agent such as clomipramine, they exhibit erectile responses to VSS comparable to those under placebo. But their self-reported sexual arousal is substantially attenuated compared with placebo and, of course, their ejaculatory response is delayed [2, 21]. Thus, while clomipramine and other ejaculatory retarding agents such as the SSRIs may delay ejaculation through monoaminergic effects, such effects may be mediated or enhanced by the attenuating effects of these agents on sexual arousal.

#### **15.4.3 Latency to Erection or Penile Tumescence in Men with PE**

Regarding whether men with PE not only have short latencies to ejaculation, but also short latencies to erection, data are mixed. A subgroup of men with PE exhibits a rapid rise to peak arousal, which then terminates quickly with ejaculation.

However, the majority of men show rates of tumescence that are comparable to or, in some instances, actually lower than those of functional counterparts [22, 23]. Recently, for example, we showed that average erectile response during VSS was consistently lower in men with PE compared with controls (see section below on genital and heart rate response, [23]).

In conclusion, although psychophysiological research has not identified consistent differences in maximum self-reported arousal, awareness of arousal, and rate of rise in penile tumescence between men with PE and others, one curious finding has emerged. Given their closer (self-reported) proximity to ejaculation than controls under VSS + VIB, the fact that men with PE do *not* consistently report *higher* levels of arousal [22] is surprising. This pattern lends support to the idea that PE men may indeed underestimate their levels of sexual arousal, or at least that there is a disconnection between ejaculation and peak arousal, events that in sexually functional men are well synchronized. In clinical circles, this point is often acknowledged by the need to help men with PE recognize the premonitory sensations of impending ejaculation [24], that is, while they may be attuned to their arousal levels, they may not be fully attuned to physiological cues signaling ejaculation.

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## 15.5 Anxiety and Affective Response of Men with PE

Relevant to the understanding of PE is whether affective states play a critical role in the etiology and/or maintenance of this condition. The affective component of sexual response—particularly anxiety—has long been theorized to play an underlying role in causing or sustaining sexual dysfunctions in men [3, 4, 25, 26]. Although most often associated with a general inhibition of erectile response, a more generalized anxiety could actually have the effect of increasing arousal [27–29]. Thus, relationships among anxiety, general emotional arousal, specific sexual arousal, and ejaculatory threshold are plausible. Nevertheless, specific affective states related to dysfunctional sexual response either could be part of the original etiology of the dysfunction or could represent a reaction to failed genital response that then exacerbates the problem [30].

Psychophysiological studies have provided some insight into the role of affect in dysfunctional response in men. Compared with sexually functional counterparts, men with ED exhibit higher negative and lower positive affect in response to erotic stimulation [29, 31, 32]. And men with PE show similar patterns of positive and negative affect as men with ED [33].

Recently, we [34] attempted to identify ways in which men with PE differ from functional counterparts on specific positive and negative emotional dimensions during VSS + VIB, as well as to identify changes in emotional responding as the result of pharmacotherapy. Consistent with previous findings, men with PE reported higher levels of negative emotions such as embarrassment/guilt, distress/worry, and anger/annoyed both prior to and during VSS + VIB than controls. Although some

negative affects diminished in PE men who responded well to the ejaculatory-retarding effects of clomipramine, levels of both guilt/embarrassed and anger/annoyed were still elevated in comparison with controls.

Positive affect was also different between men with PE and controls. Perhaps most important, the positive affect “pleasant/enjoyable” increased during erotic stimulation in men with PE who responded well to clomipramine treatment (i.e., “responders”), whereas it decreased in men with PE who responded minimally or not at all (i.e., “non-responders”) [34, 35]. Compared with placebo, clomipramine also had the effect of attenuating another positive emotion, “arousal/sensual” in both PE and control groups.

How might such changes in positive emotional response be interpreted? Attenuated “arousal/sensual” during erotic stimulation under clomipramine in men with PE may help explain why “pleasant/enjoyable” increased in PE responders during treatment. Attenuated sexual arousal due to clomipramine might have been one of several factors that counteracted the dysfunctional response of rapid ejaculation, thus allowing these men to enjoy the delay in ejaculation and to experience a greater sense of self-efficacy over their problem. However, this explanation remains incomplete—men with PE who did not respond to clomipramine in terms of ejaculatory latency also showed a decrease in arousal/sensual during pharmacotherapy, indicating that the ejaculatory-inhibiting effects of clomipramine involve more than merely decreasing sexual arousal.

In summary, the fact that successful pharmacotherapeutic treatment of rapid ejaculation imparts beneficial effects with respect to the overall enjoyment of sex suggests that the initial lower positive affect in men with PE emanates from their dysfunctional response. That is, for most men with PE, diminished positive affect is probably not a cause of the PE, but rather fallout from it. Because “pleasant/enjoyable” increased spontaneously with successful treatment—perhaps due to a greater sense of efficacy and control over ejaculation—such emotions appear to be tied directly to the man’s level of functionality. The greater the level of sexual functioning, the greater the positive affect.

In contrast, the finding that several negative emotions continued at elevated levels in men with PE—even among those benefiting from the pharmacotherapy—suggests that elevated negative affect could contribute to the maintenance (and possibly the etiology) of dysfunctional response. Further study is needed to determine whether specific negative emotions associated with sexual dysfunction might generally be resistant to the beneficial effects of ejaculatory-retarding drugs. It may be, for example, that particular negative emotional states are more dispositional (trait) than response-related (state or situational) in men with PE, an idea that has received limited support from various psychometric analyses of men with this disorder [36, 37]. Alternatively, had alleviation of the dysfunctional response been sustained through clomipramine treatment over a longer period of time, enabling men to gain greater confidence in their functionality, specific negative affects may have eventually decreased to levels comparable to controls.

## 15.6 Penile and Heart Rate Response During Arousal in PE and Control Men

Given that men with PE have short ejaculatory latencies, we might also expect them to show stronger and more rapid erectile tumescence (i.e., shorter latencies to maximum penile tumescence). Yet, psychophysiological studies have found no overall differences between PE and control groups on various erectile parameters, including overall latency to maximum erection [9, 26]. In fact, even though men with PE ejaculate rapidly, some data suggest (counter intuitively) that they might exhibit *weaker* erectile responses than controls. For example, men with PE report higher negative affect—a condition generally considered anti-erectile though not anti-ejaculatory—before and during erotic stimulation than controls [32, 34]. And they report greater difficulty getting an erection and weaker overall erections than controls, despite greater self-reported proximity to ejaculation [2]. Thus, even though men with PE ejaculate rapidly following intromission and/or once coital or manual stimulation has begun with a full erection, they might have greater difficulty and take longer to achieve an erection sufficient for intromission than functional counterparts.

To determine whether the physiological response of men with PE differs from that of sexually-functional counterparts, we [22, 23] undertook a minute-by-minute analysis of penile response and heart rate in groups of PE and functional men during combined VSS + VIB. Interestingly, four of 25 men with PE (16%) did not show any erectile response (<5 mm circumference increase), compared with one of 13 (8%) controls. Whether this difference resulted from, as hypothesized, greater inhibition of erectile response in the men with PE or from a selection bias in our groups (volunteer control subjects represent a self-selecting group) is not known. However, even those men with PE who responded with some level of erectile response tended to show lower *average* (though not peak) penile response than controls.

Patterns of heart rate distinguish men with PE from controls even more strongly than erectile response [23]. In our study and similar to other studies [38, 39], controls exhibited a pattern of decreasing heart rate initially during sexual arousal and penile tumescence to VSS + VIB, followed by a gradual leveling and slight increase in heart rate by the end of the session. *In contrast*, men with PE exhibited higher heart rates than controls throughout most of the session, with a consistent acceleration that was strongly portent of their rapid ejaculatory response. Indeed, for these men, an initial deceleration in heart rate characteristic of functional men—a typical response as subjects attend and orient towards a novel stimulus [40] - was essentially absent. Furthermore, individual patterns of heart rate in both PE and control groups were highly idiosyncratic across different testing sessions [41].

Such patterns suggest that the physiological responses of men with PE and controls may serve as distinguishing characteristics. Together with the affective and perceptual anomalies associated with erectile response in men with PE mentioned earlier, these findings suggest a possible disruption of the typical

autonomic processes involved in erection and ejaculation. For example, in men with PE, sympathetic activation associated with ejaculation may occur earlier within the sexual response cycle—an effect that may result from any number of factors including anxiety or negative affect. Early sympathetic activation may account for the accelerating heart rate in these men and may be reflected in weaker, parasympathetically-mediated erectile response. At the same time, this sympathetic activation may trigger ejaculation prematurely, perhaps even before the man reaches maximum levels of cerebrally-mediated sexual excitement. The finding that men with PE show less suppression of sympathetically-mediated skin potentials (i.e., an index of ongoing sympathetic activation) during papaverine-induced erections [42] lends further support to the idea that parasympathetic-sympathetic interaction may be altered in men with PE.

Even if “early” sympathetic activation accounts for low ejaculatory thresholds in men with PE, these data do not yet clarify why sympathetic control might dominate earlier during psychosexual stimulation in PE men than controls. For example, might higher negative affect or some other psychobiological process shift control from the parasympathetic (erectile) phase to the sympathetic (ejaculatory) phase prematurely? Or might erectile response in men with PE be under greater sympathetic influence than in functional counterparts [43], an idea consistent with recent data suggesting that psychogenic genital vasocongestion in women depends strongly on sympathetic innervation [44]?

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## 15.7 Summary and Conclusion

With the development of new pharmaceuticals for the treatment of PE, many in the health professions may mistakenly assume that PE is both understood and curable. Quite to the contrary, most current and impending solutions to PE are symptomatically based—that is, they treat the symptom of rapid ejaculation, yet offer no long lasting solution to the problem. In this respect, sexual psychophysiological analysis of PE has been an important and useful tool in identifying domains that might be further explored in developing treatments that address the actual cause(s) of PE.

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# Patient Reported Outcomes Used in the Assessment of Premature Ejaculation

# 16

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## 16.1 Introduction

Sexuality questionnaires play an integral role in the diagnosis and treatment of male and female sexual dysfunctions. They are used to (1) identify/diagnose individuals with a particular dysfunction, (2) assess the severity of the dysfunction, (3) measure improvement or satisfaction with treatment, (4) examine the impact of the dysfunction on the individual's quality of life (e.g., relationship satisfaction, mood, sexual confidence), and (5) study the impact of the dysfunction on the partner and his or her quality of life.

The development of new sexuality questionnaires and diaries, known as patient-reported outcomes (PROs), has been stimulated by the burgeoning sexual health pharmaceutical programs and guidance from regulatory agencies, such as the US food and drug administration (FDA). The latter requires objective and PRO methods to document improvements in sexual function. For instance, the three phosphodiesterase type five inhibitors (PDE5i) (sildenafil, tadalafil, and vardenafil)

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were approved, in part, because each compound demonstrated significant improvement on the international index of erectile function (IIEF) [1], a 15-item validated PRO.

PROs for premature ejaculation (PE) have lagged behind the development of questionnaires for erectile dysfunction (ED). More recently, with the advent of pharmaceutical trials for PE [2], there has been renewed interest in creating and validating PROs that identify/diagnose the condition and measure improvement with treatment.

This article reviews the PE-related PROs that have appeared in the published literature. Each questionnaire's psychometric properties and its benefits and limitations are examined and discussed. The authors hope this helps clinicians and researchers to identify brief, reliable, and valid measures that document treatment effects or identify men with PE.

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## 16.2 Definitions of Premature Ejaculation and Problems with the Current Definitions

A universally accepted definition of PE remains to be established. To date, there are at least eight definitions of PE offered by different professional organizations or researchers (see Chap. 5). All but one were derived from the consensus opinion of experts or from clinical wisdom; only the definition by Waldinger et al. [3] is the byproduct of scientific data collection from a large observational study from the general population. All but two definitions (Waldinger et al. [3] and Masters and Johnson [4]) suffer from excessive vagueness, lack of precision and undue subjectivity on the part of the diagnostician.

The most utilized definition had been based on the definition in the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition, Revision (DSM-IV-TR) [5]. It defined PE as:

- Persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it.
- The disturbance causes marked distress or interpersonal difficulty.
- The PE is not attributable exclusively to the direct effects of a substance.

The dilemma for the clinician is to objectively define “minimal sexual stimulation” or “shortly after penetration” or “before the person wishes” or “marked distress or interpersonal difficulty”? One clinician's interpretation of the DSM-IV-TR criteria is likely to differ from another clinician's interpretation. Failure to have an agreed-on definition of what constitutes PE has also hampered research efforts.

The validity of a PRO depends on the definition of the condition. PROs for PE need to discriminate between a group with the condition (PE) or those without the condition (non-PE) or to accurately assess treatment effects within a group of men with PE. Obviously, definitions without clearly defined objective criteria make development of PE PROs difficult.

Despite the convincing criticisms leveled at the definitions of PE (excessive vagueness, imprecision, and subjectivity), there is significant overlap among them. Four common factors emerge from the proposed definitions: intravaginal ejaculatory latency time (IELT), perceived control, distress, and interpersonal difficulty (related to the ejaculatory dysfunction).

Given these common factors, the issue becomes whether a diagnosis of PE should be unidimensional [6–8], based primarily on a defined IELT threshold, or multidimensional, using a defined IELT threshold and the variables of perceived lack of control, poor sexual satisfaction, and distress [9, 10]. Recent publications of observational data in men with and without PE have clarified the answer to this controversy [11–13].

An observational study of men diagnosed by clinicians as having or not having PE by Patrick et al. [11] suggests that IELT alone is not sufficient to categorize the two groups accurately. There was significant overlap between the IELTs of men with and without PE. Further analysis of the data studied [13] the interrelation between IELT, perceived control over ejaculation, decreased satisfaction with sexual intercourse, personal distress, and interpersonal difficulty related to ejaculation. These investigators found that control over ejaculation was central to understanding how PE is associated with satisfaction with sexual intercourse and ejaculation-related distress. Furthermore, the association of IELT with satisfaction with intercourse and distress related to ejaculation was mediated by perceived control over ejaculation. The results were robust; how IELT was scaled did not have an impact on the model; neither did restricting the sample to men with an IELT of 2 min or less.

In 2008, because of the concerns of clinicians and researchers alike as to the limitations of the current definitions of PE, the International Society for Sexual Medicine convened a group of PE experts to develop an evidence-based definition of PE. This group proposed a definition for lifelong PE that they felt was applicable to acquired PE as well. The definition was:

A male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, and the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy [14].

Given the evidence indicating the importance of assessing control, sexual satisfaction, and distress in relation to a man's PE, there needs to be a method to measure these subjective elements accurately. One way of doing this is by using a validated questionnaire (PRO) measure. Questionnaires have the advantage of allowing for a systematic/standardized approach to diagnosis.

Provided the measure is brief and accurate, it should facilitate the diagnosis of PE. Furthermore, in clinical research, such an approach of screening on control/sexual satisfaction/distress would allow a more comprehensive assessment of the impact of any novel treatment on PE.

In summary, the data suggest that the diagnosis of PE should be multidimensional and include IELT, the man's perceived control, sexual satisfaction, and distress. There remains some controversy as to the IELT threshold necessary to diagnose PE; further data analysis is likely to resolve this debate.

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### **16.3 Psychometric Properties of Patient-Reported Outcomes**

PRO development consists of multiple stepwise statistical procedures to ensure that the measure meets or exceeds established psychometric principles. These psychometric requirements are listed and defined in Table 16.1. It is essential that PROs demonstrate reliability, validity (known groups, convergent and divergent), and sensitivity to detect changes in a specified population. Moreover, if the PRO contains scales or domains, the items within these scales and the relation between the scales and total score must also meet established psychometric standards. Developing a PRO in this manner ensures that the clinician or investigator has a reliable tool for diagnosis or detection of change.

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### **16.4 Regulatory Requirements for Newly Developed Patient-Reported Outcomes**

New measures being developed for use in a clinical trial program, which may lead to US labeling claims, need to satisfy the requirements of the FDA guidance for industry, PRO measures: use in medical product development to support labeling claims [15]. This document clearly sets forth the psychometric tests and properties that need to be demonstrated for a new PRO to be considered validated. The FDA guidance also emphasizes that the content of the tool be developed by interviewing patients and that the language used in the PRO reflect the experience of patients. Additionally, the guidance suggests that an end point model be developed (research and model of Patrick et al. [13] are a good starting point for any new PE measure) to support why particular end points under investigation have been chosen. Any changes to a measure, inclusive of medium of administration, recall period, or change in population would require revalidation.

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### **16.5 Assessment Techniques**

Methods used to assess treatment outcome for PE include (1) patient self-report, (2) clinician judgment, (3) structured interview, (4) omnibus measures of sexual function, (5) focused self-report inventories designed specifically to evaluate outcome of treatments for PE, (6) patient diaries, and (7) timing of ejaculatory latency by stopwatch.

**Table 16.1** Validation and reliability tests for development of a questionnaire

Questionnaire structure	Definition	Acceptability level
Principal components factor analysis	Principal components factor analysis can be conducted to determine the item-scale structure of a questionnaire	All items included in a scale should load on a single unrotated factor $>0.40$ to support unidimensionality No item redundancy (inter-item correlations $<0.80$ ) Variance explained by the second factor $>20\%$ after varimax rotation to be considered a second dimension of the questionnaire No items should load $>0.40$ on more than one factor
Test-retest reliability	The stability of a measuring instrument, which is assessed by administering the instrument to respondents on two different occasions and examining the correlation between test and retest scores	Intraclass correlation coefficient $\geq 0.70$ is considered satisfactory
Internal consistency reliability	To evaluate the extent to which individual items of the instrument are consistent with each other and reflect an underlying scheme or construct	Cronbach's $\alpha$ coefficient $\geq 0.70$ is considered acceptable
Known groups validity	Known groups validity: ability of a measure to distinguish between groups known to differ, such as between different disease severity groups	Statistically significant differences are expected between these groups
Convergent and divergent validity	Convergent validity: dimensions measuring similar or overlapping concepts are expected to be substantially correlated ( $r \geq 0.40$ ) Divergent validity: dimensions measuring dissimilar concepts are expected to correlate less strongly or not at all	Once the hypothesized domains have been determined, similar and dissimilar measures should be incorporated into the validation study to test for convergent and divergent validity

(continued)

Table 16.1 (continued)

Responsiveness	Definition/test	Criteria for acceptability
Ability to detect change	To be useful for clinical trials, a measure must reflect changes in scores when change has occurred in health condition under study	Statistically significant change in scores
Interpretation of magnitude of change	Definition/test	Criteria for acceptability
Anchor-based method	A clinical anchor or patient-reported anchor can be used to establish whether or not a patient has improved. Those improving at least “slightly” inform the MID in score at end of treatment expected to be shown to indicate a meaningful change [28]	This varies from measure to measure
Distribution-based method	Effect size [28]	$\geq 0.5$
Questionnaire as diagnostic	Definition	Acceptability level
Sensitivity and specificity	Sensitivity is defined as the proportion of subjects with the disease that are diagnosed as having the disease (true-positive rate), and specificity is defined as the proportion of subjects without a disease that are diagnosed as not having the disease (true-negative rate)	Point at which the sensitivity/specificity ratio is closest to unity (this maximizes sensitivity and specificity)
Positive and negative predictive value	Positive predictive value is the precision rate of patients being diagnosed with a condition and they do actually have the condition. Negative predictive value is the precision rate of patients not being diagnosed with condition when they do not have the condition	Predictive values greater than 70 % are considered acceptable

### 16.5.1 Self-Report

Investigators have been notoriously skeptical of the value of patient self-report when conducting outcome studies. A recent study by Rosen et al. [16] reported that self-estimated and stopwatch-measured IELT were interchangeable. The authors correctly assigned PE status with 80 % specificity and 80 % sensitivity. Previously, Althof [17] correlated 13 patients' self-report of IELT during a telephone interview, a face-to-face clinical interview, and stopwatch-assessed IELT. Correlation coefficients between telephone interview and actual time and structured interview and actual time were 0.619 and 0.627, respectively. These data would suggest that self-report of IELT might suffice in a clinical situation. Clinical research demands a higher standard of objectivity requiring IELT measurements, however. Given the data, for treating clinicians patient reported IELT appears adequate.

### 16.5.2 Clinician Judgment

There are no reported studies on clinician concordance in diagnosing PE. Clinician subjectivity in interpreting the current diagnostic criterion sets would likely hamper agreement. Subjectivity in interpretation would also interfere with reliability in gauging improvement with treatment or impact on the psychosocial parameters. Patient self-report and clinician judgment, however, remain unobtrusive means of obtaining data and are the least burdensome for patients.

### 16.5.3 Inventories of Sexual Function

The Derogatis sexual function inventory (DSFI) [18] and the Golombok Russ inventory of sexual satisfaction (GRISS) [19] are omnibus sexual inventories, neither of which is specifically designed to assess any one particular sexual dysfunction. The DSFI is composed of 254 items comprising 10 subscales. This instrument offers investigators a reliable and valid means of measuring psychologic distress; however, it has few questions devoted to ejaculatory latency or voluntary control.

Similarly, the GRISS is a 28-item questionnaire designed to assess the existence and severity of sexual problems. It consists of 12 subscales, one of which is rapid ejaculation. The measure has good reliability and satisfactory validity but is more helpful with diagnosis than outcome.

### 16.5.4 Structured Interviews

Designed by Metz et al., the premature ejaculation severity index (PESI) (Metz M, Pryor J, Nessvacil R, personal communication, 1997) is a 10-item interview scale that offers a severity of distress score. It may be most helpful to clinicians

interested in pre- and posttherapy changes. It has limited utility as a research instrument, however, because the validity and reliability of this measure have never been established.

### **16.5.5 Timing of Ejaculatory Latency by Stopwatch**

Use of a stopwatch to time ejaculatory latency from vaginal penetration until ejaculation is a simple, objective, and reproducible outcome measure. The intrusiveness of stopwatch assessment may seem more severe to those unfamiliar with this approach than to subjects who participate in IELT studies. Surprisingly, most couples do not object to being asked to time their lovemaking. In fact, some men report that they enjoy competing with themselves to see if they can improve their ejaculatory latency. What remains unknown is what influence, if any, that asking couples to time lovemaking has on the outcome. Specifically, does timing, increase, decrease, or have no effect on ejaculatory latency? Is it possible that timing oneself serves as an occult treatment intervention?

It is, however, unlikely that physicians would be able to routinely require patients to time intercourse episodes before making a diagnosis of PE. It is too burdensome on the physician and patient. As mentioned previously, patient self-reported ejaculatory latency should suffice for diagnosis and treatment in a non-research setting.

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## **16.6 Patient-Reported Outcomes for Premature Ejaculation**

Table 16.2 lists the PROs available to identify/diagnose men with PE and PROs for detecting change when treating men with PE. Each measure's psychometric properties are described as well. Table 16.2 was compiled by reviewing the literature; only those measures in which the reliability and validity are documented have been included.

### **16.6.1 Patient-Reported Outcomes to Identify/Diagnose Men with Premature Ejaculation**

There are two measures available to diagnose PE. The first, the Chinese index of premature ejaculation (CIPE) [20], has five items that assess perceived time to ejaculation from intromission, ability to prolong intercourse time, sexual satisfaction, partner satisfaction, and anxiety/depression related to sexual activity. This measure does not seem to have had any psychometric analyses conducted before determining the scoring system to diagnosis absence or presence of PE (only known groups validity). Although further validation seems to be necessary, the CIPE may be used to identify men with PE but is not recommended as an outcome measure.



Table 16.2 Psychometric properties of premature ejaculation measures

Instrument	Population	Factor analysis	Reliability		Validity		Diagnostic tests			
			Internal consistency	Test-retest	Convergent-divergent	Known groups	Responsiveness	MID	Sensitivity/specificity	Positive and negative predictive value
CIPE	$n = 169$ IELT: mean = 1.6 (SD = 1.2) minutes 61 % lifelong 39 % acquired	x	x	x	x	✓	✓	✓	✓	
PEP	$n = 1,587$ ; $n = 166$ DSM-IV clinician diagnosis; DSM-IV clinician diagnosis plus IELT, 2 min >50 % intercourse episodes	n/a	n/a	✓	x	✓	x	x	x	
IPE	Study 1: 147 lifelong PE; DSM-IV clinician diagnosis Mean IELT = 1.92 (SD = 2.98) minutes; Study 2: 939 acquired or lifelong PE; DSM-IV clinician diagnosis Mean IELT = 3.9 (SD 1/4 37.4) seconds	✓	✓	✓	✓	✓	x	x	x	

(continued)

Table 16.2 (continued)

Instrument	Population	Factor analysis	Reliability			Validity			Diagnostic tests	
			Internal consistency	Test-retest	Convergent-divergent	Known groups	Responsiveness	MID	Sensitivity/specificity	Positive and negative predictive value
MSHQ-EjD	n = 1245 US men; n = 179 homosexual or bisexual men 6,909 US men with LUTS/BPH; no details on PE status within these samples	✓	✓	✓	✓	x	x	x	x	x
PEDT	n = 292; IELT = 66 (SE = 1.78) seconds n = 309 self-reported PE; IELT = 279.4 (SE = 19.22)	✓	✓	✓	✓	x	x	✓	x	x

BPH benign prostatic hyperplasia, CIPE Chinese index of premature ejaculation, IPE index of premature ejaculation, LUTS lower urinary tract symptoms, MSHQ-EjD male sexual health questionnaire-ejaculatory dysfunction, n/a not applicable, PEDT premature ejaculation diagnostic tool; PEP-premature ejaculation profile  
 ✓ feature demonstrated; x feature not demonstrated; ✓/x feature not clearly demonstrated

The second PRO, the premature ejaculation diagnostic tool (PEDT) [21, 22], is a five-item measure that evaluates difficulty in delaying ejaculation, ejaculating before the person wishes, ejaculating with little stimulation, frustration related to ejaculating prematurely, and concerns about the partner being sexually unfulfilled. The content was developed to capture the key components of PE as stated in the DSM-IV-R definition of PE and included men with IELTs of  $\leq 2$  min. It would seem acceptable to use today as the content is consistent with the ISSM definition and, importantly, the validation study included men with IELTs per the ISSM definition. The PEDT has excellent sensitivity and specificity and makes an ideal diagnostic tool (see [www.pfizerpatientreportedoutcomes.com](http://www.pfizerpatientreportedoutcomes.com) for a copy).

Psychometric analyses were conducted to ensure the items were valid and reliable. Testing was then conducted to determine the most appropriate scoring system to assess PE status. Although positive and negative predictive values were not calculated, a further study was undertaken to test the PEDT concordance in diagnosis against expert clinician diagnosis. The level of agreement between the PEDT and clinical expert was high ( $k$  statistic = 0.80; 95% confidence interval [CI]: 0.68–0.92). It has since been validated in Turkish and confirmed the strong psychometric properties of the measure and the suggested scoring to identify presence or absence of PE [23].

The limitation to using questionnaires in busy clinical practices is the time required to have the patient complete the measure and the time necessary to score the PRO and make the diagnosis. The PEDT and CIPE are brief and are quickly completed and scored, however. They are less intrusive and burdensome than asking patients to time lovemaking and provide an immediate decision regarding diagnosis.

### 16.6.2 Patient-Reported Outcomes for Determining Treatment Effects

There are five measures that assess the impact of treatment on men with PE. A summary of the development and validation of each PRO is given in Table 16.2.

The premature ejaculation profile (PEP) [13] contains four questions assessing perceived control over ejaculation, satisfaction with sexual intercourse, personal distress related to ejaculation, and interpersonal difficulty related to ejaculation (see Appendix). Each item has been validated and has shown robust psychometrics. An assessment of the items' convergent and divergent validity needs to be considered, as does a criterion for showing a meaningful change, such as minimum important difference (MID) or responder definition.

The advantage of the PEP is its brevity. This may also be a limitation, however, because each domain (control, satisfaction, distress, and interpersonal difficulty) consists of only one question, which may have an impact on the reliability of the items and may limit the sensitivity of each domain.

The Index of PE [24], with three domains covering control, sexual satisfaction, and distress, also showed strong psychometric properties (see [www.pfizerpatientreportedoutcomes.com](http://www.pfizerpatientreportedoutcomes.com) for a copy). Responsiveness has yet to be shown, and an MID or responder definition needs to be agreed on.

The newly developed Male Sexual Health Questionnaire-Ejaculation [25] has four items: three to assess function (force, volume, and frequency of ejaculation) and one to assess bother. It is best suited to evaluate delayed ejaculation rather than PE. How relevant the concepts of volume and force of ejaculation are in determining the impact on PE men's lives is unclear. The psychometric data did not provide any information on its diagnostic capability or its responsiveness or definition of MID or responder.

There were other measures mentioned in the literature; however, validation data were sparse or nonexistent. The PEQuest [26] was developed to investigate cognitive and partner-related factors in PE. Apart from information about how it was developed, however, there was limited information given as to its validation. The Yonsei-Sexual Function Inventory-II [27] similarly was developed to assess various factors related to PE (performance anxiety, patient and partner satisfaction, sexual desire, and overall sexual function); however, again, there was no validation information found in the literature to defend the measures use to assess outcome in PE clinical trials.

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## 16.7 Summary

This article has reviewed the state of the art as it relates to PROs for PE. An objective, evidence-based definition of PE has been proposed that includes an IELT cutoff, the criterion of distress and inability to delay/control ejaculation. Both the IPE and the PEP have domains that assess control and distress. They also have a domain for satisfaction which is not part of the current ISSM definition. The validation of the IPE, PEP and PEDT were in cohorts that included the  $\leq 1$  min IELT population, which would indicate their continued validity for use in screening for PE or measuring outcome in PE trials. Revisions to the DSM are projected to come out in 2013, it is unclear how PE will be defined. Any significant definition changes will affect the utility of the existing PRO measures.

Table 16.1 offers an in-depth review of the psychometric challenges that PROs must meet or exceed. Combined with the requirements of the regulatory agencies, such as the FDA, PROs have become increasingly sophisticated and reliable instruments for identifying men with PE and measuring treatment effects.

Table 16.2 reviews the available tools for clinicians and researchers and provides guidance concerning the benefits and limitations of these measures. It is important for the field to have brief but reliable instruments to make important judgments concerning diagnosis and treatment effects. The more a particular PRO is used, the more we learn about its reliability, validity, and diagnostic capability. Also, we begin to build a picture as to what an important change in score might look like. Rather than developing yet more measures for the diagnosis of PE and assessment of treatment

effects, the authors encourage researchers to use and build on the existing measures. The PEDT and IPE publications state that use is available for any interested researchers (and can be sourced across a number of languages at [www.pfizerpatientreportedoutcomes.com](http://www.pfizerpatientreportedoutcomes.com)), which is a positive move to consolidating and moving to one or two measures that all researchers can become familiar with and be more confident that diagnosis and treatment effects are reliable and valid.

## Appendix: Premature Ejaculation Profile (PEP)

### Premature Ejaculation Profile (PEP Items)

Over the past month, was your control over ejaculation during sexual intercourse:				
Very Poor	Poor	Fair	Good	Very Good
Over the past month, was your satisfaction with sexual intercourse:				
Very Poor	Poor	Fair	Good	Very Good
Over the past month, how distressed were you by how fast you ejaculated during sexual intercourse?				
Not at All	A Little	Moderately	Quite A Bit	Extremely
Over the past month, to what extent did how fast you ejaculated during sexual intercourse cause difficulty in your relationship with your partner?				
Not at All	A Little	Moderately	Quite A Bit	Extremely

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## 17.1 Introduction

Cognitive behavioral therapy (CBT) was developed from the combination of the behaviorism with cognitive therapy, and was influenced by the work of experts who considered irrational thoughts and faulty cognitive processing as the origin of emotional distress [1, 2].

CBT is an approach to therapy that accentuates the interrelationships among cognitions, emotions, and behaviors, and suggests that changing any one of these three aspects leads to changes in the others. Treatment for emotional problems targets cognitions and behaviors as a pathway to moderate emotions [3].

This type of therapy has been utilized to treat certain psychiatric disorders, including anxiety disorders, schizophrenia, mood disorders, personality disorders, and eating disorders. In the field of sexual difficulties, CBT has been shown to be effective for some types of female dyspareunia, female orgasmic disorders, vaginismus, erectile dysfunction, and premature ejaculation (PE) [4–15].

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## 17.2 Psychosexual Skills Deficit PE

Psychosexual skills deficit PE is a consequence of rudimentary sensual skills to manage the body during sexual arousal [16]. Some men may experience lifelong PE due to a restricted development of psychosexual skills. These men appear to lack dating or interpersonal skills as well as specific sensual and sexual physiologic knowledge and skills.

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Men with PE have difficulty focusing on their own sensations; experience thoughts of anticipatory failure; have difficulty relaxing their bodies while sexually aroused; experience a lack of awareness of body management techniques, such as the use of the pubococcygeal muscle in ejaculatory management; overfocus on their partner's body and reactions; and experience a restricted, uneasy, or anxious sensuality [16]. Assessment of these men's cognitive beliefs surrounding sexual performance may identify distortions (e.g., sex should be unregulated and spontaneous) [17, 18]. Other cognitive features include ineffectual distractions or unrealistic beliefs of the need to please the partner or to bring the partner to orgasm.

Assessing the man's predominant style of sexual arousal is essential. This is assessed in interview by asking the man to describe in detail the physical sensations in his body generally and the sensations in specific parts (e.g., hands, chest, stomach, penis, legs, and so forth) during arousal. Diagnostically, men with psychosexual skills deficit PE commonly find it difficult to describe these specific details [16].

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### **17.3 Therapeutic Approach to Psychosexual Skills Deficit PE**

Several CBT techniques are employed in the treatment of PE resulting from psychosexual skills deficit. In 1956, James Semans described one of the earliest published behavioral interventions for the management of PE—the stop-start technique: pause sexual stimulation at impending ejaculation [4]. A slight variation of this intervention, the squeeze technique was proposed by Masters and Johnson, in the 1970s: withdrawal and squeeze the frenulum of the penis, resulting in a partial loss of erection and total loss of urge to ejaculate [5].

There are only vague explanations for the mechanism by which the stop-start techniques work. Semans conceptualized that PE is a result of an abnormally rapid ejaculatory reflex and a failure of the man to pay sufficient attention to pre-orgasmic levels of sexual tension, and the stop-start technique altered the neuromuscular reflex mechanism of ejaculation [4]. Masters and Johnson, and Kaplan contended that the key to the success of the stop-start techniques is that they allow men the opportunity to attend to the intense body and genital sensations that occur just prior to ejaculation [5, 6].

In contrast, Zilbergeld argued that the stop-start techniques provide men with PE the opportunity to explore changes in sexual behavior. Thus, the technique may simply be altering sexual behavior sufficiently to allow men with PE to discover any of a variety of ejaculatory delaying techniques spontaneously discovered by men with good ejaculatory control [19].

There have been some attempts to modify the stop-start techniques. LoPiccolo proposed that, in addition to stopping, a man with PE should pull down on his scrotum when approaching ejaculatory inevitability [20]. This would reverse the physiological process of the elevation of the testes which normally occurs prior to ejaculation and thereby could inhibit ejaculation. The Valsalva maneuver, another variation proposed by LoPiccolo, is for the man to force exhalation when the



airway is closed. This intervention could induce activity in the sympathetic nervous system which would act counter to the process of ejaculation [20].

Other minor alterations to these behavioral therapies have been suggested over the years [6]. Sex therapists include a variety of other techniques such as: sensate focus exercises, communication training, education, sexual skills training, intercourse position, thought distractions, and reducing performance demands [21–23].

While behavioral therapies focus on altering the stimulus–response component of PE, cognitive approaches emphasize on re-evaluating and reshaping the interpretation of perceptions and feelings. Further, cognitive therapies have the objective of improving the communication of the couple, thereby increasing sexual skills and self-confidence, as well as reducing the anxiety associated with sexual activity [24–26].

The efficacy of these behavioral therapies has been attributed to heightened male awareness of sexual sensations, focus on pleasure, reduced anxiety, and a decreased emphasis or focus on intercourse [27].

Although Masters and Johnson reported an initial failure rate of only 2.2 % within a sample of 186 men and a similarly low failure rate at a 5-year follow-up [5], other studies reported substantially lower success rates using the stop-start techniques [28–30]. Using this technique, success of 62 % was reported [28], while by using the squeeze technique only 64 % of men successfully gained ejaculatory control [29], but only one-third of those men showed continued control at 3 years post treatment [30].

The treatment gains were lost over time. Decreases in motivation, additional sexual problems occurring in the relationship, changes in attraction between partners could all play a role in the loss of learned ejaculatory control. Additionally, the discrepancies between early reports of the success of the stop-start techniques and subsequent studies may reflect methodological problems [31]. In most studies, these techniques were not compared to placebo, control or wait list groups [32]. Only one recent study demonstrated an eightfold increase in intravaginal ejaculatory latency time (IELT) among men treated with behavioral techniques compared to a wait list control condition [21].

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## **17.4 Cognitive Behavioral Strategies for the Treatment of PE**

Metz and Pryor divide these strategies into two groups: individual and couple procedures [16].

### **17.4.1 Individual Procedures**

#### **17.4.1.1 Cognitive and Behavioral Pacing Techniques**

- (a) *Behavioral Stop-Start Technique*. It includes progressive masturbation training exercises to familiarize the man with sensual awareness and regulation during

sexual arousal. This approach required the participation of the couple. The clinician meets the partners individually to explain the dysfunction and the behavioral treatment. The stop-start technique involves the partner stimulating the penis until the man feels a sensation that is premonitory to ejaculation; at this time, the partner ceases stimulation until the sensation disappears. This process is continued until such time as ejaculation can be delayed indefinitely [4].

- (b) *Behavioral Squeeze Technique*. It can be used to demonstrate to the patient that the body has the capacity for some control. This technique also involves individual and couples therapy, and requires the partner to squeeze the frenulum of the penis for a few seconds once the male has achieved “full erection” and begins to sense the urge to ejaculate. This results in an immediate partial loss of erection and total loss of the urge to ejaculate. This procedure is utilized until the male has delayed ejaculating for a period of 15–20 min. Once the male is able to delay ejaculation, intromission (and eventually intercourse) can be attempted using the female superior position. During the initial attempts at intercourse, the female is instructed not to move—using a technique that is now called “quiet vagina”, for the male to develop sufficient control over his ejaculation to prolong vaginal intercourse [5].
- (c) *Cognitive Arousal Continuum Technique*. The man systematically observes, considers, and distinguishes those detailed thoughts, actions, feelings, scenarios, and sequences that characterize his individual arousal pattern. Identifying which items that are more or less arousing in relation to each other, he is able to rank-order them with an understanding of his incremental arousal. Then, during the sexual intercourse, the man is able to manage his level of sexual arousal by his judicious concentration [16, 33].

#### **17.4.1.2 Physiological Relaxation Training**

Simple and easily learned relaxation techniques that focus on the body are useful in PE treatment training. Ten to twenty minutes daily of quiet focus on breathing, body awareness, and muscle relaxation is encouraged, to concentrate on physical sensations, and to ease bodily tensions. Satisfactory sexual functioning is the result of this physiological relaxation [16].

#### **17.4.1.3 Sensual Awareness Training: Entrancement Arousal**

The man focuses on visual and tactile exploration of his own body. The aim is to become more familiar with his body visually and tactilely, and to become more conscious of his own bodily responses to touch. Men with PE are commonly surprised when they ejaculate, because they frequently do not focus attention on their body and sensations.

To achieve ejaculatory control, a man with PE needs another arousal style (entrancement arousal). Here, the focus is on his own physical or bodily sensations. This necessary focus is an aide to relaxation. Training the man to become aroused by “entrancement,” rather than “partner interaction”, provides him with the foundation for improved sexual arousal control. For example, the man focuses

on the pleasurable sensations in his penis rather than on his partner's breasts, sexual fantasy, or distractions such as sports images [34].

#### **17.4.1.4 The Pubococcygeal Muscle Control Technique**

This technique teaches the conscious capacity to relax the pelvic area's pubococcygeal (PC) muscle. It is a variation on the Kegel technique for women. The man is taught to relax the PC muscles (bulbocavernosus and ischiocavernosus muscles) while experiencing sexual arousal. This technique prepares to the natural ejaculatory-inhibiting effect of relaxing the muscles that are engaged in ejaculation. It is effective when utilized in conjunction with other techniques [16].

#### **17.4.1.5 Pelvic Floor Rehabilitation Training**

It consists of three modified techniques of rehabilitation of the pelvic floor protocol used in treating fecal and urinary incontinence: physio kinesitherapy of the pelvic floor, electro stimulation, and biofeedback. Physio kinesitherapy and electro stimulation are designed to improve the contractile strength of the perineal muscles, while with biofeedback the man learns to recognize and contract the muscles to increase the closing strength of the urethral sphincter [35].

### **17.4.2 Couple Procedures**

#### **17.4.2.1 Couples Sensate Focus Pleasuring Exercises**

Those sensate focus exercises reinforce the entrancement arousal focus established in the individual phase of therapy. Homework sessions begin with the couple relaxing and pleasuring each other until the man physiologically relaxes. After that, he lies on his back while the partner stimulates his penis very gently as he concentrates on the physical sensations he is experiencing (entrancement) [16, 34].

#### **17.4.2.2 The Partner Genital Exploration Relaxation Exercise**

Partners practice sexual leadership with each other's body, to become more comfortable with looking at each other's genitals, and to have each partner's genitals touched and looked at by the other partner in a relaxing and nonarousing way [16].

#### **17.4.2.3 Couple Use of the Behavioral Pacing Method: Stop-Start Technique**

This technique requires the man to stimulate and then stop arousal through a progressive sequence of exercises that teach him to focus on his physical sensations, learning to recognize those that proceed to orgasm. Recognizing these sensations, he learns to control his ejaculatory response. When successful alone, the man exercises the same procedure with his partner. After some (four or five) successful manual stimulation sessions, the couple tries stop-start intercourse with the penis in the vagina [16].

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#### **17.4.2.4 The Intercourse Acclimatization Technique**

The man focus on relaxing the PC muscle while the woman inserts the penis into her vagina and then he quietly rests inside. Then, he waits, expecting to reach the physical pleasure saturation point (a sensual dullness) in his penis—where the penis acclimates to the warmth and sensuousness of the vagina (or the mouth, in oral sex training). After this acclimation occurs, the penis can begin to tolerate more intense pleasure and enjoy, while maintaining ejaculatory control [16].

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### **17.5 Parameters Affecting Treatment of PE with CBT**

Three central aspects appear relevant to successful outcomes: (1) the male's attention to and awareness of sexual and visceral sensations must be heightened; (2) the couple must deemphasize the focus on intercourse and develop a broader range of sexual expression; (3) the man with PE, and to a lesser degree the partner, must develop alternative cognitive and behavioral strategies to enhance ejaculatory control [36].

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### **17.6 Conclusion**

In addressing sexual dysfunction, it is a priority to explore and challenge negative attitudes and fantasies, such as anticipating failure, distracting thoughts and focusing on negative aspects of the partner. It is fundamental to see the patient individually as well as with the partner. Interviewing them both emphasizes that PE invariably affects both partners, and its treatment occurs within the couple's relationship.

Cognitive restructuring involves helping the man identify arousal interfering thoughts, correcting cognitive distortions, and allowing erotic and positive fantasies.

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## 18.1 Introduction

Premature ejaculation (PE) involves the integration of physiological, psychobehavioural, cultural, and relationship dimensions. All these elements need to be considered in the treatment of PE [1–5].

Strong data demonstrate the negative effects of PE on both the man and his partner, contributing to an improved understanding of psychodynamic factors associated with this sexual dysfunction [6–8]. Then, psychosocial and contextual factors are all thought to have a part in the development of PE. Possible psychogenic risk factors for PE include: Anxiety, early sexual experiences, low frequency of sexual intercourse, and relational problems [6, 7, 9, 10].

Men with PE report higher levels of negative emotions such as frustration, anger, disappointment, failure, insecurity, inadequacy, guilt, humiliation, embarrassment, fear, and denial. PE can exert both an emotional and a health impact on patients [11–14].

Compared with men without PE, men with PE place significant emphasis on being able to achieve intercourse for the desired length of time and the ability to prevent or control ejaculation [15]. The PE prevalence and attitudes (PEPA) Survey investigated the prevalence of PE and its psychosexual burden on men [16]. The PEPA study demonstrated that PE has a significant negative effect on men and more a substantial impact on QoL and sexual satisfaction than erectile

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dysfunction. Further, men with PE were most aware of (>70 %) and most likely to have used (>50 %) special positions during sex, interrupted stimulation, masturbation, and having intercourse more often than usual to manage their PE [16].

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## 18.2 Psychodynamics Theories

There are multiple psychological explanations as to why men develop PE. Unfortunately, none of the theories evolve from evidence-based studies. Although untested, the theories are thought provoking [17].

The psychoanalyst Karl Abraham was the first to identify the psychodynamic basis of PE in 1927. He theorized that the cause of PE was an infantile narcissism, resulting in excessive importance being placed on the penis, and a symptom of unconscious conflicts involving hostility toward or fear of women [18]. Bernard Schapiro [19] found little or no support for this hypothesis and speculated that men with PE had specific biological organ vulnerabilities that directed the expression of the individual's psychological conflicts.

Kaplan [20] considered PE could be the result of an unconscious, deep-seated hatred of woman. By ejaculating quickly, the man symbolically "soils" the woman and robs her of sexual pleasure. This theory assumes that vaginal intercourse is the primary source of sexual pleasure for woman. Neither does it explain PE in homosexual men. Moreover, the link between male hostility towards women and PE lacks empirical evidence. Later, Kaplan suggested that most men with PE do not have personality disorders [21].

Hartmann et al. characterized men with PE as preoccupied with thoughts about controlling their orgasm, with anxious anticipation of a possible failure, thoughts about embarrassment and thoughts about keeping their erection [22].

Psychodynamic theories consider anxiety to be the primary causal agent in precipitating premature ejaculation. Anxiety is used to characterize three different mental phenomena: (1) a phobic response; (2) the end result of conflict resolution where two contradictory urges are at play (anger, guilt, hostility); (3) anticipatory anxiety (preoccupation with sexual failures and poor performance leads to deteriorating sexual function and avoidance of future sexual interactions) [17, 23, 24].

However, performance anxiety *per se* does not generally cause the initial episode of PE, but it is responsible in maintaining the dysfunction, because it distracts the men from focusing on his level of arousal, rendering him helpless in exerting voluntary control over his sexual arousal and ejaculation. With each failure, performance anxiety increases and may result in sexual avoidance behaviour. Men believe that their partners do not understand the frustration and humiliation that they experience. This disconnection between men and their partners is the basis for considerable relationship tension [17].



### 18.3 Premature Ejaculation: A Partnership Problem

Although PE is considered a Partnership problem [6, 25], couples rarely talk about the issue: the partner may fear hurting the man's feelings, while the man may be embarrassed or hope/believe the problem is temporary. Moreover, partners might believe that PE is a natural condition or a condition without solution. Frequently, neither do the partners discuss the problem owing to poor communication skills, embarrassment or frustration. In consequence, PE has significant negative impact on the man, his partner and the couple's relationship [8, 15, 26, 27].

Other negative effects include a general prejudicial feeling associated with sexual situations, and more intense feelings of embarrassment/guilt, worry/tension and fear of failure, decreased self-confidence, interpersonal difficulty, and mental preoccupation with their condition [8, 22, 28]. The inability to exert control over the timing of ejaculation is likely to result in distress and/or avoidance of sexual intimacy [1].

Partner satisfaction may play a more significant role in PE than erectile dysfunction. Because of it, relationship dysfunction is the second most common negative effect of premature ejaculation [12, 22, 29].

A partner who is not involved in the management of PE may resist the ensuing change in sexual dynamics, thereby countering the potential positive effects of treatment. In contrast, a cooperative partner can enhance the man's self-confidence and esteem, and assist in developing more ejaculatory control [1].

The insecurity of a men with PE about satisfying his partner also serves as an obstacle to initiating and maintaining new relationships [12, 13].

Assessment of the couple's sexual and dyadic relationship from the perspective of both the man and his partner is essential for developing a comprehensive treatment strategy [30].

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### 18.4 Psychodynamic Approaches

A psychosexual and medical history supports informed decisions regarding the appropriate management strategy for each individual. The quality of the phases of the sexual response cycle (desire, arousal, orgasm, and resolution) should also be considered, as well as ejaculatory response (estimated latency, sense of control, quality of orgasm/pleasure); frequency of sexual activity; the cultural background; and a brief developmental history of the disorder (generalized or situational, lifelong or acquired) [1, 31].

A lifelong history of PE that is not specific to one partner or situation could suggest a biological and/or cognitive-behavioural etiology. By contrast, PE that has developed within specific situations may suggest interpersonal and/or relationship issues [2, 30].

Asking the man about behaviours, feelings, and thoughts prior to, during, and subsequent to an episode of PE can also add depth to the patient's assessment [32].

Men tend to utilize self-help procedures or numbing creams before seeking psychological or medical treatment for premature ejaculation. These procedures may involve using multiple condoms to reduce penile sensitivity, mental distraction exercises, and aggressive thrusting [13]. Further, some men masturbate prior to sexual intercourse in order to desensitize the penis and delay subsequent ejaculation. While this technique may have some temporary benefit for younger men, it may be prejudicial for the older whose refractory period has lengthened with aging. Frequently, self-help procedures may have short-term benefits and fail to obtain ejaculatory control. It can compound the pernicious effects of PE in the long term [13].

Psychotherapy for PE is an integration of psychodynamic, systems, behavioural, and cognitive therapies within a short-term psychotherapy approach [4, 9, 21, 33–37]. Psychodynamic therapy understands PE as a metaphor in which the partners are trying to simultaneously repress and express conflicting aspects of the relationship or themselves, whereas cognitive-behavioural therapy considers PE as a conditioned or maladaptive response to interpersonal or environmental events [17] (*see Chap. 17*).

The targets of treatment are to learn to control ejaculation while understanding the meaning of the symptomatology and the context in which it occurs. Psychotherapy improves ejaculatory control by helping men and couples to: increase communication; overcome barriers to intimacy; come to terms with feelings and thoughts that interfere with the sexual function; learn strategies to control and/or delay ejaculation; lessen performance anxiety; gain confidence in their sexual performance; resolve interpersonal issues that precipitate and maintain the dysfunction; modify rigid sexual repertoires [10, 17, 30].

A combination treatment strategy that addresses all dimensions of sexual dysfunction may best ensure long-term outcomes [2, 38].

Psychotherapy alone is reserved for men and couples where the precipitating and maintaining factors are clearly psychological and/or the psychosocial barriers are too great for pharmacotherapy alone. These difficulties include: patient issues such as the degree of performance anxiety or the presence of depression; partner variables such as how the partner copes with the sexual dysfunction or how the PE obscures the woman's sexual difficulty; interpersonal nonsexual elements such as a chronically unsatisfying relationship; contextual characteristics including lack of privacy; partner's expectations from treatment [17, 30].

For single men who are not in a relationship, individual psychotherapy is the treatment of choice. Psychotherapy can only go so far without the presence of a partner, because the man cannot practice what he has learned nor work through salient interpersonal dynamics [17, 30].

For those who are in a relationship, individual psychotherapy is indicated when the psychological variables supporting the dysfunction are thought to be more intrapsychic rather than interpersonal: fear of penetrating vagina or excessive fear of or hostility to women. These conditions represent generally unresolved childhood issues. Individual psychotherapy may also be recommended when the partner refuses to participate or the relationship is unworkable [10, 30].

For partners that are psychologically healthy and motivated, conjoint psychotherapy is the treatment of choice on lifelong or acquired PE [30].

Usually, pharmacological and psychological combined therapy may offer the best of both interventions [39, 40].

### 18.4.1 Resistance

Resistance means that there is a conflict between a patient's conscious desire for change and an unconscious need to maintain the status quo [41, 42]. Patients seeking psychotherapy for PE and their partners may exhibit various forms of resistance [15, 32]; this is to be expected [17, 42].

According to Levine, there are five sources of resistance: (1) when the PE and associated problems maintain a sexual equilibrium and cover up the female partners sexual disorder or concern; (2) when the individual or couple has unrealistic expectations about sexual performance; (3) when partners have major relationship problems; (4) when male or female deceit is present; (5) when PE is the consequence of a major health problem [9].

It is difficult for patient and couple to give up comfortable, yet maladaptive behaviours. By using confrontation, interpretation, and gentle humor patients can be encouraged to relinquish resistances and "try on" new behavioural and interpersonal routines [30].

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## 18.5 Conclusion

The psychological approach remains an important treatment option for PE, due to several reasons: it is specific to the problem; it is neither harmful nor painful; it is less dependent on the man's medical history; it produces minimal or no adverse side-effects; it encourages open communication between the man with PE and his partner, which is likely to lead to a more satisfying sexual relationship [43–45].

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# Treatment of Premature Ejaculation with Selective Serotonin Re-Uptake Inhibitors

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## 19.1 Introduction

One of the most exciting aspects of the selective serotonin re-uptake inhibitors (SSRI's) is their potentially broad range of indications [1]. Although originally meant to treat depression and anxiety disorders, throughout the years the SSRIs have become popular to treat also other conditions, such as obsessive compulsive disorder, eating disorders, and premenstrual syndrome. In the last two decades, various studies have shown that some of the SSRIs are also efficacious in treating premature ejaculation (PE). Their introduction in sexual medicine has led to a revolutionary change in the understanding and treatment of PE [2].

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## 19.2 Daily Treatment with SSRIs

The first placebo-controlled SSRI treatment study of PE was published in 1994 [3]. It was demonstrated that daily use of 40 mg paroxetine significantly and clinically relevantly delayed ejaculation in men with PE. It was also the first study in which the intravaginal ejaculation latency time (IELT) was introduced as a parameter of the ejaculation time [3]. The IELT was defined as the time between the start of vaginal penetration and the start of intravaginal ejaculation [3]. In the following

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decade, a crescendo of other studies using SSRIs were published [4–23]. Remarkably, both in animal and human studies it appeared that of the SSRIs only fluvoxamine did not exert a clinically relevant ejaculation delay [9, 24]. Nevertheless, all human studies confirmed the rather strong ejaculation delaying effect of SSRIs, but due to different methods used, some of these studies produced contradictory outcome data [25]. Because of these different methods, it soon was time to conduct a systematic review and a meta-analysis of all drug-treatment studies of PE.

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### 19.3 Geometric Mean IELT and Fold-Increase

In order to better understand the results of this meta-analysis, brief attention should be given to the geometric mean IELT [26]. Based on a clinical stopwatch study [27], it appeared already in the 1990s that the IELT in a clinical sample has a skewed distribution. But apart from that, also, in individual cases of men who measured their IELT with a stopwatch, it appeared that most of these men ejaculated within a certain time frame, but that a substantial number of them also but only sometimes, experienced relatively longer ejaculation time durations. This clinical phenomenon has consequences for the statistics used in drug treatment studies of PE. By using the arithmetic mean or the median in such series of IELT data, the “outlier” IELT value may shift the mean and the median IELT to higher values, thereby overestimating the true IELT value of the individual male. Log-transforming each separate IELT measurement of each individual man resolves this statistical problem and is the basis for the calculation of the geometric mean IELT. In a positively skewed IELT distribution, the mean IELT always has a higher value than the median IELT and the median IELT value has always a higher value than the geometric mean IELT. Moreover, in our own drug treatment studies we have found that strong ejaculation-delaying drugs give rise to a strong positively skewed IELT distribution, whereas weak ejaculation-delaying drugs give rise to (much) less skewed IELT distributions and when there is hardly any ejaculation-delay even a bell-shaped IELT distribution [26]. In drug treatment studies, ejaculation delay is expressed in fold increase of the geometric mean IELT (fold increase = IELT value at end/IELT value at baseline).

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### 19.4 Meta-Analysis of Daily SSRI Studies

In 2004, Waldinger et al. published the first systematic review and meta-analysis of all drug treatment studies that had been published between 1943 and 2003 [28]. Of all 79 studies that had been published around the world, a meta-analysis was only feasible on 35 clomipramine (a tricyclic antidepressant) and SSRI daily treatment studies that were conducted between 1973 and 2003 [28]. However, the majority of these studies were not conducted according to current standards of

evidence based research. Therefore, all 35 studies were included in a meta-analysis and compared with a meta-analysis of 8 studies which in contrast were conducted according to all criteria of evidence based research. The outcome data of the SSRI treatment studies published between 2003 and 2012 hardly distort the findings of the meta-analysis and therefore its conclusions are still valid today. But, although very effective in delaying ejaculation, it should be noted, that daily and on-demand SSRI treatment studies are off-label, as they have not been approved by the Food and Drug Administration (FDA).

The meta-analysis revealed a placebo effect of a geometric mean 1.4-fold IELT increase (95 % CI: 1.2–1.7). Furthermore, it was demonstrated that the rank order of efficacy (geometric mean fold-increase of IELT) was (a) paroxetine (8.8; 95 % CI: 5.9–13.2); (b) clomipramine (4.6; 3.0–7.4); (c) sertraline (4.1; 2.6–7.0), and (d) fluoxetine (3.9; 3.0–5.4). Thus, in general, daily SSRI treatment studies generate a 2.6–13.2 geometric mean IELT fold increase, dependent on the type of SSRI. The meta-analysis showed that of all SSRIs, daily use of 20 mg paroxetine exerts the strongest ejaculation delay in the investigated males, a result that actually confirms the clinical impression of physicians that have experience in treating PE patients with various SSRIs. The meta-analysis also demonstrated that compared to stop-watch studies, open and single-blind studies lead to an exaggerated response and that retrospective assessment of ejaculation time by a questionnaire or subjective report lead to far more variability in clinical outcome values of the IELT.

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## 19.5 Dosages of Daily SSRI Treatment

Daily treatment can be performed with paroxetine 20–40 mg, clomipramine 10–50 mg, sertraline 50–100 mg, fluoxetine 20–40 mg, citalopram 20–40 mg, and escitalopram 20 mg [29]. Ejaculation delay usually starts a few days after intake. However, a clinically relevant effect only gradually occurs after 1–3 weeks. Most often the delay continues to exist for years, but sometimes may diminish after 6–12 months. The cause of this tachyphylaxis of SSRIs has not yet been clarified.

Without doubt, daily SSRI treatment is effective in delaying ejaculation. But it does not delay ejaculation in every patient and to the same extent. From my clinical experience, it is my impression that adequate or nearly adequate ejaculation delay occurs in 70–80 % of men, but that in about 20 % of the patients the SSRIs do not have any ejaculation-delaying effect. Patients should be informed before taking the medication that in about 20 % of men the SSRIs do not have the expected result, but that in principle they have quite some chance that ejaculation will be delayed within 1–3 weeks. The reason for this lack of effect in 20 % of men is not clear. In such cases one should switch to another SSRI, but it is also my experience that in such cases other SSRIs do not have an ejaculation-delaying effect either.



## 19.6 On-Demand Use of Serotonergic Antidepressants

Although on-demand use of the classical SSRIs may have some ejaculation-delaying effect, it may be insufficient for a man affected by lifelong PE who ejaculates within a few seconds to a minute. On the other hand, it is rather questionable whether on-demand and off-label SSRI treatment that affects ejaculation within a few hours is more favorable than daily drug treatment. Indeed, the on-demand use of sildenafil to treat erectile disorder has become very successful. However, erectile disorder usually affects men over the forties, whereas lifelong PE affects young men in the early twenties and older ages. Immediate sexual activity belongs to the sexual repertoire of young adults when being aroused. For such men, topical anesthetic sprays with an immediate (within 5 min) anesthetizing effect, such as TEMPE or Promescent, would be rather ideal. On-demand strategies, that do not affect ejaculation within 5–15 min, may quite negatively interfere with the spontaneity of having sex, particularly as one is inclined to or decides to have sex at the spur of the moment. A clear advantage of daily SSRI treatment is that ejaculation is nearly always delayed at every moment of the day that one wishes to be sexually active. The argument that daily treatment is not preferable because one has to wait 1–2 weeks before ejaculation delay occurs is not based on evidence. Most men with lifelong PE will report that after many years of having had PE, it is no problem to wait another 1–2 weeks before medication becomes effective. Nevertheless, on-demand SSRI treatment contributes to the armamentarium of drug treatment of PE.

In the systematic review of 2003 only eight studies on on-demand treatment with SSRIs and clomipramine were reported [30–37]. These eight on-demand studies greatly differed in methodology. A meta-analysis on the published on-demand SSRI studies could not be performed as the studies were unbalanced for the antidepressants used, baseline IELT values, design (double-blind vs. open) and assessment techniques (questionnaire vs. stopwatch). In spite of the absence of a meta-analysis on on-demand SSRI treatment studies, there are indications that on-demand use of SSRIs, like 20 mg paroxetine, delay ejaculation but considerably less than daily SSRI treatment. However, it usually takes about 4–6 h after intake of the drug, before its ejaculation-delaying effects become manifest.

Recently, both daily and on-demand SSRI treatment are recommended as one of the drug-treatment options for PE by the International Society for Sexual Medicine (ISSM) Guideline for the Treatment of PE [29].

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## 19.7 SSRI-Induced Side Effects

Patients should be informed about the short-term and long-term side effects of SSRIs. On the short term, fatigue, yawning, mild nausea, loose stools, or perspiration may occur. These side effects are usually mild, start in the first 1–2 weeks of treatment, and most often gradually disappear within 2–3 weeks [2]. Although a

head-to-head comparative study has not yet been performed, drug treatment studies seem to indicate that in contrast to the side-effects in depressed patients, diminished libido and erectile dysfunction are less frequently and also to a lesser extent reported by healthy non-depressed men with lifelong PE. A rather rare side effect of SSRIs is the risk of bleeding [38]. Clinicians should caution patients about combining SSRIs with aspirin or NSAIDs as this may further increase the risk of bleeding. A very rare side effect is priapism [39, 40]. Although very rare, it is advised to inform all patients using SSRIs about the risk of priapism and its need for immediate medical treatment. One should not prescribe these drugs to young men <18 years, and to men known with depressive disorder particularly when associated with suicidal thoughts. In those cases, referral to a psychiatrist is indicated. On the long term, weight gain might occur with an associated risk for type 2 diabetes mellitus [41]. It should also be noted that SSRIs very rarely may give rise to irreversible sexual side effects. Currently there is no explanation for this very rare phenomenon that is often associated with genital anesthesia.

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## 19.8 SSRI Discontinuation Syndrome

Importantly, patients should be advised not to stop taking the medication acutely to prevent the occurrence of an SSRI discontinuation syndrome, which is characterized by symptoms like tremor, shock-like sensations when turning the head, nausea and dizziness [42, 43]. In case patients want to stop taking the SSRI, one should inform them at the beginning that discontinuation should be carried out very gradually within about 2 and sometimes even 3 months, in order to prevent discontinuation symptoms.

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## 19.9 Wish for Pregnancy

Particularly in young patients, one should inform the patients that hardly anything is known about the effect of SSRIs on spermatozoa, as research on this topic has hardly been performed. Because of this lack of research, and in case of a wish for pregnancy I advise my patients to gradually diminish the dosage of the drug and to stop taking the drug for a certain period of time. As it takes quite some time for spermatozoa to be renewed, my advise is to make love with a condom for 3 months after discontinuation of the drug, after which pregnancy is allowed. Notably, this advise is not based on any hard evidence, but only to prevent possible problems in the future when it may perhaps appear that SSRIs affect spermatozoa in a negative way.

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## 19.10 Generic vs. Brand-Name SSRIs

A special note should be made to the use of generic SSRIs. The most relevant studies on SSRI treatment of PE have been conducted in the early and mid-nineties using the brand-name SSRIs, simply because at that time generic SSRIs were not

yet on the market. In contrast, today generic SSRIs are frequently prescribed. In a review of the few publications comparing the bioequivalence and efficacy of brandname and generic psychoactive drugs, it was shown that there are differences between the generic drugs and the brand-name drugs which had not been noted in the original bioequivalence studies [44]. This issue has consequences for drug treatment of PE.

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### **19.11 Paroxetine Hemihydrate**

Daily treatment studies of PE with paroxetine have been performed with paroxetine hydrochloride hemihydrate and not with the generic drug paroxetine hemihydrate and/or paroxetine mesylate. The ejaculation-delaying efficacy and relative mild-side effect profile of paroxetine hemihydrate has been repeatedly demonstrated in well-controlled studies. Based on these studies, there are no real objective contraindications to use the generic paroxetine hemihydrate to treat PE.

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### **19.12 Paroxetine Mesylate**

Drug treatment studies on PE have not been performed with paroxetine mesylate. There are some indications that particularly the side-effect profile of the generic paroxetine-mesylate is different from paroxetine hemihydrates [44, 45]. Therefore, and due to the lack of placebo-controlled comparative studies investigating the efficacy and side effect profile of both paroxetine hemihydrate and paroxetine mesylate in the treatment of PE, it is advised to prescribe only paroxetine hydrochloride hemihydrate to men with lifelong PE and not paroxetine mesylate [2].

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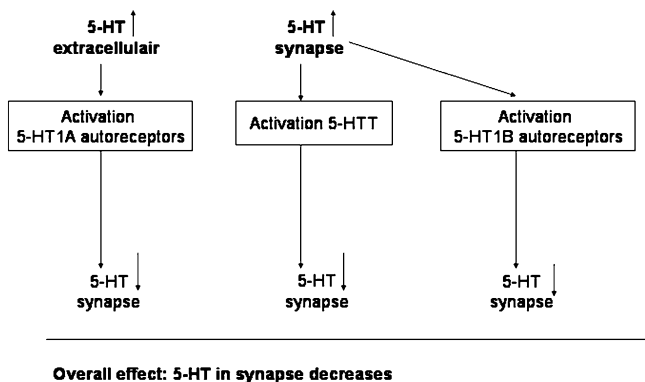
### **19.13 Scientific Rationale of Daily SSRI Treatment**

The clinically very relevant ejaculation delay induced by daily treatment with SSRIs and the substantially lower ejaculation delay induced by on-demand SSRI treatment is in line with current understanding of the neurotransmission of serotonin (5-hydroxytryptamine; 5-HT) in the central nervous system [46].

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### **19.14 Serotonergic Neurons Regulate their Own Activity by Three Mechanisms**

One of the basic features of serotonergic neurotransmission is the phenomenon that any acute increase of 5-HT release into the synapse is immediately followed by activity of the neuron to diminish the extra 5-HT level [47, 48]. Under normal



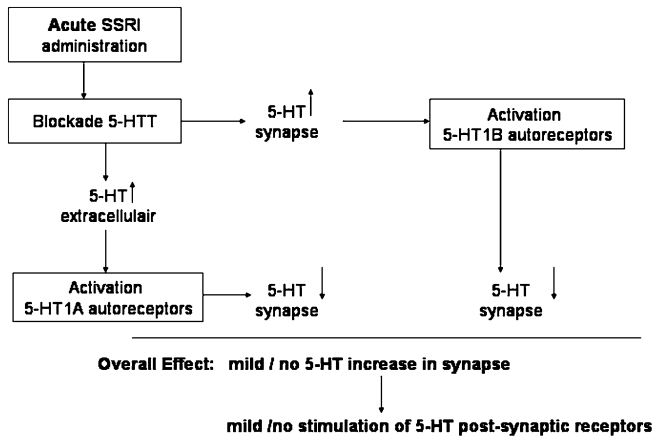
**Fig. 19.1** Mechanism 1, 2 and 3 leading to homeostasis of the central serotonergic neuron [47]

physiological conditions 5-HT activates (presynaptic) 5-HT<sub>1A</sub> autoreceptors on the cell bodies of serotonergic neurons. Activation of these 5-HT<sub>1A</sub> autoreceptors decreases firing of the 5-HT neuron and consequently lowers the 5-HT release from the presynaptic neuron into the synaptic cleft (mechanism 1). After release of 5-HT in the synapse, presynaptic 5-HT<sub>1B</sub> autoreceptors become activated that in turn inhibit the 5-HT release from the presynaptic neuron into the synaptic cleft (mechanism 2). This feedback mechanism of the neuron probably prevents overstimulation of (post) synaptic 5-HT receptors. Another automechanism to prevent overstimulation of postsynaptic 5-HT receptors is the immediate removal of 5-HT in the synapse back into the presynaptic neuron by 5-HT transporters (5-HTT) at the presynaptic endings and at the serotonergic cell bodies (mechanism 3) (Fig. 19.1).

This complex feedback mechanism in the central serotonergic system is meant to sustain homeostasis [47]. However, it has also consequences for drug treatment of PE. Particularly, for on-demand treatment with SSRIs [47].

### 19.14.1 Acute SSRI administration

All 5-HT transporters are blocked after acute SSRI administration, leading to higher 5-HT levels in the synaptic cleft and in the space around the cell bodies [49]. The increased 5-HT levels activate 5-HT<sub>1A</sub> autoreceptors and consequently lead to lower 5-HT release into the synaptic cleft within minutes [50]. The diminished release of 5-HT in the synaptic cleft compensates (completely or partially) the initially increased 5-HT concentrations as the result of the SSRI-induced blockade of the 5-HT reuptake by transporters from the synapse into the presynaptic neuron. Higher 5-HT concentrations in the synapse will increase the activation of presynaptic 5-HT<sub>1B</sub> autoreceptors that by itself will attenuate 5-HT release. The net effect of acute SSRI administration, under physiological



**Fig. 19.2** Effect of acute SSRI administration on the serotonergic neuron [47]

conditions, is only a mild or no increase of 5-HT neurotransmission and mild or no stimulation of all postsynaptic 5-HT receptors (Fig. 19.2).

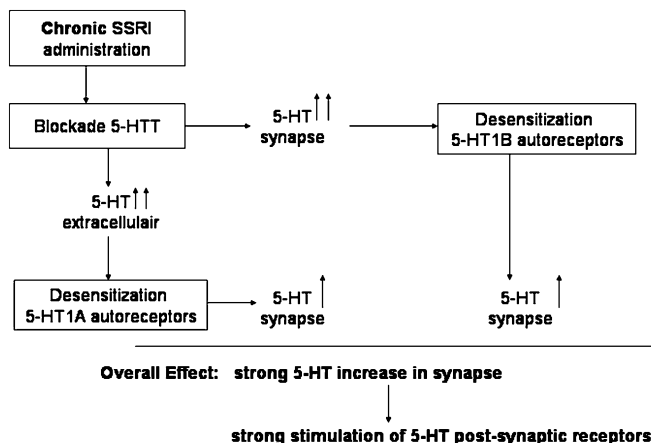
In other words, based on these data, it follows that on-demand SSRI treatment will acutely (i.e., within 1–2 h) not lead to relevant stimulation of 5-HT postsynaptic receptors, as there is hardly any 5-HT increase in the synapse and hardly any stimulation of postsynaptic 5-HT receptors. If postsynaptic 5-HT receptors are not or hardly activated clinically relevant ejaculation delay will not occur [47].

Indeed, animal studies have shown that acute administration of the five SSRIs (fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram) has no significant effects on ejaculation time and number of ejaculations [51]. And also human studies indicate that on-demand use of the classical SSRIs do not lead to a similar strong ejaculation delay as can be induced by daily treatment with SSRIs.

### 19.14.2 Chronic SSRI Administration

In contrast to acute administration, chronic administration of SSRIs leads to a number of adaptations that are pivotal for inducing relevant ejaculation delay. The ongoing blockade of 5-HTTs results in a persistent increase of 5-HT levels in the synapse and in the space around the cell bodies. This leads to desensitization of 5-HT<sub>1A</sub> autoreceptors over the course of a few weeks [52], possibly also to desensitization of 5-HT<sub>1B</sub> autoreceptors [53], and consequently to less inhibition on 5-HT release into the synapse. The net effect of chronic SSRI administration is more 5-HT release into the synapse, stronger enhancement of 5-HT neurotransmission and consequently stronger activation of postsynaptic 5-HT receptors compared with acute SSRI administration [54] (Fig. 19.3).

Based on these insights into serotonergic neurotransmission, it appears that daily SSRI treatment leads to very relevant stimulation of 5-HT postsynaptic



**Fig. 19.3** Effect of chronic SSRI administration on the serotonergic neuron [47]

receptors and consequent clinically very relevant ejaculation delay after 1–2 weeks of continuous intake [47].

Indeed, animal studies have shown that chronic administration of fluoxetine and paroxetine results in increased values of ejaculation latency time [55–57]. Moreover, human studies have repeatedly shown the clinically very relevant ejaculation delay induced by daily treatment of paroxetine, sertraline and clomipramine.

## 19.15 Conclusion

Of the SSRIs, daily treatment with paroxetine, sertraline, fluoxetine, and citalopram gives rise to a clinically relevant ejaculation delay within 2–3 weeks. On-demand use of SSRIs gives rise to much less ejaculation delay. Both treatment strategies with the classical SSRIs are off-label but are recommended as one of the treatment options of PE by the ISSM guideline for the treatment of PE. Before prescribing an SSRI, patients should be informed about the SSRI-induced side effects, the SSRI-discontinuation syndrome, and the very rare known side effects.

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## 20.1 Introduction

Over the past 20–30 years, the premature ejaculation (PE) treatment paradigm, previously limited to behavioral psychotherapy, has expanded to include drug treatment [1–3]. Animal and human sexual psychopharmacological studies have demonstrated that serotonin and 5-hydroxytryptamine (5-HT) receptors are involved in ejaculation and confirm a role for selective serotonin re-uptake inhibitors (SSRIs) in the treatment of PE [4–6]. Multiple well-controlled evidence-based studies have demonstrated the efficacy and safety of SSRIs in delaying ejaculation, confirming their role as first-line agents for the treatment of lifelong and acquired PE [7]. More recently, there has been increased attention to the psychosocial consequences of PE, its epidemiology, its etiology and its pathophysiology by both clinicians and the pharmaceutical industry [8–13].

PE has been estimated to occur in 4–39 % of men in the general community [12, 14–19] and is often reported as the most common male sexual disorder. There is, however, a substantial disparity between the incidence of PE in epidemiological studies which rely upon either patient self-report of PE and/or inconsistent and poorly validated definitions of PE [11, 13, 19], and that suggested by community-based stopwatch studies of the intravaginal ejaculation latency time (IELT), the time interval between penetration and ejaculation [10]. The latter demonstrates that the distribution of the IELT is positively skewed, with a median IELT of 5.4 min (range, 0.55–44.1 min), decreases with age and varies between countries,

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and supports the notion that IELTs of less than 1 min are statistically abnormal compared to men in the general Western population [10].

The population of men with PE is not homogenous and comprises lifelong (primary) and acquired (secondary) PE [20]. Ejaculatory latency time is probably a genetically determined biological variable which differs between populations and cultures, ranging from extremely rapid through average to slow ejaculation. The view that some men have a genetic predisposition to lifelong PE is supported by animal studies showing a subgroup of persistent rapidly ejaculating Wistar rats [6], an increased familial occurrence of lifelong PE [5], a moderate genetic influence on PE in the Finnish twin study [21], and the recent report that genetic polymorphism of the 5-HT transporter gene determines the regulation of IELT [22]. Acquired PE is commonly due to sexual performance anxiety [23], psychological or relationship problems [23], erectile dysfunction (ED) [24], and occasionally prostatitis [25], hyperthyroidism [26], or during withdrawal/detoxification from prescribed [27] or recreational drugs [28].

The first contemporary multivariate evidence-based definition of lifelong PE was developed in 2008 by a panel of international experts, convened by the International Society for Sexual Medicine (ISSM), who agreed that the diagnostic criteria necessary to define PE are time from penetration to ejaculation, inability to delay ejaculation and negative personal consequences from PE. This panel defined lifelong PE as a male sexual dysfunction characterized by "...ejaculation which always or nearly always occurs prior to or within about 1 min of vaginal penetration, the inability to delay ejaculation, on all or nearly all vaginal penetrations, and the presence of negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy" [29].

The panel concluded that there is insufficient published evidence to propose an evidence-based definition of acquired PE [29]. However, recent published data suggests that men with acquired PE have similar IELTs and report similar levels of ejaculatory control and distress, suggesting the possibility of a single unifying definition of PE [30].

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## 20.2 Pharmacological Treatment of Premature Ejaculation

The off-label use of antidepressant SSRIs including paroxetine, sertraline, fluoxetine, citalopram, and fluvoxamine, and the serotonergic tricyclic clomipramine has revolutionized the approach to and treatment of PE. These drugs block axonal re-uptake of serotonin from the synapse by 5-HT transporters, resulting in enhanced 5-HT neurotransmission, stimulation of postsynaptic membrane 5-HT<sub>2C</sub> receptors and ejaculatory delay. However, the lack of an approved drug and the total reliance on off-label treatment represents a substantial unmet treatment need.

## 20.3 Dapoxetine

Dapoxetine ((+)-(S)-N,N-dimethyl-( $\alpha$ )-[2(1naphthalenyloxy)ethyl]-benzenemethanamine hydrochloride, Janssen Cilag) is the first compound specifically developed for the treatment of PE. Dapoxetine is a potent SSRI (pK<sub>i</sub> = 8nM), structurally similar to fluoxetine (Fig. 20.1) [31]. Equilibrium radioligand binding studies using human cells demonstrate that dapoxetine binds to 5-HT, norepinephrine (NE) and dopamine (DA) re-uptake transporters and inhibits uptake in the following order of potency: NE < 5-HT  $\gg$  DA [32]. Brain positron emission tomography (PET) studies have demonstrated significant displaceable binding of radiolabeled dapoxetine in the cerebral cortex and subcortical gray matter [33].

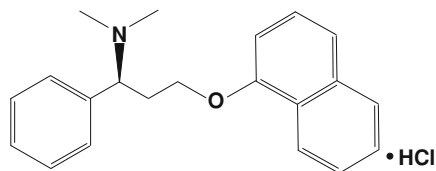
### 20.3.1 Pharmacokinetics and Metabolism

Dapoxetine undergoes rapid absorption and elimination resulting in minimal accumulation and has dose-proportional pharmacokinetics, which are unaffected by multiple dosing and do not vary between ethnic groups (Fig. 20.2) [34–36]. The pharmacokinetic profile of dapoxetine suggests that it is a good candidate for on-demand treatment of PE.

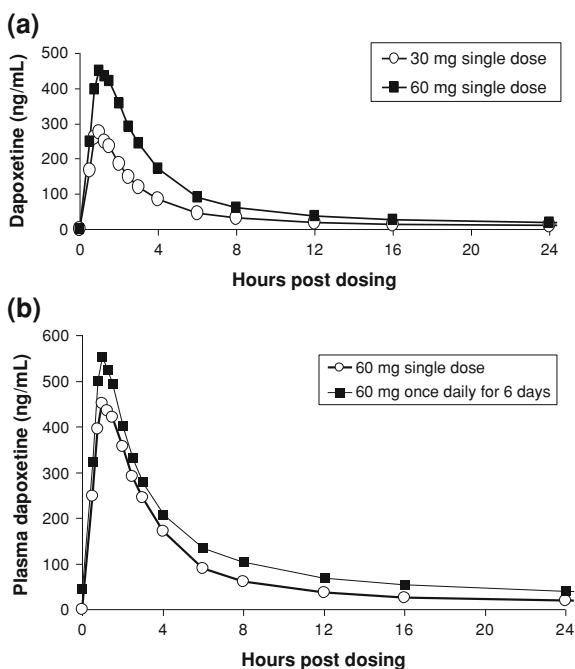
The pharmacokinetics of both single doses and multiple doses over 6–9 days (30, 60, 100, 140, or 160 mg) of dapoxetine have been evaluated. In a randomized, double-blind, placebo-controlled trial, single doses and multiple doses over 6 days of dapoxetine (60, 100, 140, or 160 mg) were administered to 77 healthy male volunteers [34, 35, 37]. Dapoxetine has a  $T_{\max}$  of 1.4–2.0 h and rapidly achieves peak plasma concentration ( $C_{\max}$ ) following oral administration. Both plasma concentration and area under the curve (AUC) are dose dependent up to 100 mg. The mean half-life of dapoxetine after a single dose was estimated using modeling as 1.3–1.5 h. Dapoxetine plasma concentrations rapidly decline to about 5 % of  $C_{\max}$  at 24 h. The terminal half-life of dapoxetine was 15–19 h after a single dose and 20–24 h after multiple doses of 30 and 60 mg, respectively.

In a second pharmacokinetic study, single doses and multiple doses of dapoxetine (30, 60 mg) were evaluated in a randomized, open-label, 2-treatment, 2-period, crossover study of 42 healthy male volunteers over 9 days [36]. Subjects received a single dose of dapoxetine 30 mg or 60 mg on day 1 (single-dose phase) and on days 4–9 (multiple-dose phase). Dapoxetine was rapidly absorbed, with mean maximal plasma concentrations of 297 and 498 ng/ml at 1.01 and 1.27 h after single doses of dapoxetine 30 and 60 mg, respectively (Table 20.1). Elimination of dapoxetine was rapid and biphasic, with an initial half-life of 1.31 and 1.42 h, and a terminal half-life of 18.7 and 21.9 h following single doses of dapoxetine 30 and 60 mg, respectively. The pharmacokinetics of dapoxetine and

**Fig. 20.1** Molecular structure of dapoxetine: (+)-(S)-N,N-dimethyl-( $\alpha$ )-[2(1naphthalenyloxy)ethyl]-benzenemethanamine hydrochloride



**Fig. 20.2** Plasma concentration profiles of dapoxetine after administration of a single dose or multiple doses of dapoxetine 30 mg (a) and dapoxetine 60 mg (b) [36]



its metabolites were not affected by repeated daily dosing and steady state plasma concentrations were reached within 4 days, with only modest accumulation of dapoxetine (approx. 1.5-fold) (Fig. 20.2b).

Food does not have a clinically significant effect on dapoxetine pharmacokinetics. Mean maximal plasma concentrations of dapoxetine decrease slightly after a high-fat meal, from 443 ng/ml (fasted) to 398 ng/ml (fed), and are delayed by approx. 0.5 h following a high-fat meal (1.30 h fasted, 1.83 h fed) [35]. The rate of absorption is modestly decreased, but there is no effect of food on the elimination of dapoxetine or the exposure to dapoxetine, as assessed by the area under the plasma concentration vs. time curve (AUC). The frequency of nausea is decreased after a high-fat meal (24 % [7/29] of fasted subjects and 14 % [4/29] of fed subjects, respectively).

Dapoxetine is extensively metabolized in the liver by multiple isozymes to multiple metabolites, including desmethyldapoxetine, didesmethyldapoxetine and dapoxetine-n-oxide, which are eliminated primarily in the urine [34, 36]. Although didesmethyldapoxetine is equipotent to the parent dapoxetine, its substantially lower plasma concentration, compared with dapoxetine, limits its pharmacological

**Table 20.1** Pharmacokinetics of single doses of dapoxetine (30, 60 mg) and effect of food on pharmacokinetics [34]

	Dapoxetine 30 mg	Dapoxetine 60 mg
$C_{\max}$ (ng/ml)	297	349
$T_{\max}$ (hr)	1.01	1.27
Initial $T^{1/2}$ (h)	1.31	1.42
Terminal $T^{1/2}$ (hr)	18.7	21.0
Effect of High Fat Meal		
$C_{\max}$ (fasted)	–	443
$C_{\max}$ (high fat meal)	–	398
$T_{\max}$ (hr) (fasted)	–	1.30
$T_{\max}$ (hr) (high fat meal)	–	1.83

activity and it exerts little clinical effect, except when dapoxetine is coadministered with CYP3A4 or CYP2D6 inhibitors.

### 20.3.2 Animal Studies

Animal studies using rat experimental models have demonstrated that acute treatment with oral, subcutaneous, and IV dapoxetine inhibits ejaculation at doses as low as 1 mg/kg. Dapoxetine appears to inhibit the ejaculatory reflex at a supraspinal level with the lateral paragigantocellular nucleus (LPGi) as a necessary brain structure for this effect [38].

Clement et al. reported the effects of IV dapoxetine on the emission and ejection phases of ejaculation using p-chloroamphetamine (PCA)-induced ejaculation as an experimental model of ejaculation in anesthetized rats [39]. Intrase seminal vesicle pressure and electromyograms of bulbospongiosus muscles were used as physiologic markers of the emission and ejection phases, respectively. At all doses, dapoxetine significantly reduced the proportion of rats displaying PCA-induced ejaculation in a dose-dependent manner, from 78 % of rats with vehicle to 33, 22, and 13 % of rats following IV dapoxetine 1, 3, and 10 mg/kg, respectively. Dapoxetine significantly decreased the AUC of PCA-induced intrase seminal vesicle pressure increases and bulbospongiosus muscle contractile bursts by 78 % at all doses, and by 91 % following dapoxetine 1 and 10 mg/kg and by 85 % following dapoxetine 3 mg/kg.

Using a different animal experimental model of the ejaculatory reflex in rats, Giuliano et al. measured the latency, amplitude and duration of pudendal motoneuron reflex discharges (PMRD) elicited by stimulation of the dorsal nerve of the penis before and after IV injection of vehicle, dapoxetine or paroxetine (1, 3, and

10 mg/kg) [40]. At the three doses of dapoxetine tested, the latency of PMRD following stimulation of the dorsal nerve of the penis was significantly increased and the amplitude and duration of PMRD decreased from baseline values. Acute IV paroxetine appeared less effective than dapoxetine.

In a behavioral study of sexually experienced rats, Gengo et al. reported that treatment with subcutaneous or oral dapoxetine significantly delayed ejaculation compared to saline control ( $16 \pm 4$  min with subcut. versus  $10 \pm 1$  min in saline controls,  $p < 0.05$ ) when administered 15, but not 60 or 180 min prior to exposure to receptive females [41]. The greatest delay in ejaculatory latency was observed in animals with shorter baseline latencies and oral dapoxetine did not affect the latency in rats with a baseline latency longer than 10 min.

### 20.3.3 Clinical Efficacy

The results of two phase 2 and five phase 3 trials have been published [42–47].

#### 20.3.3.1 Phase 2 Trials

Dapoxetine dose-finding data has been derived from two multicenter phase 2 studies and used to determine the appropriate doses for phase 3 studies. Both studies used a randomized, placebo-controlled, double-blind, 3-period, crossover study design and subjects with PE diagnosed according to DSM-IV criteria and a baseline IELT  $< 2$  min on 75 % of  $\geq 4$  sexual intercourse events. Study drug was administered 1–2 h prior to planned sexual intercourse and subjects were required to attempt intercourse at least twice a week. The primary outcome measure was the partner-operated stopwatch IELT.

In study 1, 128/157 randomized subjects completed the study [43]. Subjects were randomized to receive dapoxetine 20 mg, dapoxetine 40 mg, or placebo for 4 weeks with no washout period between treatment arms. Baseline IELT (mean baseline IELT = 1.34 min.) was estimated by patient recall. In study 2, 130/166 randomized subjects completed the study [42]. Subjects were randomized to receive dapoxetine 60 mg, dapoxetine 100 mg, or placebo for 2 weeks, separated by a 3 day washout period. Baseline IELT (mean baseline IELT = 1.01 min.) was measured by partner operated stopwatch.

The intention-to-treat analysis of both studies demonstrated that all four doses of dapoxetine are effective, superior to placebo and increased IELT 2.0–3.2-fold over baseline in a dose-dependent fashion (Table 20.2) [42, 43]. The magnitude of effect of dapoxetine 20 mg on IELT was small. The most commonly reported adverse events (AEs) were nausea, diarrhoea, headache, dizziness. The incidence of most AEs appeared to be dose-dependent. The most common adverse event was nausea and occurred in 0.7, 5.6, and 16.1 % of subjects with placebo, dapoxetine 60 mg and dapoxetine 100 mg, respectively. Overall, dapoxetine 60 mg was better tolerated than dapoxetine 100 mg. Based on these results, doses of 30 mg and 60 mg were chosen for further investigation in phase 3 efficacy and safety studies.

**Table 20.2** Results of dapoxetine phase 2 and 3 studies [42]

	Phase- 2 studies				Phase- 3 studies (pooled)				
	Study 1	Study 2			Study 1-5				
Age range (years)	18-60	18-65			18-82				
Inclusion criteria, IELT	DSM-IV TR, <2 min estimated	DSM-IV TR, <2 min by stopwatch			DSM-IV TR, <2 min by stopwatch				
Number (subjects)	157	166			6,081				
Treatment (period)	4 weeks per treatment	2 weeks per treatment			9-24 weeks, parallel, fixed dose				
Washout (period)	None	72 h			None				
Dapoxetine dose	20 mg (n = 145)	40 mg (n = 141)	Placebo (n = 142)	60 mg (n = 144)	100 mg (n = 155)	Placebo (n = 145)	30 mg (n = 1,613)	60 mg (n = 1,611)	Placebo (n = 1,608)
Mean baseline IELT	1.34	1.34	1.34	1.01	1.01	1.01	0.9	0.9	0.9
Mean treatment IELT	2.72*	3.31†	2.22	2.86†	3.24†	2.07	3.1†	3.6†	1.9
IELT fold increase	2.0	2.5	1.7	2.9	3.2	2.0	2.5	3.0	1.6

(continued)



Table 20.2 (continued)

	Phase- 2 studies				Phase- 3 studies (pooled)				
	Study 1		Study 2		Study 1–5				
“Good/very good” control									
Baseline (%)	–	–	–	–	–	–	0.3	0.6	0.5
Study end (%)	–	–	–	–	–	–	11.2 <sup>†</sup>	26.2 <sup>†</sup>	30.2
“Good/very good” satisfaction									
Baseline (%)	–	–	–	–	–	–	15.5	14.7	15.5
Study end (%)	–	–	–	–	–	–	24.4 <sup>†</sup>	37.9 <sup>†</sup>	42.8
“Quite a bit/extreme” personal distress									
Baseline (%)	–	–	–	–	–	–	73.5	71.3	69.7
Study end (%)	–	–	–	–	–	–	41.9 <sup>†</sup>	28.2 <sup>†</sup>	22.2
“Quite a bit/extreme” interpersonal distress									
Baseline (%)	–	–	–	–	–	–	38.5	38.8	36.1
Study end (%)	–	–	–	–	–	–	23.8 <sup>†</sup>	6.0 <sup>†</sup>	12.3
Discontinuation due to AE	0	2	0	0	0	9	3.5	8.8	1.0

\* $p = 0.042$ , <sup>†</sup> $p < 0.0001$  vs. placebo

### 20.3.3.2 Phase 3 Trials

The five randomized, placebo-controlled, phase 3 clinical trials comprised two identically designed studies conducted in the United States [44], an international study conducted in 16 countries in Europe, Argentina, Brazil, Canada, Israel, Mexico, and South Africa [45], a North American safety study [46], and an Australian and Asia–Pacific country study [47]. The treatment period ranged from 9–24 weeks. Overall, 6,081 men with a mean age of 40.6 years (range, 18–82 years) from 32 countries were enrolled with 4,232 (69.6 %) subjects completing their study (Table 20.2). This is the largest efficacy and safety database for any agent intended to treat PE.

The DSM-IV-TR criteria and a baseline IELT  $< 2$  min on 75 % of  $\geq 4$  sexual intercourse events were used to enroll subjects in four of the five phase 3 studies [44, 45, 47]. Baseline average IELT was 0.9 min for subjects overall. However, 58 % of subjects also met the ISSM criteria for lifelong PE [48]. Subjects reported having had PE for an average of 15.1 years, with 64.9 % of subjects classified by the investigator as having lifelong PE at screening. Demographic and baseline characteristics were similar across studies allowing an analysis of pooled phase 3 data.

Outcome measures included stopwatch IELT, the premature ejaculation profile (PEP), a validated tool that includes measures of perceived control over ejaculation, satisfaction with sexual intercourse, ejaculation-related personal distress, ejaculation-related interpersonal difficulty [49], and subject response to a multi-dimensional clinical global impression of change (CGIC) in PE question: “Compared to the start of the study, would you describe your PE problem as much worse, worse, slightly worse, no change, slightly better, better, or much better?”

An analysis of pooled phase 3 data confirms that dapoxetine 30 and 60 mg increased IELT and improved patient reported outcomes (PROs) of control, ejaculation-related distress, interpersonal distress and sexual satisfaction, compared to placebo. Efficacy results were similar among each of the individual trials and for a pooled analysis, indicating that dapoxetine is consistently more efficacious than placebo regardless of a subject’s demographic characteristics.

Increases in mean average IELT (Table 20.2) were significantly greater with both doses of dapoxetine vs. placebo beginning with the first dose of study medication (dapoxetine 30 mg, 2.3 min; dapoxetine 60 mg, 2.7 min; placebo, 1.5 min;  $p < 0.001$  for both) and at all subsequent time points (all  $p < 0.001$ ). By week 12, mean average IELT had increased to 3.1 and 3.6 min. with dapoxetine 30 and 60 mg, respectively (versus 1.9 min. with placebo;  $p < 0.001$  for both; Table 20.2).

However, as IELT in subjects with PE is distributed in a positively skewed pattern, reporting IELTs as arithmetic means may overestimate the treatment response and the geometric mean IELT is more representative of the actual treatment effect [50]. Geometric mean average IELT increased from approx. 0.8 min at baseline to 2.0 and 2.3 min with dapoxetine 30 and 60 mg, respectively (vs. 1.3 min with placebo;  $p < 0.001$  for both). Furthermore, as subjects have a broad range of baseline IELT values (0–120 s), reporting mean raw trial-end IELT

may be misleading by incorrectly suggesting all subjects respond to that extent. The trial-end fold increase in geometric mean IELT compared to baseline is more representative of true treatment outcome and must be regarded as the contemporary universal standard for reporting IELT. Geometric mean IELT fold increases of 2.5 and 3.0 were observed with dapoxetine 30 and 60 mg, respectively, vs. 1.6 for placebo ( $p < 0.0001$  for both, Table 20.2). Fold increases were greater among men with very short baseline IELT values, suggesting that dapoxetine may be a useful treatment option for men with severe forms of PE, including anteportal ejaculation. Subjects with baseline average IELTs of 0.5–1.0 min, and  $\leq 0.5$  min showed fold increases of 2.4 and 3.4, respectively, with dapoxetine 30 mg, and 3.0 and 4.3 with dapoxetine 60 mg compared to 1.6 and 1.7, respectively, with placebo treatment.

Control over ejaculation was reported as “good” or “very good” by  $<1.0$  % of subjects at baseline and improved to 26.2 % and 30.2 % with dapoxetine 30 and 60 mg, respectively, vs. 11.2 % with placebo by week 12 ( $p < 0.001$  for both; Table 20.2). Approximately 15 % of subjects reported “good” or “very good” satisfaction with sexual intercourse at baseline; by week 12, this increased to 37.9 % and 42.8 % with dapoxetine 30 and 60 mg, respectively, versus 24.4 % with placebo ( $p < 0.001$  for both; Table 20.2). While approx. 70 % of subjects across groups reported “quite a bit” or “extremely” for their level of ejaculation-related personal distress at baseline, by week 12 this decreased to 28.2 % and 22.2 % with dapoxetine 30 and 60 mg, respectively, vs. 41.9 % with placebo ( $p < 0.001$  for both; Table 20.2). Approximately one-third of subjects reported “quite a bit” or “extremely” for their level of ejaculation-related interpersonal difficulty at baseline; by week 12 this decreased to 16.0 % and 12.3 % with dapoxetine 30 and 60 mg, respectively, vs. 23.8 % with placebo ( $p < 0.001$  for both; Table 20.2).

A significantly greater percentage of subjects reported that their PE was “better” or “much better” at week 12 with dapoxetine 30 (30.7 %) and 60 mg (38.3 %) than with placebo (13.9 %;  $p < 0.001$  for both). Similarly, 62.1 % and 71.7 % of subjects reported that their PE was at least “slightly better” at week 12 with dapoxetine 30 and 60 mg, respectively, compared to 36.0 % with placebo ( $p < 0.001$  for both).

Several studies have reported that the effects of PE on the partner are integral to understanding the impact of PE on the male and on the sexual relationship [9, 51–53]. If PE is to be regarded as a disorder that affects both subjects and their partners, partner PROs must be regarded as important measures in determining PE severity and treatment outcomes. Female partners reported their perception of the man’s control over ejaculation and CGIC, their own satisfaction with sexual intercourse, interpersonal difficulty and personal distress. A significantly greater percentage of female partners reported that the man’s control over ejaculation was “good” or “very good” with dapoxetine 30 (26.7 %) and 60 mg (34.3 %) vs. placebo at week 12 (11.9 %;  $p < 0.0001$  for both). Similarly, a significantly greater percentage of female partners reported that the man’s PE was at least “better” with dapoxetine 30 (27.5 %) and 60 mg (35.7 %) vs. placebo (9.0 %;  $p < 0.001$  for both). A greater percentage of female partners reported that their own satisfaction with sexual intercourse was “good” or “very good” with dapoxetine 30 (37.5 %) and 60 mg

(44.7 %) vs. placebo (24.0 %;  $p < 0.001$  for both). Finally, there were significant decreases in both ejaculation-related personal distress and interpersonal difficulty in female partners of men treated with dapoxetine 30 and 60 mg vs. placebo ( $p < 0.001$  for both) [45].

## 20.4 Safety and Tolerability

Across trials, dapoxetine 30 and 60 mg were well tolerated with a low incidence of severe AEs. More than 50 % of all phase 3 AEs were reported at the first follow-up visit after 4 weeks of treatment and typically included gastrointestinal and central nervous system symptoms. The most frequently reported AEs were nausea, diarrhea, headache, dizziness, insomnia, somnolence, fatigue, and nasopharyngitis (Table 20.3). Unlike other SSRIs used to treat depression, which have been associated with high incidences of sexual dysfunction, [54, 55] dapoxetine was associated with low rates of sexual dysfunction. The most common AE in this category was ED (placebo, 1.6 %; dapoxetine 30 mg prn, 2.3 %; dapoxetine 60 mg prn, 2.6 %; dapoxetine 60 mg qd; 1.2 %). AEs were dose-dependent and generally coincided with the pharmacokinetic profile of dapoxetine, occurring at the approximate time of peak serum concentrations [ $\sim 1.3$  h] and lasting for approx. 1.5 h. Most AEs were mild to moderate in severity, and few subjects across groups reported severe ( $\sim 3$  %) or serious ( $\leq 1$  %) AEs. Adverse effects led to the discontinuation of 1.0, 3.5, 8.8, and 10.0 % of subjects with placebo, dapoxetine 30 mg prn, dapoxetine 60 mg prn, and dapoxetine 60 mg qd, respectively.

### 20.4.1 Cardiovascular Safety

The cardiovascular assessment of dapoxetine was conducted throughout all stages of drug development, with findings from preclinical safety pharmacology studies, phase 1 clinical pharmacology studies investigating the effect of dapoxetine on QT/corrected QT (QTc) intervals in healthy men, and phase 3, randomized, placebo-controlled studies evaluating the safety (and efficacy) of the drug. Preclinical safety pharmacology studies did not suggest an adverse electrophysiologic or hemodynamic effect with concentrations of dapoxetine up to two-fold greater than recommended doses [56]. Phase 1 clinical pharmacology studies demonstrated that dapoxetine did not prolong the QT/QTc interval and had neither clinically significant electrocardiographic effects nor evidence of delayed repolarization or conduction effects, with dosing up to four-fold greater than the maximum recommended dosage [57]. Phase 3 clinical studies of dapoxetine in men with PE indicated that dapoxetine was generally safe and well tolerated with the dosing regimens used (30 mg and 60 mg as required) [44–47, 58, 59].

Special attention was given to cardiovascular-related safety issues since syncope has been reported with marketed SSRIs and there were five cases of vasovagal syncope during dapoxetine phase 1 studies [57]. Events of syncope were reported

**Table 20.3** Treatment-emergent adverse events occurring in  $\geq 2$  % of subjects in pooled phase 3 data [44]

Adverse event n (%)	Placebo (n = 1,857)	Dapoxetine 30 mg prn (n = 1,616)	Dapoxetine 60 mg prn (n = 2,106)	Dapoxetine 60mg qd (n = 502)	Total dapoxetine (n= 4,224)
Nausea	41 (2.2)	178 (11.0)	467 (22.2)	86 (17.1)	731 (17.3)
Dizziness	40 (2.2)	94 (5.8)	230 (10.9)	75 (14.9)	399 (9.4)
Headache	89 (4.8)	91 (5.6)	185 (8.8)	56 (11.2)	332 (7.9)
Diarrhea	32 (1.7)	56 (3.5)	145 (6.9)	47 (9.4)	248 (5.9)
Somnolence	10 (0.5)	50 (3.1)	98 (4.7)	18 (3.6)	166 (3.9)
Fatigue	23 (1.2)	32 (2.0)	86 (4.1)	46 (9.2)	164 (3.9)
Insomnia	28 (1.5)	34 (2.1)	83 (3.9)	44 (8.8)	161 (3.8)
Nasopharyngitis	43 (2.3)	51 (3.2)	61 (2.9)	17 (3.4)	129 (3.1)

during the clinical development program, with the majority occurring during study visits (on site) on day 1 following administration of the first dose when various procedures (e.g., orthostatic maneuvers, venipunctures) were performed, suggesting that the procedures contributed to the incidence of syncope. Across all five trials, syncope (including loss of consciousness) occurred in 0.05, 0.06, and 0.23 % of subjects with placebo, dapoxetine 30 mg, and dapoxetine 60 mg, respectively. Syncope was not associated with symptomatic or sustained tachyarrhythmia during Holter ECG monitoring in 3,353 subjects [45–47, 58]. The incidence of Holter-detected nonsustained ventricular tachycardia was similar between dapoxetine-treated subjects and those who received placebo, suggesting that dapoxetine is not arrhythmogenic and that tachyarrhythmia is thus unlikely to be the underlying mechanism responsible for syncope seen in the dapoxetine clinical program. There was a statistically nonsignificant increase in the number of single ventricular and supraventricular ectopic beats in the dapoxetine groups, but this finding is not considered clinically meaningful, given the generally benign nature of ventricular ectopic beats occurring on their own in the absence of structural heart disease [60]. Syncope appeared to be vasovagal in nature and generally occurred within 3 h of dosing. Syncope was more common with the first dose of dapoxetine, occurring in 0.19 % of subjects with the first dose of dapoxetine vs. 0.08 % with a subsequent dose. Syncope occurred more frequently when dapoxetine was administered onsite (0.31 %) vs. offsite (0.08 %), which may relate to onsite study-related procedures such as venipuncture or orthostatic maneuvers that are known to be associated with syncope. This was consistent with previous reports showing that these and similar factors contribute to or trigger vasovagal syncope. Findings of the dapoxetine development program demonstrate that dapoxetine is associated with vasovagal-mediated (neurocardiogenic) syncope. No other associated significant cardiovascular adverse events were identified.

### 20.4.2 Neurocognitive Safety

Studies of SSRIs in patients with major psychiatric disorders, such as depression or obsessive compulsive disorder, suggest that SSRIs are potentially associated with certain safety risks, including neurocognitive adverse effects such as anxiety, hypomania, akathisia, and changes in mood [61–64]. Systematic analysis of randomized controlled studies suggested a small increase in the risk of suicidal ideation or suicide attempts in youth [64] but not adults [64, 65]. However, these SSRI safety risks have not been previously evaluated in men with PE. In the North American safety study [46] and the International Study [45], SSRI-related neurocognitive side effects such as changes in mood, anxiety, akathisia or suicidality or sexual dysfunction were evaluated using a range of validated outcome measures including the Beck Depression Inventory II (BDI-II), the Montgomery–Asberg Depression Rating Scale (MADRS), the Hamilton Anxiety Scale (HAM-A), the Barnes Akathisia Rating Scale (BARS), and the International Index of Erectile Function (IIEF). Dapoxetine had no effect on mood, and was not associated with anxiety, akathisia, or suicidality.

### 20.4.3 Withdrawal Syndrome

Chronic SSRI treatment for psychiatric conditions is known to predispose patients to withdrawal symptoms if medication is suspended abruptly [62, 66]. The SSRI withdrawal syndrome is characterized by dizziness, headache, nausea, vomiting, and diarrhoea and occasionally agitation, impaired concentration, vivid dreams, depersonalization, irritability, and suicidal ideation [67, 68]. The risk of dapoxetine withdrawal syndrome was assessed with the discontinuation-emergent signs and symptoms (DESS) checklist following a 1-week withdrawal period during which subjects were re-randomized to either continue treatment with on-demand dapoxetine, daily dapoxetine or placebo or to switch from dapoxetine to placebo. The DESS comprises 43 possible withdrawal signs and symptoms, each rated and scored as new/old, worse/unchanged improved, or absent. There was a low incidence of SSRI withdrawal syndrome across treatment groups that was similar among patients who continued to take dapoxetine or placebo and those who switched to placebo during a 1-week withdrawal period. In the International study, the incidence of discontinuation syndrome was 3.0, 1.1, and 1.3 % for those continuing to take dapoxetine 30, 60 mg prn and placebo, respectively, and 3.3 % for those who switched from dapoxetine 60 mg prn to placebo [45]. No subjects switching from dapoxetine 30 mg prn to placebo in this study showed evidence of the discontinuation syndrome. Dapoxetine is the only SSRI for which these symptoms have been systematically evaluated in a PE population. The lack of chronic serotonergic stimulation with on-demand dapoxetine precludes serotonin receptor desensitization and the down-regulation of post-synaptic serotonin receptors that typically occurs with chronic SSRI use, such that on-demand dosing for PE may minimize the risk of withdrawal symptoms [69].

## 20.5 Drug Interactions

No drug–drug interactions associated with dapoxetine have been reported. Co-administration of dapoxetine with ethanol did not produce significant changes in dapoxetine pharmacokinetics [70]. Mean peak plasma concentrations of dapoxetine, its metabolites, and ethanol did not significantly change with coadministration and there were no clinically significant changes in ECGs, clinical laboratory results, physical examination, and no serious AEs. Dapoxetine pharmacokinetics were similar with administration of dapoxetine alone and coadministration of tadalafil or sildenafil; the three treatments demonstrated comparable plasma concentration profiles for dapoxetine [71]. Dapoxetine absorption was rapid, and was not affected by coadministration of tadalafil or sildenafil. Following the peak (i.e.,  $C_{\max}$ ), dapoxetine elimination was rapid and biphasic with all three treatments, with an initial half-life of 1.5–1.6 h and a terminal half-life of 14.8–17.1 h. Plasma dapoxetine concentrations were less than 5 % of  $C_{\max}$  by 24 h. Dapoxetine  $AUC_{\text{inf}}$  remained unchanged when tadalafil was administered concomitantly; concomitant administration of sildenafil increased the dapoxetine  $AUC_{\text{inf}}$  by 22 %. However, this was not regarded as clinically important as dapoxetine pharmacokinetics were similar. Dapoxetine had no clinically important effects on the pharmacokinetics or orthostatic profile of the adrenergic alpha-antagonist tamsulosin in men on a stable tamsulosin regimen [72].

Coadministered potent CYP2D6 (desipramine, fluoxetine) or CYP3A4 (ketoconazole) inhibitors may increase dapoxetine exposure by up to two-fold. Coadministration of dapoxetine and potent CYP3A4 such as ketoconazole is contraindicated. Caution should be exercised in coadministration of dapoxetine and moderate CYP3A4 inhibitors and potent CYP2D6 inhibitors such as fluoxetine. Doses up to 240 mg, four-fold the recommended maximum dose, were administered to healthy volunteers in the phase 1 studies and no unexpected AEs were observed.

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## 20.6 Dosage and Administration

The recommended starting dose for all patients is 30 mg, taken as needed approx. 1 to 3 h prior to sexual activity. The maximum recommended dosing frequency is once every 24 h. If the effect of 30 mg is insufficient and the side effects are acceptable, the dose may be increased to the maximum recommended dose of 60 mg.

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## 20.7 Regulatory Status

Dapoxetine was originally developed by Eli Lilly and Co. as an antidepressant. The patent was sold to Johnson & Johnson in December 2003. In 2004, a New Drug Application (NDA) for dapoxetine was submitted to the FDA by the ALZA Corporation, a division of Johnson & Johnson, for the treatment of PE. The FDA

issued a “not approvable” letter for dapoxetine in October 2005, requiring additional clinical efficacy and safety data. Following completion of three additional efficacy/safety 3 studies, an expanded dossier of safety and efficacy data was submitted to health authorities and dapoxetine received approval in Sweden, Finland, Austria, Portugal, Germany, Italy, Spain, Mexico, South Korea, and New Zealand in 2009/2010. Approvals for dapoxetine are also anticipated in other European countries. In addition, filings for approval have been submitted in several other countries. Dapoxetine is not approved in the USA where phase 3 study continues.

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## 20.8 The Place of Dapoxetine in the Treatment of Premature Ejaculation

Men complaining of PE should be evaluated with a detailed medical and sexual history, a physical examination and appropriate investigations to establish the true presenting complaint, and identify obvious biological causes such as ED or genital/lower urinary tract infection. The multivariate evidence-based ISSM definition of lifelong PE provides the clinician a discriminating diagnostic tool and should form the basis for the office diagnosis of lifelong PE [73]. Recent data indicate that men with acquired PE have similar IELTs and report similar levels of ejaculatory control and distress, suggest the possibility of a single unifying definition of PE [30].

The dapoxetine phase 2 and 3 studies' enrollment criteria may result in a subject population which is not totally representative of men who actively seek treatment for PE. The use of the authority-based and not evidence-based DSM-IV-TR and baseline IELT74]. This potential for errors in the diagnosis of PE was demonstrated in two recent observational studies in which PE was diagnosed solely by the application of the DSM-IV-TR definition [11, 75]. In one study, the IELT range extended from 0 to almost 28 min in DSM-IV-TR diagnosed PE, with 48 % of subjects having an IELT in excess of 2 min. In addition, several studies suggest that 80–90 % of men seeking treatment for lifelong PE ejaculate within 1 min [76–78]. These data form the basis for the operationalization of IELT in the ISSM definition of lifelong PE to “...less than about one minute...” [29]. However, in the 58 % of phase 3 subjects who met the ISSM criteria for lifelong PE, IELT fold increases were superior to and PRO/CGIC scores equivalent to the entire study population, suggesting that the flawed inclusion criteria did not affect the study conclusions.

Effective pharmacological treatment of PE has previously been limited to daily off-label treatment with paroxetine 10–40 mg, clomipramine 12.5–50 mg, sertraline 50–200 mg, fluoxetine 20–40 mg. and citalopram 20–40 mg (Table 20.4) [79]. Following acute on-demand administration of an SSRI, increased synaptic 5-HT neurotransmission is down-regulated by presynaptic autoreceptors to prevent over-stimulation of postsynaptic 5-HT<sub>2C</sub> receptors. However, during chronic daily SSRI administration, a series of synaptic adaptive processes which may include presynaptic autoreceptor desensitization, greatly enhances synaptic 5-HT neurotransmission [80]. As such, daily dosing of off-label antidepressant SSRIs is likely



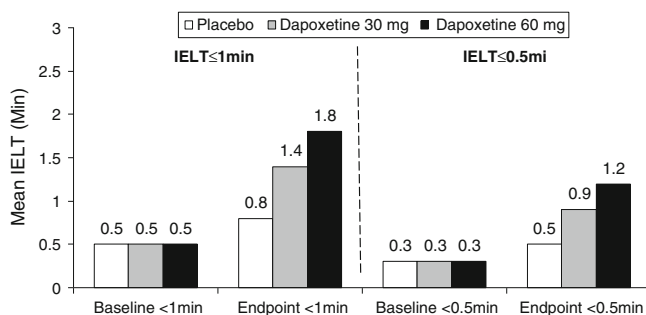
**Table 20.4** Comparison of fold increases in IELT with meta-analysis data for daily paroxetine, sertraline, fluoxetine, clomipramine [7] and phase 3 data for on-demand dapoxetine [44]

Drug	Regulatory approval for PE	Dose	Mean fold increase in IELT
SSRIs antidepressant			
Paroxetine	No	10–40 mg/day	8.8
Sertraline	No	25–200 mg/day	4.1
Fluoxetine	No	5–20 mg/day	3.9
Serotonergic tricyclic antidepressant			
Clomipramine	No	25–50 mg/day	4.6
Dapoxetine	Yes	30–60 mg 1–3 h prior to intercourse	2.5–3.0
Placebo	–	–	1.4

to be associated with more ejaculatory delay than on-demand dapoxetine although well-designed controlled head-to-head comparator studies have not been conducted. A meta-analysis of published efficacy data suggests that paroxetine exerts the strongest ejaculation delay, increasing IELT approx. 8.8 fold over baseline [81]. Whilst daily dosing of off-label antidepressant SSRIs is an effective treatment for men with anteportal or severe PE with very short IELTs. The higher fold increases of dapoxetine in this patient population suggest that dapoxetine is also a viable treatment option (Fig. 20.3). There is currently no published data which identify a meaningful and clinically significant threshold response to treatment. The point at which the IELT fold-increase achieved by intervention is associated with a significant reduction in personal distress probably represents a measure of intervention success. These data is currently not available but the author’s anecdotal impression, derived from treatment of patients, suggests that a 3–4 fold-increase in IELT, as seen with dapoxetine, represents the threshold of intervention success. Similarly, there are no current data to suggest that fold increases above this threshold are associated with higher levels of patient satisfaction.

Dapoxetine can be used in men with either lifelong or acquired PE. Treatment should be initiated at a dose of 30 mg and titrated to a maximum dose of 60 mg based upon response and tolerability. In men with acquired PE and comorbid ED, dapoxetine can be co-prescribed with a phosphodiesterase type-5 inhibitor drug.

The criteria for the ideal PE drug remains controversial. However, many men will prefer the convenience of “on-demand” dosing of dapoxetine compared to daily dosing. Men who infrequently engage in sexual intercourse may prefer on-demand treatment, whilst men in established relationships may prefer the convenience of daily medication. Well-designed preference trials will provide additional detailed insight into the role of on-demand dosing.



**Fig. 20.3** IELT at endpoint for baseline IELT  $\leq 1$  min and  $\leq 0.5$  min for placebo, dapoxetine 30 mg (IELT fold increase  $< 0.5$  min 3.4,  $< 1$  min 2.7), and dapoxetine 60 mg (IELT fold increase  $< 0.5$  min 4.3,  $< 1$  min 3.4) [58]

As any branch of medicine evolves, many drugs are routinely used “off-label” but may be regarded as part of standard care for a condition. Although off-label drug use is common, it is often not supported by strong evidence [82]. Although the methodology of the initial off-label daily SSRI treatment studies was poor, later double—blind and placebo-controlled studies of relatively small study populations ( $< 100$  subjects) confirmed their efficacy [81, 83–87]. However, few studies included control over ejaculation and PE-related distress, or both as enrolment criteria or used validated patient-reported outcome instruments to evaluate these parameters. Furthermore, reporting of treatment-related adverse effects has been inconsistent across these trials. Unlike dapoxetine, most off-label SSRI drugs have not been specifically evaluated for known class-related safety effects including potential for withdrawal effects, treatment-emergent suicidality, and effects on mood and affect in men with PE. These studies fail to provide the same robust level of efficacy and safety evidence found in the dapoxetine phase 3 study populations of over 6,000 subjects. Although regulatory approval is not always synonymous with superior treatment outcomes, it does assure prescribers that expert and regulatory peer review has demonstrated drug efficacy and safety.

## 20.9 Conclusions

Dapoxetine is an effective, safe and well-tolerated on-demand treatment for PE and, in the opinion of the author, is likely to fulfil the treatment needs of most patients. Although daily off-label antidepressant SSRI are effective treatments for PE, supportive studies are limited by small study populations, infrequent use of PROs of control, distress, and satisfaction as outcome measures and inconsistent reporting of known SSRI class-related safety effects. Currently, dapoxetine has the largest efficacy and safety database for use in men with PE, and it is the only agent for which SSRI class-related effects have been studied in a PE population.

**Conflict of Interest** Associate Professor McMahon is an investigator, member of an advisory board and speaker's panel for Janssen-Cilag and Bayer Schering.

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# Use of Local Anesthetics in the Treatment of Premature Ejaculation

Wallace Dinsmore and Emma McCarty

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## 21.1 Current Approaches to Treatment

There are a range of treatment options for men with PE, directed at different components of the complex mechanism of the ejaculatory process. These include behavioral therapy, systemic treatments, and topical therapies. However, there are currently no pharmacological agents approved for use in PE, and all drugs have to be administered off-label.

Current recommendations from the American Urological Association (AUA) [1] and the second International Consultation on Sexual Dysfunctions (ICSD) [2] recognize that PE is a self-reported diagnosis and emphasize the importance of obtaining a comprehensive sexual history when making a diagnosis; no laboratory or physiological tests are usually required. It is recommended that clinicians also determine if there is concomitant ED and, if present, it should be treated first [2].

The management algorithm for PE produced by the ICSD recommends pharmacotherapy with a selective serotonin reuptake inhibitor (SSRI) or topical anesthetics as the first-line treatment in patients with lifelong PE and as second-line treatment in patients with acquired PE [2]. In reality, pharmacotherapy is likely to be used first-line in both cases, owing to the limited availability of skilled sex therapists and relationship counsellors.

The choice between oral therapy with SSRIs (daily or as-needed), or the use of a topical agent is a decision to be made jointly by the patient or couple and the physician after the physician has ascertained their desires and expectations. If acceptable to the patient or couple, a trial of a topical agent could be a prudent first step, owing to the favorable risk/benefit ratio of these products. This is reflected in

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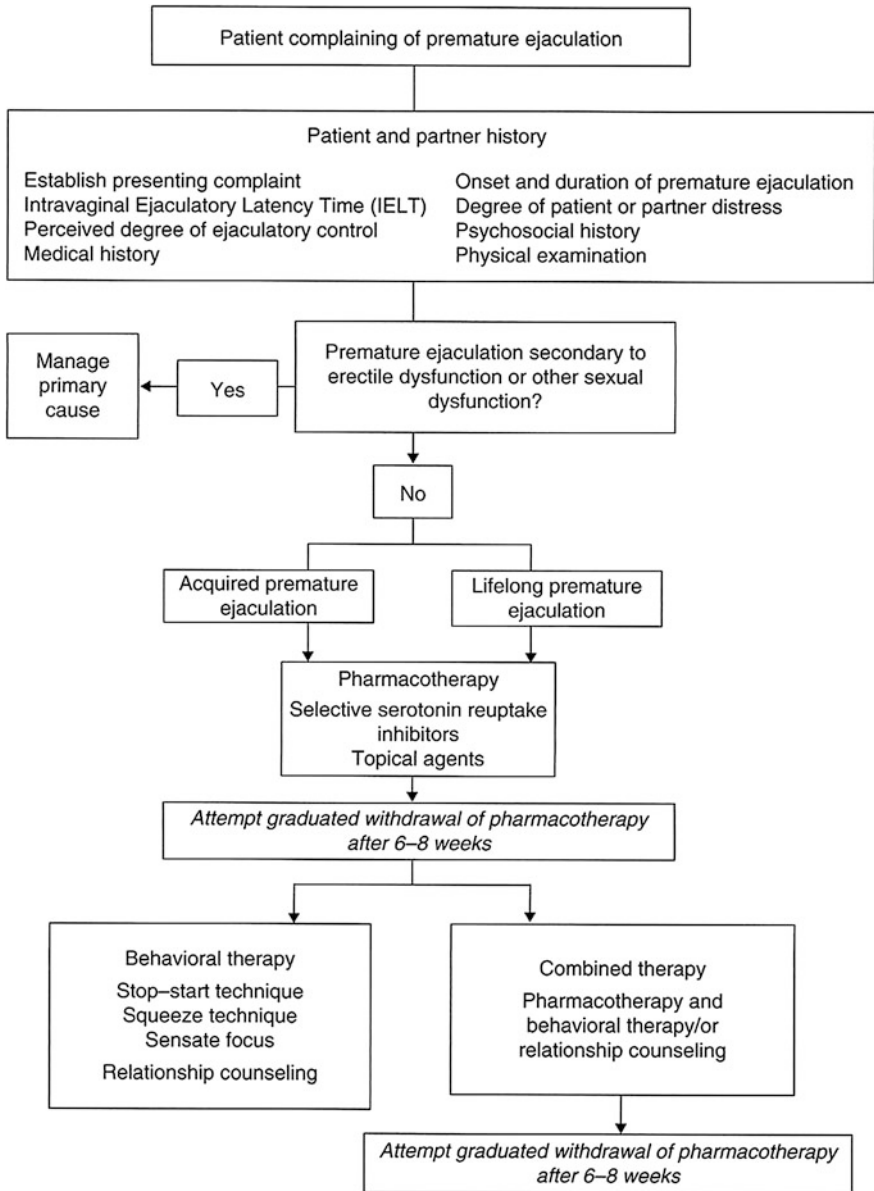


Fig. 21.1 Management algorithm for PE modified from Lue et al. [2]

the treatment algorithm in Fig. 21.1, which is modified from the ICSD recommendations [2].

Delayed ejaculation is a common side-effect of many psychotropic or antidepressant drugs, in particular of the serotonergic tricyclic antidepressant clompiramine and the SSRIs fluoxetine, paroxetine, and sertraline [3–5]. These drugs, which are primarily indicated for the treatment of depression, can increase the level of serotonin in the brain, inhibiting the ejaculatory reflex center, and they can prolong IELT for several minutes.

Dosing levels of SSRIs are generally lower for PE than for depression, and various dosing regimens have been tested (including continuous, daily, or situational). Despite this, the adverse-event profile appears to be similar; adverse events include dry mouth, drowsiness, nausea, and reduced libido [6].

There is also the potential for development of a serious drug interaction that can lead to serotonergic syndrome, which manifests itself as headache, nausea, sweating, and dizziness in mild cases and as hyperthermia, rigidity, and delirium in severe cases [6]. Many physicians may consider the side-effects hard to justify for the treatment of PE, in which the primary outcome is patient satisfaction, although the AUA has suggested that the level of adverse events is acceptable for the benefit derived by the patient with PE, and the type and rate of occurrence of side-effects also appears to be acceptable to most patients [6].

Dapoxetine, a novel SSRI, is the first oral agent specifically developed for the management of PE and it has been shown to be effective, well tolerated, and suitable for on-demand use [7]. Further research with this drug continues despite the US Food and Drug Administration's non-approval of dapoxetine for the treatment of PE in 2005 [7]. The drug (as Priligy) has been approved in several European countries.

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## 21.2 Rationale for the Use of Local Anesthetics

There are a variety of theories concerning the etiology of PE [2].

Historically, PE was considered a learned behavior and, as a result, behavioral therapy was the standard treatment. However, it is now generally accepted that both biological and psychological factors are important in the etiology of PE. Men with PE appear to have a heightened sensory response to penile stimulation, with a vibration threshold significantly lower than normal individuals [8, 9]. They also generally exhibit other abnormal reflex pathways for the ejaculatory process leading to the conclusion that there is a link between penile hypersensitivity and premature ejaculation [10]. Considering these sensory differences, drugs that selectively produce some degree of penile desensitization or act within the

afferent–efferent reflex could provide effective therapy. Thus, reducing the sensitivity of the glans penis with local anesthetics could delay ejaculatory latency without adversely affecting the sensation of ejaculation [10]. In fact the use of topical anesthetic creams was first described by Schapiro back in 1943 [11].

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## **21.3 Current Status of Local Anesthetic Treatments for PE**

Apart from the limited approval of dapoxetine (Priligy), there is no approved pharmacological therapy for PE. This has led to the use of over-the-counter remedies and the ‘off-label’ use of local anesthetics. However, there are also novel desensitizing agents in development specifically designed to treat PE.

Compared with oral treatments for PE, topical treatments are appealing in that they can be applied on an as-needed basis and because systemic sideeffects are likely to be minimal. However, the application of a desensitizing agent to the penis does have the potential for some degree of penile hypoesthesia and theoretically, transvaginal contamination and female genital hypoesthesia as side-effects.

An important consideration for physician and patient, in this era of evidence-based medicine, is whether there is adequate supportive clinical data for the use of these off-label and novel topical agents. The efficacy and adverse-events profiles for topical treatments, where available, are discussed in the following sections.

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## **21.4 Over-the-Counter Topical Treatments**

### **21.4.1 Lidocaine Spray**

Lidocaine 9.6 % spray, marketed as ‘Studd 100’ or ‘Premjact’, has been available over the counter for over 25 years in some countries and, as their names suggest, these are marketed as products for delaying ejaculation. However, the absence of reliable data from clinical trials means that the validity of the claims by the manufacturers cannot be assessed.

### **21.4.2 Severance Secret-Cream**

Severance secret-cream (SS-cream; Cheil Jedan Corporation, Seoul, Korea), developed at the Yong-Dong Severance Hospital in Korea is made with extracts from nine natural products. Some of these products have local anesthetic as well as vasoactive properties. Several studies using SS-cream on men with PE have been carried out in Korea, however the cream is not approved for use in Europe or the USA and is not legally available outside Korea.

SS-cream is applied to the glans penis 1 h before intercourse and washed off immediately prior to coitus. Both the latency and amplitude of somatosensory evoked potential measured at the glans penis were increased over baseline although lower than that of normal men [9].

This product has been shown to increase the penile vibratory threshold at the glans penis in a dose-dependent fashion [12]. Xin et al. reported significantly prolonged ejaculatory latency in 89.2 % of patients treated with SS-cream [13]. Adverse effects were noted in 5.9 % of patients; these included mild local irritation (local burning or pain) and delayed ejaculation.

The prolongation of IELT has been shown to be dose dependent with an optimal dose of 0.2 g cream. In a multi-center, double-blind study involving 106 patients, the use of 0.2 g of SS-cream was reported to increase the mean stopwatch-measured IELT from a baseline of 1.37 to 10.92 min, compared with 2.45 min with placebo ( $p < 0.001$ ) and was 27 times more effective than placebo in increasing sexual satisfaction ( $p < 0.001$ ). However, almost 19 % of episodes of use were associated with mild localized irritation, including pain and burning, and 12 patients reported negative sexual sideeffects such as delayed ejaculation, an-ejaculation, and erectile dysfunction [14].

Despite these promising results, SS-cream has an unpleasant smell and color, which makes it unacceptable to many patients. A reformulation has resulted in 'renewed SS-cream' (RSSC) which is a new topical agent composed of the two main components of the original SS-Cream: Korean ginseng and *Bufo venenum* in a hydrobase and enhancer without the unpleasant smell or color [15]. So far, only the results of animal studies have been published. The authors claim that RSSC delays the latencies of the spinal somatosensory evoked potentials in rabbits more effectively than the original SS-cream. However, the ingredient *Bufo venenum* has been shown to produce contact dermatitis [16] and the likelihood of this cream gaining regulatory approval outside of Korea appears to be remote.

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## 21.5 Off-Label Topical Treatments

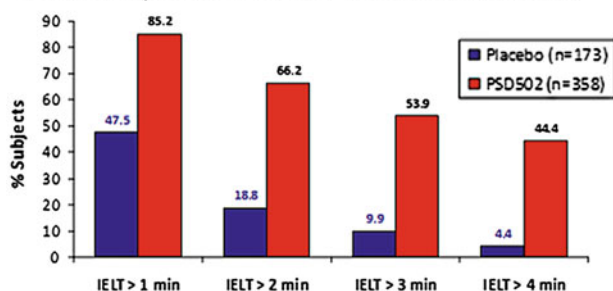
### 21.5.1 Lidocaine–Prilocaine Cream

Separately, lidocaine and prilocaine are crystalline solids. When mixed together in equal quantities by weight, however, they form a liquid eutectic mixture that can be formulated into preparations without the use of a non-aqueous solvent. This allows higher concentrations of anesthetic to be formulated into the preparation and maintained during application. EMLA (eutectic mixture of local anesthetic; AstraZeneca) is a local anesthetic cream containing 2.5 % each of lidocaine and prilocaine for topical application. Developed to anesthetize intact skin, it is available as an over-the-counter product in some countries.

The first pilot study evaluating lidocaine–prilocaine cream for the treatment of PE included 11 subjects [17]. The cream (2.5 g) was applied to the whole glans and shaft of the penis 30 min prior to intercourse and covered with a condom, which could be removed prior to intercourse (and the cream wiped off) if desired. Nine of the 11 patients rated their performance as 'excellent' or 'better' and all 11 partners were satisfied with the treatment results [17].

## TEMPE PIVOTAL STUDIES

## Subjects (%) With IELT &gt;1 to &gt;4 Min: End of 3-Month, Double-Blind Treatment Phase



A significantly greater proportion of total patients from both studies in the treatment groups had mean IELTs of >1 min, >2 min, >3 min, and >4 min than in the placebo group ( $p < 0.0001^*$ ). Baseline 0.53-0.60 minutes

For all between-treatment comparisons in individual studies

**Fig. 21.2** IELT in men using TEMPE vs. placebo

In order to determine the optimal time that the anesthetic cream should be on the penis prior to intercourse, Atikeler et al. carried out a placebo-controlled trial with 40 patients (10 in each treatment group), varying the application time from 20 to 45 min, with a condom. In the 20- and 30-min application groups the IELT increased compared to placebo, but all men in the 45-min group suffered from penile numbness and loss of erection. The optimal application time was considered to be 20 min [18].

The largest double-blind, placebo-controlled clinical trial of lidocaine-prilocaine cream to date involved 42 patients, 21 in each group [19]. Patients were asked to apply a thin layer of cream to the glans penis, extending the coverage for up to 2 cm on the penile shaft. They were then asked to cover the cream with a condom for 10–20 min before intercourse and to use this treatment each time they had intercourse over 30–60 days. The treatment resulted in a 5.6-fold increase in IELT from 1.49 to 8.45 min. However, only 29 of the initial 42 participants completed the study. Of the patients completing the study, 11 out of the 16 who responded reported ‘great’ or ‘excellent’ sexual satisfaction.

Loss of penile sensation, retarded ejaculation, and penile irritation were a problem for 5 men, and 1 female partner reported decreased vaginal sensitivity.

It can be concluded that lidocaine–prilocaine cream has some degree of efficacy in the treatment of PE but is inconvenient, messy, and slow-acting, and it is not approved for this indication. It also has problems associated with hypoesthesia.

## 21.6 Novel Topical Agents in Development

### 21.6.1 Dyclonine–Alprostadil Cream

A cream containing 0.5 % dyclonine (a local anesthetic commonly used in dentistry) and 0.4 % alprostadil has been in development as a potential agent for use in PE. To date the only available report (abstract only) is a pilot study involving 30 patients which shows a synergistic effect when the cream containing both dyclonine and alprostadil was compared with one containing the individual components only [20]. Mild to moderate local side effects were noted in 17.5 % of subjects. More research is needed to further evaluate this potential of this product in the management of PE.

### 21.6.2 Prilocaine–Lidocaine Spray

TEMPE (topical eutectic mixture for premature ejaculation. Plethora Solutions Ltd.) is a proprietary formulation of lidocaine and prilocaine in a metered dose aerosol delivery system specifically designed for use in PE; the system delivers 7.5 mg lidocaine base plus 2.5 mg prilocaine base per actuation. The mixture is alcohol-free so there is little chance of stinging on application, and although it is oil-free, the mixture forms a clear, slightly oily, odourless solution that remains adherent to the application site. It may be wiped off if necessary with a damp cloth so no condom is required [21].

The metered dose spray delivery system allows the desensitizing agents to be deposited in a dose-controlled, concentrated film on the glans penis, and they can then penetrate the glans within 5–10 min [21]. The eutectic mixture is slower to penetrate intact keratinized skin and as such is not likely to anesthetise the shaft of the penis or the hands [21].

In the first open label pilot study, 11 patients recorded stopwatch-timed IELTs at baseline and on five subsequent encounters when using the spray 15 min before intercourse [21]. The average IELT increased from 1 min 24 s to 11 min 21 s ( $p = 0.008$ ), representing an average eight-fold increase. In addition, 8 out of 11 patients and 7 out of 11 partners rated their sexual satisfaction as ‘better’ or ‘much better’.

In a more recently published phase 2, placebo-controlled trial, 54 patients using the prilocaine–lidocaine spray were able to prolong their IELT from a baseline of 1.0–4.9 min [22]. The treatment was also well tolerated, with only 3 (12 %) patients experiencing hypoesthesia and a fourth patient experiencing loss of erection. None of the adverse events resulted in treatment discontinuation. The spray was also well tolerated by the female partners, with only one partner

**Table 21.1** Safety: 3-month, double-blind treatment phase

Combined Treatment-Related AEs			
Patient	n(%)	Partner	n(%)
Total <sup>a</sup>	21(5.8)	Total <sup>a</sup>	24(6.6)
Reproductive system		Reproductive system	
Ejaculation failure	2(0.5)	Vaginal pain	1(0.3)
Loss of erection	11(3.0)	Vulvovaginal burning sensation	18(4.9)
Genital burning sensation	1(0.3)	Vulvovaginal discomfort	3(0.8)
Genital erythema	2(0.5)	Vulvovaginal pruritus	1(0.3)
Hypoesthesia of male genital	5(1.4)		
Orgasm abnormal	1(0.3)		
Other		Other	
Headache	2(0.5)	Anorectal discomfort	1(0.3)
Hypoesthesia	1(0.3)	Paresthesia oral	1(0.3)
Skin irritation	1(0.3)	Headache	1(0.3)
		Hypoesthesia	1(0.5)
		Dysuria	1(0.3)

One serious AE, no systemic AEs

Low incidence of local AEs in patients in the PSD502 group (5.8 %), and the placebo group (0.6 %)

Low incidence of local AEs in partners in the PSD502 group (6.6 %), and the placebo group (1.7 %)

In these combined studies, TEMPE appears to be safe and well tolerated

<sup>a</sup> A subject with multiple AEs within a primary system organ class is counted only once in the total row

experiencing a mild burning sensation during intercourse; which again, did not result in discontinuation.

The clinical development program comprising two double-blind placebo-controlled multi-center phase 3 clinical trials has been completed [23, 24]. Over 550 patients, all meeting the ISSM definition of PE [25], have been evaluated using IELT and the domains of two questionnaires [index of premature ejaculation (IPE) and the premature ejaculation profile (PEP)]. The IELT data are summarized in Fig. 21.2. The changes in IELT were mirrored in all domains of the IPE and PEP completed by the patients and in the PEP domain scores for partners [23, 24]. There was no evidence of tachyphylaxis and indeed with time, as sexual confidence presumably improved, the treatment became even more effective.

There was little or no evidence of systemic side effects and with only minimal desensitization of the genitalia in either patient or partner which as evidenced by IPE and PEP scores did not detract from sexual satisfaction (Table 21.1, [23, 24]).

## 21.7 Discussion

Compared with systemic treatments for PE, topical local anesthetic treatments offer certain advantages: they can be applied as needed and systemic side effects are unlikely. However, they do have a number of potential drawbacks: they can be messy, can interfere with spontaneity, and could cause numbness in the man or his partner. Dependent on formulation, they may also require a period of time between application and maximum effect and need either to be used with a condom or be washed or wiped off before intercourse, which could have an effect on spontaneity and may decrease arousal. The local anesthetic cream formulations (lidocaine-prilocaine, dyclonine-alprostadil, and EMLA<sup>®</sup>) require a 5–20 min application and the potential use of a condom, whereas the spray formulation (lidocaine–prilocaine, TEMPE) has 5–15-min application time and is easy to administer, remains adherent to the glans penis after application and is less likely to penetrate intact keratinized skin causing anesthesia of the shaft of the penis [10].

Historically, the evaluation and comparison of the outcomes of clinical trials for PE agents was problematic until an evidence-based definition of PE was forthcoming [25]. A critical review of the methodology of studies in PE has revealed the scale of the differences and the resultant difficulties in comparing results from these studies [26]. It is therefore important to exercise a degree of caution when comparing results. Recommendations for standards for clinical trials in PE [2, 26, 27] include the use of a precise definition of PE (e.g., ejaculation that occurs within 1 min after vaginal penetration in more than 90 % of intercourses); a randomized, double-blind, prospective design; the use of validated outcome measures (such as IELT); the use of a stopwatch at each coitus, both during baseline and during drug treatment and “validated” patient and partner reported outcomes. It would appear that the phase 3 studies on TEMPE were conducted to these exacting standards [23, 24].

In conclusion, if approved, topical aerosol application of TEMPE may provide a safe and effective, on-demand treatment option for men with PE.

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### 22.1 Physiology and Pathophysiology of Erectile Function

The occurrence of spontaneous penile erection in response to sexual stimuli depends upon a complex series of events and requires appropriate functioning of the nervous systems, vascular, and endocrine systems as well as the erectile tissue in the penis. Any condition and/or state that disrupts the functionality of any of the systems/organs involved in the genesis of penile erections can cause ED. Typically ED is classified as psychogenic and organic with the latter being sub-classified into vasculogenic, neurogenic, myogenic (alterations in corpus cavernosal smooth muscle structure and/or function), endocrine, and drug-induced [51]. Of note, there is commonly a combination of pathophysiological mechanisms, such as in diabetes where neural, vascular, and erectile tissue structural factors are at play.

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### 22.2 Neural Regulation

The central, autonomic and somatic nervous systems participate in the regulation of penile erections.

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### 22.2.1 Central

Sexual stimulation produces cerebral impulses that generate penile erection by (i) inhibiting sympathetic pathways, (ii) stimulating parasympathetic pathways and (iii) stimulating somatic pathways. While many areas have been found to play a role, the medial preoptic area (MPOA) and the paraventricular nucleus (PVN) of the hypothalamus seem to be particularly important, and dopamine appears to potentiate the ability of these areas to induce erections, likely through the stimulation of oxytocin [31, 75]. Neurologic disorders that disrupt the central pathways involved in penile erections include tumors, stroke, encephalitis, Parkinson's disease, dementia, Shy-Drager syndrome (olivopontocerebellar degeneration), and temporal lobe epilepsy [72]. In contrast, patients with lesions of the pyriform cortex and amygdaloid complex (Klüver-Bucy syndrome) tend to have more frequent erections and hypersexuality. Psychogenic erectile dysfunction (ED) has been hypothesized to occur due to direct inhibition of the spinal erection center by the brain as an exaggeration of the normal suprasacral inhibition and/or excessive sympathetic outflow or elevated peripheral catecholamine levels, which may increase penile smooth muscle tone to prevent its necessary relaxation [72].

### 22.2.2 Autonomic

Erections are facilitated by the parasympathetic and inhibited by the sympathetic nervous systems [31]. The penis receives abundant parasympathetic innervation from the sacral nerve roots S2–4, while the sympathetic fibers have their origin in the thoracolumbar nerve roots T12–L2, and run along the pre-aortic plexus into the hypogastric plexus [52].

### 22.2.3 Somatic

Somatic dorsal nerves of the penis form the first portion of the sacral nerve circuit that synapses with parasympathetic sacral neurons responsible for tumescence. This circuit is of critical importance in the induction of a reflexogenic erection mediated by genital touch rather than non-tactile erotic stimuli [24]. The somatic nervous system is also responsible for contraction of the bulbospongiosus and ischiocavernosus muscles during maximal arousal, leading to engorgement of the corpus spongiosum and the glans penis during the rigid erection phase as well as ejaculation [24]. Lesions of the spinal cord, such as those occurring during multiple sclerosis, spinal cord injury, tumor, syringomyelia, transverse myelitis, disk disease and myelodysplasia, can lead to ED. Men with sacral spinal cord lesions can maintain the ability to erections, but these are usually less rigid.

The importance of inhibiting the sympathetic tone for the occurrence of centrally mediated (psychogenic) erections is underscored by the fact that these do not occur in individuals with spinal cord lesions above T9 [18]. On the other

hand, these men are able to achieve erections by direct penile stimulation (reflexogenic erections), mediated by the sacral reflex arc [23, 24]. In spite of various refinements in surgical techniques, nerve damage during pelvic surgery is still a common cause of ED, albeit less frequently than in the past [87]. Whether or not the preservation of accessory pudendal vessels during radical prostatectomies changes postoperative erectile outcomes is debatable [56]. Pelvic fractures can also cause ED due to cavernous nerve injury, vascular injury, or both. Peripheral neuropathies, involving autonomic or somatic nerves can also result in ED and have been observed in patients without any other identifiable cause for ED [12].

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### 22.3 Vascular Factors

Arterial inflow of the penis is provided by the internal pudendal artery, which becomes the common penile artery after giving off a perineal branch. Accessory internal pudendal arteries commonly exist, and can arise from the external iliac, obturator, vesical, and/or femoral arteries [27]. The common penile artery divides into three branches: dorsal, bulbourethral, and cavernosal arteries. The latter then supplies the trabecular erectile tissue and the sinusoids through its helicine branches. Normal erectile function requires not only the patency of these vessels but also their ability to dilate, an effect mediated by the endothelium. The same conditions that are known to be risk factors for coronary artery disease, such as aging, smoking, hypertension, diabetes mellitus, dyslipidemia, physical inactivity, and chronic kidney disease can result in ED by interfering with vascular function [38]. Approximately 70 % of patients with chronic kidney disease self-report ED [58]. A variety of mechanisms can be involved, including disturbance of the hypothalamic-pituitary-gonadal axis, vascular disease, peripheral neuropathy, psychological factors [62].

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### 22.4 Endocrine Factors

Androgen receptors exist at all levels of the neural axis involved in erections (central, spinal, and peripheral, and its administration has been shown to reverse the reduction in erections observed in castrated animals [31]. Moreover, there is an abundance of preclinical data supporting the importance of testosterone in maintaining the structure and function of the cavernous tissue and modulating NOS expression and PDE5 expression (TraishEurUrol 2007). Clinically, however, the situation is much less clear. Meta-analyses of testosterone replacement in hypogonadal men with ED, alone or in combination with a PDE5 inhibitor, have found wide inconsistencies between trials, making definitive conclusions about its effect impossible [14, 78]. Hyperprolactinemia has been identified as another endocrine cause for ED. Increased prolactin level can not only suppress testosterone but probably also interfere with neurotransmission in the brain [15].

Diabetes mellitus can cause ED due to testosterone deficiency, vascular disease, neurologic disease and/or direct damage to erectile tissue [20].

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## 22.5 Cavernosal Smooth Muscle Factors

The three essential factors are (i) relaxation of the cavernosal muscle cells, (ii) increase in arterial inflow and (iii) restriction of venous outflow.

Sexual arousal leads to relaxation of the cavernous smooth muscle and progressive dilatation of the sinusoids. Eventually, the subtunical veins become compressed between sinusoids and the tunica albuginea, a dense fibrotic covering sheath that limits expansion of the erectile tissue, leading to increased pressure, which is translated to rigidity. The compression of the tunical emissary veins results in a near complete obstruction to venous outflow from the corporal bodies and a fully erect penis. The interaction between the erectile tissue and the tunica albuginea is known as the venoocclusive mechanism [36]. Tunical injury, fibroelastic structural alterations, collagenization of the muscle, and insufficient trabecular smooth muscle relaxation can cause venoocclusive dysfunction. These can originate from conditions such as Peyronie's disease, penile fractures, diabetes mellitus, priapism, surgical shunts for the treatment of priapism, low testosterone, and/or chronic ischemia from prolonged periods without erections.

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## 22.6 Molecular Mechanisms

Release of nitric oxide (NO) from the cavernous nerve terminals is an important step in the initiation of penile erections [65]. Neuronal NO is produced by activity of the enzyme neuronal nitric oxide synthase (nNOS). NO activates the soluble protein guanylatecyclase, which in turn cleaves GTP to cyclic GMP [8]. Cyclic GMP effects are mediated primarily by protein kinase G (PKG), and include (i) closing membrane-bound calcium channels, impeding the entrance of calcium into the cells, (ii) opening membrane-bound potassium channels, leading to cellular hyperpolarization and (iii) sequestration of intracellular calcium in the sarcoplasmic reticulum. cGMP and PKG have also been demonstrated to play a role in the inhibition of inositol triphosphate (IP3) generation, inhibition of Rho-kinase, stimulation of myosin light-chain phosphatase (MLCP), and phosphorylation of heat shock proteins [17, 50]. With hyperpolarization and a decline in cytosolic calcium concentration, uncoupling of the actin and myosin cross-bridges occurs, resulting in smooth muscle relaxation and vasodilation [86].

The maintenance of penile erections is also fundamentally dependent on NO. Endothelial nitric oxide synthase (eNOS) is activated through an Akt-dependent mechanism due to shear stress from increased blood flow past the endothelium [37]. Endothelial dysfunction is characterized by a decreased NO bioavailability, and the mechanisms for such include decreased eNOS expression and activity,

dysregulation of eNOS phosphorylation, increased NO scavenging by ROS or oxidized low-density lipoprotein (LDL), eNOS uncoupling, decreased levels of eNOS cofactors and substrate, impaired interaction of eNOS with its regulatory proteins, and increased interaction with a contractile signaling-pathway [57]. Other signal transduction pathways not mediated by NO have also been described, but these are most likely secondary [65]. Acetylcholine, vasoactive intestinal polypeptide (VIP), prostaglandins, endothelium-derived hyperpolarizing factor (EDHF), and endothelin have been implicated [24].

Penile detumescence involves the cessation of NOS release by nerve endings and endothelium, lowering NO levels, and cyclic GMP production. The smooth muscle cells regain their basal tone, once the cyclic GMP is degraded, a step performed by phosphodiesterases. While most phosphodiesterases have been found to be expressed in the cavernous tissue, PDE5 is by far the most important one [44]. Reduced levels of intracellular cGMP lead to release of calcium from the sarcoplasmic reticulum, smooth muscle contraction, and opening of the sub-tunical veins facilitating blood outflow, resulting in flaccidity.

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## 22.7 Role of Adrenaline in Detumescence

Physical and/or psychological stress leads to activation of the sympathetic nervous system, which involves the release of noradrenaline in the peripheral tissues and the systemic release of adrenaline and noradrenaline by the adrenal medulla. Animal studies demonstrate that the stimulation of sympathetic nerves or systemic infusion of epinephrine causes detumescence of the erect penis [25, 26]. Noradrenaline is likely the most potent neurotransmitter in regards to inhibiting and/or aborting penile erections, exerting such effect by binding to alpha receptors [26, 76]. Alpha-1 receptors on cavernous smooth muscle cell membrane increase the intracellular inositol triphosphate (IP<sub>3</sub>), increasing the intracellular calcium concentration and, thereby, lead to constriction of the cavernous arteries and corporeal sinusoids. Moreover, alpha-2 receptors inhibit adenylatecyclase, the enzyme responsible for converting GTP into cyclic AMP. Men with psychogenic ED have higher noradrenaline levels than healthy volunteers or those with organic ED [42]. Moreover, amongst men with psychogenic ED, those with higher noradrenaline levels tend to be less responsive to intracavernosal prostaglandin E<sub>1</sub> [42].

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## 22.8 Premature Ejaculation (PE)

The diagnosis of premature ejaculation relies upon the identification of three factors: (i) short ejaculatory latency, (ii) lack of control of the timing of ejaculation and (iii) resultant distress and/or interpersonal difficulty.

An expert committee from the ISSM defined lifelong PE as “a male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, and the inability to

delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy” [6]. In regard to secondary (acquired) PE, the committee stated that there is insufficient data to propose a specific definition, and that the criterion for lifelong PE might be applicable to secondary PE as well. From a practical perspective, secondary PE differs in the sense that it develops in individuals who previously have had normal ejaculatory function. Considering that a significant proportion of patients presenting with complaints of ejaculating earlier than what they thought appropriate fit the above definition, two additional clinical entities have been described: (i) natural variable PE, characterized by inconsistent early ejaculations, considered to be a normal variation in sexual performance, (ii) premature-like ejaculatory dysfunction is characterized by preoccupation with a false subjective perception of rapid ejaculation [82].

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## 22.9 Etiology of PE

While still limited, there is correlational evidence that possibly explains, at least in part, the etiology of PE. Lifelong PE is nowadays thought to be genetically determined, being related to an inherited altered sensitivity of central 5-HT receptors [40, 80, 81]. In contrast, acquired PE can be caused by sexual performance anxiety [33], psychological or relationship problems [54, 33], ED [45], prostatitis/chronic pelvic pain syndrome [32, 69], hyperthyroidism [16] or during withdrawal/detoxification from prescribed [4] or recreational drugs [61].

Anxiety has been long portrayed as the most likely cause of PE [41, 89]. One theory suggests that sympathetic activation would hasten emission and thereby reduces the ejaculatory threshold [41, 89]. Another concept suggests that excessive performance anxiety would distract men recognizing prodromal sensations that precede ejaculatory inevitability [43, 79]. It is important to recognize that PE might cause or further exacerbate anxiety, particularly anxiety related to sexual performance. Thereby, even if anxiety was not the primary issue causing PE it might arise as a contributing factor.

Suppressed TSH levels were found to be significantly associated with PE in patients presenting to an andrology clinic [21]. Moreover, a multicenter study of patients with thyroid dysfunction found that 50 % of patients with hyperthyroidism suffered from PE, which resolved in more than two-thirds of patients upon normalization of thyroid function [16]. Men with lifelong PE do not appear to have an increased incidence of altered thyroid function [85].

Numerous studies of patients with prostatitis or chronic pelvic pain syndrome (CPPS) have found that rapid ejaculation is common complaint among these patients, occurring in 26–77 % [13, 32, 49, 66, 77]. Furthermore, up to 64 % of patients with PE have evidence of prostatic inflammation [69, 70, 90]. It has been speculated that inflammation of the prostate could alter sensation and modulation of the ejaculatory reflex [70].

## 22.10 Prevalence of Secondary PE

While complaints of ejaculating too quickly occur in 20–30 % of men in general according to most studies [3, 46, 64, 71], PE, as per the above criteria, is a lot less common. Multinational, community-based studies using stopwatch or timer measurements have found that an IELT of 1.5 min corresponds to the 2.5th percentile [83, 84]. This means that assuming these studies had samples representative of the general population, the prevalence of PE (as opposed to the subjective complaint of ejaculating too quickly) is unlikely to be greater than 3–5 %.

Multiple studies have observed that ED and PE often coexist [5, 22, 45, 64, 67, 88]. These two entities not only share anxiety as a possible etiology, but also have a bidirectional relationship, meaning that either one can cause/exacerbate the other, potentially creating a vicious cycle [39]. The increased sympathetic activity can result in ED and/or PE as per the previously described mechanisms. A study of more than 800 men attending an outpatient clinic for sexual problems found that anxiety symptoms, as assessed by a validated questionnaire, were significantly associated with erectile difficulties and PE [22].

The Premature Ejaculation Prevalence and Attitudes (PEPA) Survey, an internet study that gathered results from 12,133 men across three countries, found that self-reported ED rates were 31.9 and 11.8 % in men with and without PE, respectively [64]. Of note, PE was defined as self-reported low or absent control over ejaculation that bothered the respondent and/or the sexual partner.

A study of 12,558 Italian men found that ED is more common in men with PE, much more so in those with acquired PE [11]. The Global Study of Sexual Attitudes and Behaviors found that men with PE have an odds ratio of 3.7–11.9 of having ED [45]. In a nationally representative sample of 1,475 Swedish men, 23 % of men reporting erectile difficulties also reported that ejaculation occurred shortly after penetration [30].

While these large cross-sectional studies clearly establish the frequent coexistence of the two conditions, they do not provide information about temporality and consequently causality. In a cohort of 184 men attending a sexual dysfunction clinic, 121 complained of ED, 52 of PE, and 11 of both conditions [39]. Interestingly, careful evaluation and administration of the IIEF-5 demonstrated that 24 % of patients only complaining of ED actually had experienced PE prior to ED onset. Moreover, antecedent or concurrent ED was identified by the IIEF-5 in 40 % of patients complaining of PE only. Patients with ED and PE were initially treated with a PDE5 inhibitor alone, which resulted in partial or complete resolution of PE in 30 % of cases.

Possible explanations for the increased prevalence of PE among ED patients include the fact that subjects with impaired erectile function may require greater amounts of sexual stimulation to achieve an erection and/or “rush” vaginal penetration for fear of loss of sustaining, both of which may decrease IELT. On the other hand, PE can result in ED. One theory is that the conscious effort to delay ejaculation by reducing the level of excitation might result in loss of penile



**Table 22.1** Prospective Prevalence Studies

Author	N / Study	PE definition	ED definition	Findings
Fugl-Meyer [30]	1,475 / community-based survey	Self-reported ejaculation shortly after penetration	Self-reported	PE in 23% of patients with ED
Basile Fasolo [11]	12,558 / Subjects attending urology/andrology clinic after invitation	Self-reported, as per DSM-IV	Self-reported dissatisfaction with erections	OR for ED: Lifelong PE: 2.5 Acquired PE: 9.6
Corona [21]	882 men attending sexual health clinic	Reported IELT <1min	SIEDY	20.9% had ED and PE; 5% had only PE
Porst [64]	12,133 / Internet survey	Self-reported low/absent control over ejaculation that bothered the respondent and/or the sexual partner	Self-reported	ED Prevalence - PE = 31.9% - No PE = 11.8%
El-Sakka [28]	1680 / ED clinic	Lack of control with ejaculation shortly after penetration	EFD-IIIEF	PE prevalence - Overall: 45% - Mild ED: 29% - Severe ED: 52%

erection. Interestingly, various studies have demonstrated that the prevalence of PE is positively associated with ED severity [21, 28, 29]. In one of these studies, PE was present in 29.5 % of men with mild ED, and in 52.4 % of those with severe ED [29].

Prevalence findings are summarized in Table 22.1.

## 22.11 Studies of Secondary PE Management

PDE5 inhibitors are recommended as the first line of treatment for patients with ED (and no correctable cause) [35, 55]. Moreover, a few studies have suggested that these agents might prolong IELT even in patients with lifelong PE and normal erectile function [10]. The speculative rationale for their use includes: (i) possible reduction of performance anxiety due to more rigid and more sustainable

erections, (ii) re-setting of the erectile threshold to a lower level of arousal, requiring less penile stimulation to cause rigidity and thus decreasing the post-ejaculatory latency time, (iii) peripheral modulation of smooth muscle activity of vas deferens, seminal vesicles, prostate and urethra, (iv) induction of peripheral analgesia, and (v) a central effect involving increased nitric oxide and reduced sympathetic tone [1]. It is likely that their effect is most likely related to factors (i) and (ii) above.

In a cohort of 459 men with ED, 399 responded to treatment with a PDE5 inhibitor [19]. Of the responders, 28 % (112 patients) developed PE, defined as IELT <2min. Treatment of these men with on-demand sertraline 50mg improved mean IELT from 34.6 to 111.6 s, however, the improvement was much less pronounced than in a contemporary group of men with primary PE without ED, in whom the mean IELT increased from 46.0 to 247.2 s. Another study of 45 men with ED and PE investigated the effects of sildenafil treatment on both conditions [48]. Improvement of erectile function and IELT was achieved in 27 patients (60 %), and a further 13 individuals had improved erections but unchanged IELT. Satisfaction rate was 81 % among the patients who showed improvement in both conditions, vs. 7 % (one patient) among the ones that were still experiencing PE.

Combined data from two phase 3 dapoxetine trials have been recently reported [63]. These studies included 753 men with acquired PE who had mild or no ED as per the erectile function domain of the IIEF (patients with a score of <22 were excluded). Subjects were randomized to receive dapoxetine 30, 60 mg, or placebo on an as needed basis. The 60 mg resulted in statistically significant improvement in IELT versus placebo in patients with no ED as well as dose with mild ED, whereas the 30 mg dose was superior to placebo only in patients with no ED. Of note, treatment with dapoxetine did not result in consistent improvement in patient-reported outcomes in patients with mild ED. Among these, rates of satisfaction with sexual intercourse were 17.5, 32.6 and 36.1 % in the placebo, dapoxetine 30 and 60 mg groups, respectively. These results support the recommendations from the current guidelines, which state that ED should be addressed first when both conditions are present.

Cognitive behavioral therapy when combined with pharmacotherapy has been found to be an effective intervention for acquired PE related to sexual performance anxiety, allowing a substantial proportion of men to maintain improvements on ejaculatory latency and control following cessation of pharmacotherapy [34, 60]. Different studies have found that the combination of behavioral therapy with an SSRI or PDE5 inhibitor achieves better results than pharmacotherapy alone [47, 74]. Psychological therapy aims at indirectly increasing IELT by increasing confidence (in sexual performance) and decreasing (performance) anxiety. For patients in stable relationships psychotherapy can also assist in increasing communication with the partner and resolving interpersonal problems.

Similarly, in patients with ED the combination of psychotherapy and a PDE5 inhibitor has been found to afford better results than either treatment alone [2, 9, 53].

Treatment results are summarized in Table 22.2.

**Table 22.2** Treatment results for patients with PE and ED

Author	N / Patients	Treatment	Results	Comments
Chia [19]	112 men with secondary PE whose ED resolved with PDE5i	Sertraline 50mg PRN	IELT improved from 34.6 to 111.6 seconds	Improvement less impressive than in patient with lifelong PE
Li [48]	45 patients with ED and PE	Open-label Sildenafil 50-10mg PRN	ED improved in 88% ED and PE improved in 60%	“Satisfaction” PE and ED resolved: 81.4% Only ED resolved: 7.6%
Li [47]	90 patients with ED and PE	Randomized - Drug therapy -Drug + behavioral therapy	IELT Drug: 4.7 Combination: 5.8	“Effectiveness” 1 month after treatment Drug: 30% Combination: 82.9%
Porst [63]	753 men with acquired PE and no or mild ED	Randomized - Placebo -Dapoxetine 30 -Dapoxetine 60mg PRN	60 mg improved IELT in all patients. 30mg improved IELT only in patient with no ED.	Dapoxetine did not consistently improve patient-reported outcomes in patients with mild ED

## 22.12 Clinical Care Pathway

Evaluation involves a comprehensive sexual history and physical exam focusing on identifying factors that may contribute to its occurrence and persistence. IELT alone is not sufficient to define PE. Important aspects to be explored in history are summarized in Table 22.3. The use of stopwatch to measure IELT is probably only required for research purposes. Validated questionnaires include the Premature Ejaculation Diagnostic Tool (PEDT) [73], the Premature Ejaculation Profile (PEP) [59], the Index of Premature Ejaculation (IPE) [7], and the Male Sexual Health Questionnaire Ejaculatory Dysfunction (MSHQ-EjD) [68]. The ISSM suggests the preferential use of the PEP or IPE for the monitoring of treatment response.

To address erectile function, the erectile function domain of the IIEF can be used.

Physical exam and adjunctive testing are directed toward identifying and/or better characterizing factors contributing to occurrence of PE. Thereby one should look for features of erectile dysfunction and its correlates, prostatitis/chronic pelvic pain syndrome, and hyperthyroidism.

**Table 22.3** Important aspects on history

IELT
Perceive control over ejaculation
Distress caused by PE
Onset of symptom
Correlation with psychological issues
Psychosocial history
Erectile function
LUTS / Pelvic pain
Medication / substance use
Medical history
Impact on QOL / relationship
Previous therapy for PE

The first step in the treatment is to correct potential causes. Any degree of erectile impairment should be treated promptly. Addressing psychological issues is advisable, if these are not thought to be the culprit. In an individualized fashion the practitioner can decide to concurrently start therapies directed towards the PE *per se*, or leave those for the cases that do not respond to initial treatment. Patients should be reassessed for treatment response, which should include a validated questionnaire such as the PEP or IPE.

If the response to treatment is deemed suboptimal, specific treatments for PE, which include SSRI and/or topical anesthetics, should be employed. No studies have compared the efficacy of different treatments specifically in patients with acquired PE. Treatment options should be attempted according to patient preference.

When patients are started on PE-specific therapy, it is sensible to make an attempt at withdrawing treatment once the factor initially thought to be contributing to the PE has been corrected. Because there is no data in the literature to suggest an optimal timing, this should be an informed decision made by patients.

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# Treatment of Premature Ejaculation and Comorbid Endocrine and Metabolic Disorders

# 23

Giovanni Corona, Giulia Rastrelli and Mario Maggi

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## 23.1 Introduction

Recent evidence has pointed out the possibility that gonadal, thyroid, and pituitary hormones (oxytocin and prolactin) might be involved in the control of the ejaculatory process and its overall latency time, along with all other aspects of the male reproduction system [1–14].

In line with this hypothesis we recently demonstrated that in a large consecutive series ( $n = 2652$ ) of patients with sexual dysfunctions, thyroid-stimulating hormone (TSH) levels progressively increased from patients with severe premature ejaculation (PE) towards those with anejaculation [9]. Conversely, the opposite was observed for T levels [9].

Associations between delayed ejaculation (DE) and PE and hypo- [11] and hyperthyroidism [1, 5, 9, 11], respectively, have been extensively documented, also in animal models [6, 14]. The relationship between thyroid hormones and ejaculatory mechanisms has not yet been completely understood. In light of the widespread distribution of thyroid hormone nuclear receptors within the brain, it can be hypothesized that thyroxin specifically alters the activity of the central serotonergic pathway [15], leading to diminished control of ejaculation. Alternatively, it is

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possible that thyroid hormone receptors act directly on the male genital tract, since they have been detected within the animal [16] and human testis [17].

Testosterone might have both a central and peripheral action on the ejaculatory process. Androgens profoundly influence male sexual behavior, acting on several areas within the central and peripheral nervous system, most of them related to the ejaculatory reflex. Androgen receptors are expressed in the medial preoptic area, the bed nucleus of the stria terminalis, the median amygdala and the posterior thalamus, all regions deeply involved in the supraspinal control of ejaculation [18]. Interestingly, the bulbocavernosus muscle, like other muscles of the pelvic floor involved in the ejaculatory ejection of the seminal bolus (ischiocavernosus and levator ani muscle), is specifically androgen-dependent [19]. Testosterone can also positively affect the emission phase of the ejaculatory reflex. The integrated system NO–PDE5 (nitric oxide–phosphodiesterase type 5), one of the most important factors involved in the contractility of the male genital tract (MGT), is under T control. In an experimental model of hypogonadotropic hypogonadism, we found that in vas deferens of T-deficient rabbits cyclic guanosine monophosphate (cGMP) degradation was reduced and PDE5 less expressed and biologically active [20]. T administration completely reverted these alterations [20]. Hence, it is possible that hypogonadism-associated DE is a result of an increased inhibitory nitrenergic tone on smooth muscle cells of MGT. Testosterone can be aromatized by cytochrome P450 aromatase to an active estrogen, 17 $\beta$ -estradiol, and the enzyme aromatase is widely expressed in MGT, in particular in epididymis [21]. In epididymis, testosterone, but more efficiently its metabolite estradiol, can revert hypogonadism-induced down-regulation of RhoA/ROCK pathway (a calcium-sensitizing pathway) and restore contractility [22]. Hence, in our view, low T should be suspected and analyzed in all subjects with delayed ejaculation. To support this view better, interventional studies showing that treating hypogonadism ameliorates ejaculatory difficulties are currently being performed.

In line with the aforementioned evidence, the following section is focused on the treatment of possible endocrine disorders associated with ejaculatory disturbances.

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## 23.2 Hyperthyroidism

Hyperthyroidism is a quite common endocrine disease with a prevalence of 0–2 % in men and incidence of 20/10,00,000/year in the general population with male/female ratio of 1:5 [23, 24]. The institution of effective therapy requires an accurate determination of the etiology of the disorder (Table 23.1). In this regard it is helpful to recognize the distinction between disorders resulting from thyroid glandular hyperactivity—characterized by excessive new synthesis and secretion of thyroid hormones—and those disorders in which a true glandular hyperactivity is absent. The general term thyrotoxicosis refers to the clinical and biochemical manifestations of excess thyroid hormone at the tissue level, without regard to exact etiology, whereas the term hyperthyroidism is more properly reserved for disorders characterized by thyroid glandular hyperfunction. Causes of hyperthyroidism include Graves'

**Table 23.1** Main causes of thyrotoxicosis in males

<i>Associated with sustained hormone overproduction (hyperthyroidism)</i>
Graves disease
Toxic multinodular goiter
Toxic adenoma
Iodine-induced (jodbasedow)
TSH secreting pituitary adenoma
<i>Not associated with hyperthyroidism</i>
Thyrotoxicosis factitia
Subacute thyroiditis
Chronic thyroiditis with transient thyrotoxicosis (painless thyroiditis, hyperthyroiditis, silent thyroiditis)
Ectopic thyroid tissue (functioning metastatic thyroid cancer)

disease, toxic multinodular goiter, and solitary hyperfunctioning nodules (Plummer's disease) (Table 23.1). Other causes of thyrotoxicosis are painless thyroiditis and subacute thyroiditis, characterized by a transient excess of circulating thyroid hormones due to thyroid cell damage, or factitious ingestion of thyroid hormones or ectopic thyroid hormone production (Table 23.1). Finally a rare cause of hyperthyroidism is the pituitary TSH-secreting adenoma (Table 23.1).

The necessity for this distinction is rooted in the associated requirement for differing therapeutic strategies. In fact, although adjunctive therapy such as beta-adrenergic blockade and sedation may be applicable to both diagnostic categories, definitive therapy, as indicated in Table 23.2, differs greatly.

As mentioned above, hyperthyroidism has been associated with PE and replacement therapy might improve the problem.

### 23.2.1 Management

The choice of therapy involves multiple considerations (Table 23.2) [25]. The physician should carefully go over each treatment's benefits and risks with the patient and make specific recommendations; ultimately however, the decision must respect the patient's reasonable preferences.

### 23.2.2 Medical Therapy

*Thionamides.* This class of compounds shares the thionamide grouping which, by acting as a substrate for the thyroid peroxidase enzyme, confers the ability to inhibit competitively the organification and coupling steps in thyroid hormone synthesis.

**Table 23.2** Treatment Selection in Patients with Thyrotoxicosis.  $^{131}\text{I}$ : radioiodine

Diagnosis and patient characteristics	$^{131}\text{I}$	Surgery	Antithyroid drug
Graves' disease	Preferred therapy	Preferred therapy	Preferred therapy
Mild active ophthalmopathy	Acceptable therapy	Preferred therapy	Preferred therapy
Smokers	Acceptable therapy	Preferred therapy	Preferred therapy
Moderate to severe ophthalmopathy	Absolute contraindication	Preferred therapy	Preferred therapy
Large goiter, obstructive symptoms	Acceptable therapy	Preferred therapy	Acceptable therapy
Thyroid nodule			
With suspicious biopsy results	Contraindication	Preferred therapy	Contraindication
With benign biopsy results	Preferred therapy	Preferred therapy	Preferred therapy
High surgical risk	Preferred therapy	Relative contraindication	Preferred therapy
High surgical risk with short life expectancy and incontinence	Relative contraindication	Relative contraindication	Preferred therapy
Previous thyroid surgery	Preferred therapy	Relative contraindication	Preferred therapy
Toxic adenoma and toxic nodular goiter	Preferred therapy	Preferred therapy	Acceptable but less desired therapy
Large goiter and obstructive symptoms	Acceptable therapy	Preferred therapy	Relative contraindication
Thyroid nodule with suspicious biopsy results	Relative contraindication	Preferred therapy	Relative contraindication
High surgical risk	Preferred therapy	Relative contraindication	Acceptable therapy
High surgical risk with short life expectancy	Relative contraindication	Relative contraindication	Preferred therapy

Adapted from Ref. [25]

Propylthiuracil (PTU) and methimazole (MMI) are the two available drugs. PTU and MMI are almost completely adsorbed after oral administration. The half-life of MMI is 6–8 h and its action lasts 40 h. The half-life of PTU is 1–2 h and its action lasts 24 h [24, 25]. Thionamides can be used both in the primary treatment of

**Table 23.3** Incidence of major toxic reactions with antithyroid drugs in adults

Side Effect	Frequency	Comments
Polyarthrititis	1–2 %	–
ANCA+ vasculitis	Rare	Mostly PTU
Agranulocytosis	0.1–0.5 %	More common with PTU
Hepatitis	0.1–0.2 %	PTU only
Cholestasis	Rare	MMI only

ANCA+ Antineutrophil cytoplasmic antibody-positive; PTU propylthiouracil, MMI methimazole

hyperthyroidism and as a preparation for radiometabolic or surgical treatment. The initial dose is still a matter of debate: generally the initial dose of MMI is 10–30 mg per day in one or two oral administrations, while that of PTU is 100–300 mg per day every 6 h. Although both drugs are effective in controlling hyperthyroidism, MMI normalize thyroid activity more rapidly compared to PTU [26, 27]. As previously stated, the thionamide derivatives have no effect on the release of preformed thyroid hormones. Hence, an initial clinical effect is not noted until 1–2 weeks after initiation of thionidamide therapy and frequently a euthyroid state is not attained until after 6–8 weeks or longer. Beta-blockers can be used to attenuate symptoms in this period. When the serum thyroid hormone levels have been normalized, the patient is placed on a lower maintenance dose such as 5–10 mg of MMI or 50–100 mg of PTU daily. At this point, management may vary depending on the type of definitive therapy planned for the individual patient. In the case of Graves' disease the duration of therapy should be between 12 and 18 months, since periods of treatments inferior to 12 months lead to a higher possibility of recurrence, while periods superior to 18 months do not lead to higher percentages of remission [28]. Followup visits should be arranged every 4–6 weeks during the initial stage and every 2–3 months thereafter, in order to adequately adjust the thionamide dosage.

Thionamides can be associated with a variety of *side effects* with different severity levels grouped as minor and major (Table 23.3) [24, 25, 28]. Minor side effects are found in 1–5 % of patients and include pruritis, urticaria, arthralgia, nausea sickness, and olfaction disorders (more frequent with MMI). Major side effects include agranulocytosis, hepatotoxicity, aplastic anemia, and vasculitis and occur in approx 0.2–0.5 % of cases [25, 28]. Thus complete blood-cell count and liver function tests along with thyroid function evaluation should be assessed at each control during thionamide therapy.

*Potassium perchlorate*. This can be used in the treatment of thyrotoxicosis caused by the excess of exogenous iodine. The drug competitively inhibits the uptake of iodine by thyroid cells and accelerates its release. It should be noted that this drug can produce various side effects, among which the most important is bone-marrow depression [24, 25].

*Lithium Carbonate.* The antithyroidal effect of lithium has been known since 1960. It seems that lithium, similarly to iodine, blocks the release of thyroid hormone for a transitory period. Sometimes it has been used as an adjunctive therapy to radiometabolic therapy to prevent the increase of serum thyroid hormone concentration [24, 25].

*Glucocorticoids.* Glucocorticoids are used in thyrotoxicosis due to subacute thyroiditis for its as an anti-inflammatory action and reduction in the peripheral conversion of T4 into T3 [24, 25].

### 23.2.3 Radioiodine Therapy

Radioiodine is given orally as a single dose of  $^{131}\text{I}$ -labeled sodium iodide in liquid or capsule form. The mechanism of action of  $^{131}\text{I}$  is through the production of an intense radiation thyroiditis followed by progressive interstitial fibrosis and glandular atrophy resulting in destruction of the synthetic capacity of the thyroid. The cell necrosis induced by  $^{131}\text{I}$  occurs gradually and an interval of 6–12 weeks or longer must elapse before a hypothyroid or euthyroid state is achieved [24, 25]. Retreatment with radioiodine is necessary in 14 % of patients with Graves' disease, in 10–30 % of patients with toxic adenoma, and in 6–18 % of patients with toxic nodular goiter [24, 25]. Moderately severe ophthalmopathy may be a contraindication to treatment with radioiodine since radioiodine may exacerbate the condition especially in subjects who smoke (Table 23.2).

### 23.2.4 Surgery

Surgery is the gold standard in the presence of a large multinodular goiter. In addition, it should be the treatment of choice in certain circumstances such as in patients with Graves' disease due to a very large diffuse goiter (greater than 60 gm) for which a sustained remission with thionamide therapy is unlikely [24, 25]. In the hands of an experienced neck surgeon, thyroid surgery is safe and highly effective. Possible adverse effects include recurrent nerve injury with phoniatric problems and the development of hypoparathyroidism.

### 23.2.5 Ejaculation Disease Outcomes

So far, two studies have specifically evaluated the efficacy of anti-thyroid treatment in hyperthyroid patients with premature ejaculation. Carani et al. [11], in a series of 34 subjects with hyperthyroidism (Graves' disease in 19, Plummer's disease in six and toxic multinodular goiter in nine), showed that medical treatment was able to reduce the prevalence of PE from 50 to 15 % at the end of treatment, a figure similar to that found in the general population (14 %) [29].

**Table 23.4** Causes of hypothyroidism

<i>Thyroprivic</i>
Postablative hypothyroidism
Primary idiopathic hypothyroidism
Sporadic athyreotic cretinism (thyroid aplasia or dysplasia)
<i>Trophoprivic</i>
Infiltrative disorders of pituitary or hypothalamus
<i>Goitrus</i>
Hashimoto thyroiditis
Endemic iodine deficiency
Antithyroid agents (para-aminosalicylic acid, phenilbutazone, resorcinol, lithium, cruciferous plants, cassava)
Iodide goiter and hypothyroidism
Heritable defects in hormone biosynthesis and action
Peripheral resistance to thyroid hormone (may be nongoitrous)

Similar results were thereafter reported by Cihan et al. [5]. In a series of 43 hyperthyroid subjects (Graves' disease in 17, Plummer's disease in two and toxic multinodular goiter in 24) the rate of PE declined from 72.1 % at the baseline to 25 % after achieving euthyroidism. Interestingly, the same study also demonstrated that compared with other treatments the surgically treated group reported higher mean intravaginal ejaculatory latency time (IELT).

### 23.3 Hypothyroidism

Hypothyroidism is one of the most common chronic endocrine disorders in the Western population, with annual incidence rates of two in 10,000 for males [30–32]. The diagnosis is confirmed by elevated basal serum TSH and reduced free triiodothyronine (FT3) and thyroxine (FT4). Subclinical manifestation is present in about 5 % of the total population and it is characterized by normal thyroid hormones (FT3 and FT4) and elevated TSH levels (between 5 and 10 mU/l). Table 23.4 summarizes the most important causes of hypothyroidism. The most common cause of hypothyroidism in developed countries is autoimmune thyroiditis. Radioiodine ablation or surgical thyroidectomy are also responsible for an important number of cases. Less often, hypothyroidism may be drug induced or be secondary to disorders of the pituitary and hypothalamus (central or secondary hypothyroidism). In some parts of the world, iodine deficiency remains highly prevalent, with all of the subsequent consequences of deficits. As mentioned



above, primary hypothyroidism has been associated with DE and replacement therapy might improve the problem.

### 23.3.1 Treatment Management

*Levothyroxine sodium.* Levothyroxine sodium is the monosodium salt of the *levo* isomer of thyroxine. L-Thyroxine (L-T4) is the thyroid preparation of choice for the treatment of primary hypothyroidism. L-T4 is well absorbed (about 90 %) by the small intestine with an approximate 7 day half-life. Since T4 is converted into the more active hormone T3 in peripheral tissues, a preparation consisting solely of T4 provides a stable and physiological amount of T3 to the peripheral tissues. Younger patients (under 50) may start with a full replacement dose, 1.6–1.8 µg/kg body weight per day [30–32]. Older patients, and patients with cardiovascular disease, are usually started at doses of 25 or 50 µg/day, increasing the dose at intervals [30–32]. Treatment is monitored primarily by assessing the serum level of TSH. Since levothyroxine has a long half-life, normally 7 days and longer in those with T4 deficiency, it is customary to monitor dosage at 6 weeks intervals, and to adjust dosage until TSH is normalized. Thereafter, follow-up at 6–12 month intervals is recommended. Interestingly, the Carani et al. [11] study reported a possible improvement of delayed ejaculation also in subjects with mild or sub-clinical hypothyroidism (TSH between 5 and 10 mU/L and normal FT3 and FT4). Two different recent meta-analyses showed that subclinical hypothyroidism increases the risk of ischemic heart disease (both prevalence and incidence) especially in younger subjects (<65 years old) [33, 34].

### 23.3.2 Ejaculation Disease Outcomes

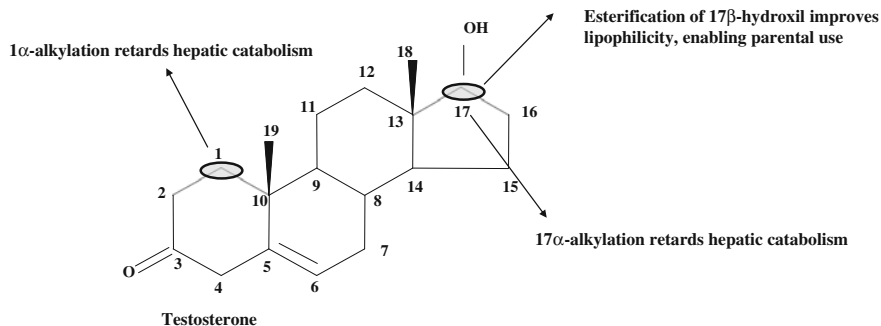
So far only one study has specifically evaluated the efficacy of thyroid treatment in hypothyroid patients with delayed ejaculation. Carani et al. [11] in a series of 14 subjects with hypothyroidism due to chronic lymphocytic thyroiditis, showed DE was resolved in half of the patients after thyroid hormone normalization. Hence, hypothyroidism should be ruled out in each patient with DE and if present an adequate treatment might improve both sexual and general health.

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## 23.4 Hypogonadism

### 23.4.1 Testosterone Preparations

Native T administered by mouth is well absorbed by portal blood, but it rapidly undergoes liver metabolism, so that a small portion actually reaches the systemic circulation [35, 36]. A similar outcome is obtained when native testosterone is



**Fig. 23.1** Chemical structure of Testosterone and possible site of structural modification to improve its bioavailability and pharmacokinetics

injected parenterally. Chemical modifications were introduced to improve T bioavailability and pharmacokinetics, essentially retarding the rate of absorption or decreasing its liver catabolism. Three general types of modification of T are clinically useful: esterification of the  $17\beta$ -hydroxyl group, alkylation at the  $17\alpha$  position and modifications of the A, B, and C rings (Fig. 23.1). Alkylation in the  $17\alpha$  position prevents rapid breakdown in the liver, however, it causes hepatotoxicity, and therefore these preparations are no longer recommended. Alkylation at position one as well as esterification of the  $17\beta$ -hydroxyl group, which also prevent premature metabolism, do not have this side effect. Esterification with carboxyl groups in the  $17\beta$ -position increases lipophilia and enables intramuscular administration in an oil solution [35, 36]. However, esters, which enter the circulation, display the same short half-life as that of T itself. The prolonged effect is therefore exclusively based on delayed release from the depot injection.

### 23.4.2 Oral Testosterone Preparations

The only T preparation available for oral administration is T-undecanoate (TU), which bypasses the liver via its lymphatic absorption and enables delivery of testosterone to the systemic circulation [35, 36]. The absorption with this formulation via lymphatic route is highly dependent on the lipid content of food intake resulting in an irregular serum testosterone pattern during the course of the day (Table 23.5).

### 23.4.3 Transbuccal Testosterone Preparations

A different option for oral administration is a novel sustained-release muco-adhesive buccal-T-table requiring twice-daily application to the upper gums. Transbuccal administration provides the absorption of T through the oral mucosa avoiding intestinal pass and liver inactivation. Testosterone buccal systems will

**Table 23.5** Testosterone preparations

Formulation	Chemical structure	T 1/2	Standard dosage
<b>Oral agents</b>			
Testosterone undecanoate <i>Trade name</i> Andriol Testocaps <sup>®</sup>	17- $\alpha$ -hydroxyl-ester	4 h	2–3 days 120–240 mg
Methyltestosterone <i>Trade names</i> Android <sup>®</sup> Testred <sup>®</sup> Virilon <sup>®</sup>	17- $\alpha$ -alkylated	3.5 h	2–3 days 20–50 mg
Mesterolone <i>Trade name</i> Proviron <sup>®</sup>	1-alkylated	8 h	100–150 mg 2–3 days
<b>Intramuscular agents</b>			
Testosterone enanthate <i>Trade names</i> Testoenant <sup>®</sup> Testoviron <sup>®</sup>	17- $\alpha$ -hydroxyl-ester	4–5 days	• every 2–3 weeks 250
Testosterone cypionate <i>Trade name</i> Delatestril <sup>®</sup>	17- $\alpha$ -hydroxyl-ester	8 days	• every 2–3 weeks 200 mg
Testosterone propionate <i>Trade name</i> Testoviron <sup>®</sup>	17- $\alpha$ -hydroxyl-ester	20h	• every 2 days 100
Testosterone undecanoate in castor oil <i>Trade name</i> NEBIDO <sup>®</sup>	17- $\alpha$ -hydroxyl-ester	34 days	every 10–14 weeks 1,000 mg
<b>Subcutaneous agents</b>			
Surgical implants <i>Trade name</i> Testopel <sup>®</sup>	Native testosterone	–	4–6 200 mg implants lasting up to 6 months
<b>Controlled release T-Buccal formulation agents</b>			
Testosterone buccal <i>Trade name</i> Striant <sup>®</sup>	Native testosterone	12 h	30 mg/twice daily

(continued)

**Table 23.5** (continued)

Formulation	Chemical structure	T 1/ 2	Standard dosage
<b>Transdermal agents</b>			
Testosterone patches <i>Trade names</i> Androderm <sup>®</sup> Testopatch <sup>®</sup>	Native testosterone	10 h	5–10 mg/day
Testosterone gel <i>Trade names</i> Androgel <sup>®</sup> Testogel <sup>®</sup> Testim <sup>®</sup> Fortigel <sup>®</sup> Tostrex <sup>®</sup>	Native testosterone	6 h	40–80 mg/day
Underarm testosterone (testosterone solution 2 %)	Native testosterone	NA	60–120 mg/day

NA not available

soften and mould to the shape of the gum and will gradually release medication. However, they will not dissolve completely in the mouth and must be removed after 12 h (Table 23.5). Men treated with buccal formulation 30 mg twice a day and compared to a group of patients given 5 mg of T gel formulation daily showed no differences in mean T serum levels and its effects on sexual functioning were comparable to giving injectable enanthate T [35, 36].

### 23.4.4 Transdermal Testosterone Preparations

There are a variety of transdermal approaches which have been developed (Table 23.5). They should be used daily and normally provide uniform T serum levels during the treatment. The transdermal T-patches available can produce consistent delivery of T into the systemic circulation, mimicking circadian rhythms; however they are frequently associated with adverse skin reactions at the patch site [35, 36].

Transdermal T gel, 1 or 2 % colorless hydroalcoholic T gels provide continuous delivery of T for 24 h after a single daily application [35, 36]. When an open system of T hydroalcoholic gel is applied to the skin, the steroid is rapidly absorbed into the stratum corneum, which forms a reservoir and acts as a rate-controlling membrane. Dose adjustment should be considered since skin absorption can vary among men. Testosterone gels have an excellent safety profile, and have been shown to normalize serum T levels.

Recently, the U.S. Food and Drug Administration approved another transdermal T formulation, a topical, alcohol-based T (2 %) solution applied to the underarm once daily, using a metered dose applicator (Table 23.5). A phase three multi-center, open-label 120 day clinical study, involving 135 men (mean age 52 years), demonstrated that 84 % of men who completed the study achieved average serum testosterone concentration within the normal range of 300–1,050 ng/dl. In addition a significant ( $p < 0.0001$ ) improvement of positive mood (+13 %), sexual desire (+79 %), sexual activity (+104 %), and sexual performance (+35 %) were also observed [37].

### 23.4.5 Injectable Testosterone Preparations

Injectable  $17\beta$ -hydroxyl esters in oily depot are another possible formulation [35, 36]. When T is injected into muscle, usually in the buttocks, it is absorbed directly into the blood stream. Essentially, injectable preparations can be divided according to their half-lives. The propionate-T ester is a short-term formulation, not widely used because it requires the administration of fractionated doses weekly (usually 50 mg every 2–3 days) and 200–250 mg of cypionate and enanthate-T esters must be injected every 2–4 weeks. In general, after the administration of these two preparations, serum T reaches supra-physiologic levels after 24 h, followed by a gradual decline to hypogonadal levels over the following two weeks [35, 36]. This effect may create a sense of euphoria in the period immediately following injection and a subsequent rapid return of hypogonadal symptoms as T levels fall. This wide fluctuation in T concentrations could lead to frequent side effects, also dangerous ones, such as polycythemia [35, 36] (Table 23.5). More recently, a new, longer lasting injectable formulation of T-undecanoate has been introduced [35, 36]. Its fatty acid side-chain of medium length in  $17\beta$ -position (11 vs. 7 carbon atoms) increases half-life in comparison to other esters. A dosing regimen of 1,000 mg every 12 weeks, following a six week loading dose has been recommended (Table 23.5). It is injected slowly into the muscle of the buttock where it forms a reservoir. The testosterone is gradually released all the time from the reservoir into the bloodstream and does not usually reach supra or sub-physiological levels, keeping serum levels physiologically within the normal range.

### 23.4.6 Pellet Testosterone Preparations

An even longer-lasting option is the implantation of T pellets, available in the USA, UK, and Australia. The pellets, made from pure crystals of T, are inserted subcutaneously and held with a retention suture, and erosion at the surface of the pellets leads to systemic absorption. The procedure is invasive and may be unattractive to patients [35, 36] (Table 23.5).

### 23.4.7 Testosterone Replacement Therapy Follow Up

Patients should be monitored at 3–6 months during the first year, and at least annually thereafter [38–40]. At each visit a careful clinical and andrological evaluation, including digital rectal examination (DRE), is mandatory. Biochemical assessment must include the evaluation of PSA and hematocrit. Metabolic parameters such as glycemia and lipid profile can also be measured, while liver function is no longer required using the new available T formulations.

Prostate biopsy should be performed in the presence of clinical suspicion (palpatory nodule at DRE). In addition, prostate biopsy should be considered for PSA levels higher than 4 ng/ml, an increase in serum PSA concentration >1.4 ng/ml within any 12 month period of TRT or a PSA velocity of >0.4 ng/ml/yr using the PSA level after six months of testosterone administration as the reference (only applicable if PSA data are available for a period exceeding two years) [38–40].

### 23.4.8 Testosterone Replacement Therapy Outcomes in Patients with Ejaculatory Dysfunction

Although potentially TRT might improve DE, no study has ever assessed this possibility. Similarly, due to obvious ethical problems, no studies have ever evaluated the treatment of PE with androgen deprivation therapy. Since epidemiological evidence has recently sustained a possible association between hypogonadism and DE, it is our opinion that T should be evaluated in each patient with DE. TRT might represent an important strategy in improving a disease as difficult to treat as DE. Interventional studies are advisable to better clarify this point.

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## 23.5 Conclusions

Several epidemiological and experimental studies have documented an association between premature ejaculation and hyperthyroidism. Restoring euthyroidism can improve ejaculatory latency although a limited number of subjects has been evaluated. Conversely, hypogonadism and hypothyroidism might be associated with DE. In the latter cases a possible improvement of IELT has been reported only after a successful treatment of hypothyroidism.

Treatment of thyroid diseases might improve ejaculatory dysfunction and in particular premature ejaculation. However, it is important to emphasize that only a limited number of subjects have been evaluated. Accordingly, guidelines from the International Society for Sexual Medicine do not recommend routine TSH screening in men with acquired PE [7]. Larger and longer studies are advisable in order to better clarify these points.

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# Complementary, Surgical, and Experimental Modalities for Management of Premature Ejaculation

# 24

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## 24.1 Introduction

Research on the prevalence and management of premature ejaculation (PE) has historically been hampered by lack of clarity regarding what constitutes early ejaculation of clinical relevance; thus, inclusion criteria for studies on PE have often been heterogeneous. There has been a recent movement towards subclassification of early ejaculation into four separate conditions: including (i) lifelong (or primary) PE, (ii) acquired (or secondary) PE, (iii) PE-like disorder (ejaculation-related distress in a patient whose ejaculatory latency is within the population based reference range), and (iv) natural variable PE (occasional short ejaculatory latency in men who otherwise have normal ejaculatory function) [1, 2]. The majority of clinical research to date has focused on the condition now most clearly understood as lifelong PE.

The International Society for Sexual Medicine (ISSM) defines lifelong PE as “A male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within about 1 min of vaginal penetration, and the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy” [3]. While this is widely accepted as the only evidence-based definition of lifelong PE, it is limited to heterosexual activity because the vast majority of studies on PE have been limited to heterosexual men. There has been scant clinical research on distressing early ejaculation during noncoital sexual

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activity such as digital, oral, and anal sex in heterosexual and homosexual dyads. Further research is required for operational definition of sexual distress and early ejaculation in conditions other than heterosexual coitus.

Many studies on PE therapy have been of short duration and have not investigated recurrence of symptoms after treatment cessation [4]. The general lack of long-term followup data has limited the number of drugs that have been widely approved for the treatment of PE. Currently, the only medication approved by any pharmaceutical regulatory body for the management of PE is the short-acting selective serotonin reuptake inhibitor (SSRI) dapoxetine. Dapoxetine has been approved for use in several European countries but has not received approval from the United States Food and Drug Administration (USFDA) [5].

Although the USFDA did not grant approval to dapoxetine as a treatment for PE, a number of other therapeutic modalities have been utilized in the United States and other countries for the management of this prevalent and vexing medical condition. These therapies include off-label use of SSRIs, topical anesthetics applied to the penis, and psychosexual therapy with or without instruction on techniques to delay ejaculation. These standard recommendations for management of PE have been codified in the 2004 American Urologic Association (AUA) Guidelines on the management of PE, the 2009 European Association of Urology (EAU) Guidelines on erectile dysfunction (ED) and PE, and the International Society for Sexual Medicine (ISSM) Guidelines for the Diagnosis and Treatment of PE [6–8].

In this manuscript we will summarize management strategies for lifelong PE that have been reported in the biomedical literature but have not been included as recommended treatment options by either the AUA, EAU, or ISSM guidelines [6, 8]. While some utility may be expected from use of these therapies in men with PE, further data are required before any can be considered standard of care. Furthermore, some of these treatments may carry known or occult risks and should therefore be utilized only in a carefully controlled research setting.

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## 24.2 Methods

An English-language Pubmed literature search was carried out using the term “premature ejaculation therapy”. Manuscripts addressing SSRI, topical anesthetics, and behavioral/psychotherapy were excluded except in cases where these modalities were used as a comparator group or as part of combination therapy. All other manuscripts detailing alternative means of PE management were retrieved and critically reviewed. Results are summarized by class of treatment.

The gold standard for objective measurement of response to treatment for PE during coitus is the intravaginal ejaculatory latency time (IELT) [9]. Measurement of IELT is best accomplished by activation of a stopwatch at the moment of vaginal penetration with stop at the moment of ejaculation. Many studies have relied on this precise methodology whereas others have relied in patient/partner estimates of IELT. An additional consideration when interpreting therapeutic

response to treatments for PE is the influence of positive skew (i.e., dramatic increases in a few subjects that may overinflate the mean IELT) in treatment groups. Geometric mean IELT (calculated by mean of log transformed raw IELT results) provides a more accurate measurement of treatment response than arithmetic mean IELT [10]. As most studies to date have utilized arithmetic mean IELT, in this manuscript “IELT” will refer to stopwatch-timed measurements of ejaculatory latency and “mean IELT” will refer to *arithmetic* mean IELT unless otherwise specified.

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## 24.3 Summary of the Literature

### 24.3.1 Erectogenic Agents

Facilitation of penile erection may be of benefit in men with PE as ED may have a comorbid and synergistic effect with PE [11]. Men with both ED and PE should undergo treatment of ED first as in some cases patient-reported “PE” is secondary to concerns of the potential for erectile failure and subsequent “speeding up” of sexual stimulation for fear of inability to maintain erection for prolonged periods [6]. While this is an established therapeutic algorithm, studies of variable scientific rigor have also investigated the use of phosphodiesterase type-5 inhibitors (PDE5I) or intracavernous injection (ICI) with vasodilators as means to treat PE in the absence of clinical ED [11].

#### 24.3.1.1 Rationale for Use of Erectogenic Medications in PE

Treatments for ED are the only contemporary medical interventions that have received USFDA approval for the management of a sexual concern in men [12]. As these medications are widely available and generally safe, there has been understandable interest in their application to nearly every male sexual problem, including ejaculatory dysfunction. Enhancement of erectile function has been shown to boost confidence and enable a more relaxed approach to sexual activity; this may have important effects on perceptions of ejaculatory control [13, 14]. Furthermore, erectogenic agents may reduce erection refractory time and permit repeated episodes of sexual activity; this has been suggested as a management scheme for men with early ejaculation [15].

While a role for psychobehavioral management of PE is readily apparent, there has also been interest in direct physiological mechanisms of ejaculation that may be amenable to manipulation of the same molecular pathways that are central to penile erection [16]. Nitric oxide (NO) and its downstream effectors (including cGMP) play a number of critical roles in the genitourinary tract [17]. The importance of NO/cGMP signaling in penile vasodilation and subsequent erection is well-established [18]. More recent studies have investigated the activity of the NO/cGMP pathway on smooth muscle activity of the genitourinary organs involved in emission and ejaculation.

Machtens et al. evaluated the effects of NO-donating drugs on adrenergic-induced tension and spontaneous phasic contractility of human seminal vesicles *in vitro*. It was determined that adrenergic tension was attenuated, in a dose-dependent fashion, by a variety of NO donating drugs (including sodium nitroprusside) as well as by the adenylyl cyclase activating agent forskolin. Based on these observations the authors posited that contractility of the seminal vesicles is influenced by modulation of the NOcGMP pathway [19]. This research group expanded upon these findings in a subsequent publication confirming the effects of the phosphodiesterase (PDE) inhibitors vinpocetine (PDE1 inhibitor), rolipram (PDE4 inhibitor), sildenafil, and vardenafil (both PDE5 inhibitors) on human seminal vesicles *in vitro*. Phasic contractile activity induced by means of electrical field stimulation of the SV tissue was most effectively inhibited by the PDE4 inhibitor rolipram and the PDE5 inhibitors sildenafil and vardenafil [20]. These findings were replicated by Gajar et al. using human seminal vesicle strips precontracted with noradrenaline or potassium chloride and treated with sildenafil [21].

It is reasonable to speculate that increased NO production and reduced sympathetic tone from PDE5I may lead to smooth muscle dilatation of the vas deferens and seminal vesicles with subsequent delay of seminal emission [13]. The role of NOcGMP signaling in the normal physiology of ejaculation is at this time incompletely understood and a topic for further *in vivo* research [16].

#### **24.3.1.2 Use of Phosphodiesterase Type 5 Inhibitors as Monotherapy**

PDE5I have been investigated *in vivo* for the management of PE as monotherapy or in conjunction with other pharmacotherapies. While *in vitro* studies have suggested benefit from PDE5I in the treatment of PE, *in vivo* human data have been more controversial. None of the following studies used the current definition of lifelong PE because all were conducted prior to release of the 2008 ISSM statement on this condition [3].

Abdel-Hamid et al. compared on-demand (3–5 h prior to intercourse) use of clomipramine hydrochloride 25 mg, sertraline hydrochloride 50 mg, paroxetine hydrochloride 20 mg, sildenafil citrate 50 mg, and the “squeeze” technique of Masters and Johnson in a prospective, blinded, randomized, crossover study enrolling 31 patients with lifelong PE (IELT less than 2 min and lack of sense of control over ejaculation) over five 4 week consecutive treatment periods. Each change of intervention occurred after a 2 week washout period. The median IELT was significantly increased from a baseline median of 1–4, 3, 4, 15, and 3 min during treatment with clomipramine, sertraline, paroxetine, sildenafil, and pause-squeeze technique, respectively [13]. Limitations of this study include small sample size, lack of a placebo arm and retrospective recall as the means of reporting IELT. While the drug therapy portion of the trial was blinded, it is not possible to blind patients allocated to the pause-squeeze arm. Furthermore, on-demand use of standard SSRI for PE has been reported to be less efficacious than chronic dosing given the relatively long period of time necessary for accumulation of drug [22]; chronic therapy with SSRI might have yielded more substantially improvements.

Mathers et al. conducted a randomized prospective crossover study to determine the effectiveness of SSRI and PDE5I in 49 patients with primary PE (mean IELT <1.5 min at least half of the time) who had failed 6 weeks of behavioral psychotherapy for the condition. Men were randomized to receive the SSRI sertraline 50 mg 4 h or vardenafil 10 mg 30 min before intercourse for 6 weeks before being crossed over to the other medication after a one-week washout. Mean IELT in these 49 patients was 0.59 min; mean IELT increased to 5.01 min in the vardenafil group and 3.12 min in the sertraline group. Also noted was significant improvement in partner sexual satisfaction with both treatments [23]. Limitations of this study include the lack of placebo control, open label design and questions about patient selection.

Wang et al. evaluated the efficacy and safety of sildenafil alone in the treatment of lifelong PE (IELT <2 min, mean for all groups slightly over 1 min in this study) in a prospective, randomized, non-blinded trial of 180 men divided into three groups: 50 mg sildenafil 1 h before intercourse, 20 mg paroxetine daily, and squeeze technique daily for 6 months. Mean IELT at 3 months was 6.2, 4.9, and 2.8 min for the sildenafil, paroxetine, and squeeze technique cohorts and these values were essentially stable at 6 month followup; these differences were statistically significant from baseline for all groups but greatest efficacy was noted in the sildenafil arm [24]. Limitations of this study includes the lack of a placebo arm and nonblinding with respect to treatment arm.

Aversa et al. investigated on-demand vardenafil (10 mg) in men with lifelong PE (IELT <1 min) with either no or mild ED as determined by score of 22 or greater on the International Index of Erectile Function Erectile Function domain (IIEF-EF). The study consisted of 42 men in a 16 week, double-blind, placebo-controlled, cross-over study with no washout period at time of cross-over. Mean geometric IELT increased from 0.6 to 4.5 min ( $p < 0.01$ ) in the vardenafil arm compared to 0.7–0.9 min ( $p = ns$ ) in the control arm during the first portion of the trial. Interestingly, after cross over, men initially treated with vardenafil had a decline in mean IELT to 3.2 min which was still significantly greater than what was observed at baseline; men who crossed over from placebo to vardenafil experienced an increase in mean IELT from 0.9 to 2.0 min. Also reported were significantly reduced postejaculatory refractory time and increased ejaculatory control, improved overall sexual satisfaction, and improved distress scores in vardenafil-treated men [25]. It is particularly interesting that IELT decreased when the vardenafil group switched to placebo but remained above baseline; this suggests either some residual effect of vardenafil on ejaculation or that improvements in sexual confidence after the treatment period led to persistent clinical benefit.

In the largest placebo-controlled study to date on the use of PDE5I for PE, McMahon et al. evaluated PDE5I for PE in a multicenter, 8 week, double-blind, placebo-controlled, parallel group, flexible-dose study of sildenafil (50–100 mg on demand) in 157 patients between 18 and 65 years of age with lifelong PE (IELT less than 2 min on at least 75 % of attempts at intercourse). The investigators did not find a statistically significant increase in IELT in men treated with sildenafil versus placebo. However, confidence, perception of control over ejaculation, and

overall sexual satisfaction were significantly increased in the treatment group. No statistically significant difference was demonstrated in a substudy of 17 patients enrolled in a two-way crossover study of ejaculatory response to vibrotactile stimulation 1 h after a single dose of sildenafil 100 mg or placebo [14]. A caveat of this study is that patients with mild ED (defined by IIEF-EF score of 22–25) were included; [26] Nevertheless, this study suggests that PDE5 inhibitors are not effective for the treatment of PE although they may have beneficial impact on some other aspects of sexual function in addition to the treatment of ED.

### **24.3.1.3 Use of Phosphodiesterase Type-5 Inhibitors in Combination Therapy**

In a prospective study of 138 men with PE (patient estimated IELT <3 min), Chen evaluated the use of sildenafil as adjuvant therapy in cases of failure of (in sequence) lidocaine ointment and the selective serotonin reuptake inhibitor paroxetine. Subjects were initially treated with lidocaine ointment; 100 men who were not initially satisfied were given paroxetine 20 mg daily for 30 days followed by on-demand 7 h before intercourse. Of those 100 men treated with paroxetine, 58 desired further improvement and were given sildenafil on demand (25–100 mg flexible dosing). Of those 58, 56 reported subjective satisfaction with this combination treatment [27]. Limitations of this study include the lack of placebo control, nonblinded interventions, nonvalidated measures of success measurements, lack of a clinical trial design, and inclusion of men with IELT of up to 3 min. Furthermore, behavioral counseling was made available to all subjects during treatment and may have influenced outcome.

Salonia et al. reported on 80 men with PE (IELT <1 min) randomized to treatment with paroxetine 10 mg daily for 21 days followed by on-demand dosing of paroxetine 20 mg 3–4 h before intercourse or the same algorithm with adjuvant sildenafil 50 mg 1 h before intercourse. Mean IELT increased from 0.33 to 3.7 and 4.2 min at 3 and 6 months, respectively, in the paroxetine monotherapy group. Significant improvements were also noted in the paroxetine plus sildenafil treatment arm, with mean IELT rising from 0.35 min to 4.5 and 5.3 min at 3 and 6 months, respectively. Improvements in IELT were significantly greater in the combination treatment arm compared to the paroxetine monotherapy arm [28]. This study is hampered by lack of a placebo arm and a subject pool that included 18 patients with acquired PE. Furthermore, while 14 patients were excluded from this analysis due to “ED” the mean IIEF scores at baseline were 26 and 27 for the monotherapy and combination treatment group; it is implied that at least some of the patients in each group may have had IIEF-EF scores below the standard cutoff for ED (IIEF <26) [26]. No comment is made on the number of men with IIEF-EF scores in the less than 26 range.

Mattos evaluated the effect of the PDE5I tadalafil 20 mg taken within a 36-hour window before intercourse with or without the SSRI fluoxetine at a 90 mg once weekly dose. Sixty men with lifelong PE (IELT <90 s) and no evidence of ED (IIEF-EF  $\geq$ 26) were enrolled in a twelve-week prospective randomized

double-blind placebo-controlled trial with four treatment groups: (1) tadalafil 20 mg plus fluoxetine 90 mg, (2) fluoxetine 90 mg plus placebo, (3) tadalafil 20 mg plus placebo, and (4) double placebo capsules (control). There was a significant increase in IELT for all treatment arms compared to the double placebo arm with mean change greatest in the combination treatment arm (mean increase 286 s) followed by the fluoxetine monotherapy arm (mean increase 177 s) and then the tadalafil monotherapy arm (mean increase 137 s). It is noteworthy that there was also a statistically significant albeit slight (mean increase 18 s) increase in mean IELT in the group treated with double placebo [29]. Limitations include small sample size and an irregular dosing regimen for both tadalafil and fluoxetine. It is unclear how the regimen of once weekly fluoxetine was selected by these investigators but it likely does not represent an adequate trial of the medication.

In a prospective randomized trial of 91 married men, Hosseini compared the efficacy of fluoxetine monotherapy versus combined fluoxetine and sildenafil in patients with PE (IELT <1 min) without a clear organic cause. The authors report that the subject pool “did not have ED according to the IIEF” but fail to outline their specific exclusion criteria. The patients were randomly divided to receive 20 mg fluoxetine daily for 4 weeks and then 20 mg as needed 2–3 h before sexual activity for 4 months OR the fluoxetine regimen plus 50 mg sildenafil as needed 1 h before sexual activity for 4 months. Mean IELT in the fluoxetine only group was 0.5, 3.4, and 4.3 min at baseline, 2 months, and 4 months respectively. In the combination therapy group mean IELT was 0.55, 4.2, and 5.1 min at the same time points. While both therapies led to statistically significant improvements, the change was significantly greater in the combination therapy group [30]. Limitations include lack of clarity regarding IIEF inclusion criteria and lack of a placebo control for sildenafil.

#### **24.3.1.4 Use of Erectogenic Intracavernous Injections**

Fien evaluated the effectiveness of ICI using vasoactive drugs in the treatment of lifelong PE (defined as anteportal or immediate ejaculation after penetration) in a prospective trial of eight patients who were not “impotent” (not otherwise defined) after failure of behavioral therapies including the Masters and Johnson’s penile squeeze technique, the gluteal muscle contraction technique, mental divergence, and a 15 min masturbation exercise. All eight had success with the intracavernous treatment of tailored amounts of bimix solution (papaverine hydrochloride 30 mg/ml and phentolamine mesylate 1 mg/ml) with erections lasting 2 and 4 h despite ejaculation. Three of the patients reported cure during the course of treatment and stopped all therapy [31]. There were significant limitations of this study including no comparison group, incomplete characterization of erectile function, lack of placebo control group, and overall small sample size. Furthermore, this therapy does not truly address issues of PE but rather medically induces erection that is not reversed by ejaculation. While not a true therapy for PE, ICI is widely marketed to men with PE by “men’s health” clinics, some of which charge significantly inflated prices for injectable erectogenic agents.

### **24.3.1.5 Summary on Erectogenic Therapy for ED**

Studies of erectogenic agents in the treatment of PE are summarized in Table 24.1. Treatments for ED clearly have a strong influence on sexual satisfaction and function in men. While these studies lend some credence towards use of PDE5I or injectable vasoactive agents in cases of clinical PE, it is not clear from published data that these drugs directly influence ejaculatory latency. It is tempting to speculate that the positive effects of erectogenic agents in clinical PE is related to greater subjective sexual confidence or to changes in sexual behavior rather than a direct effect of the drug on ejaculatory function. As fixed dosing regimens were utilized in the majority of comparative studies to date, it may also be that inadequate dose titration explains differences observed in treatment arms. Use of erectogenic drugs for management of ejaculation concerns remains a fertile ground for further research and development but at this time medications for facilitation of penile erection should not be construed as standard of care for lifelong PE in the absence of ED.

## **24.3.2 Sexological/Behavioral/Functional Approaches**

The ‘conditioning’ hypothesis of Rowland and Motofei separates the physiological ejaculatory processes into “hardwired” (unchangeable) and “softwired” (amenable to modulation) central and peripheral networks. Although these “hard-wired” components might respond in a graded manner to external modulators, they themselves are not the primary source of the modulation. While it seems likely that men cannot willfully and directly change underlying neurobiological responses (e.g., receptor sensitivity, inhibitory postsynaptic potentials, neurotransmitter release, etc.) in order to affect their orgasmic response, intentional modification of arousal, libido or motivation may alter the triggers for ejaculation. This view argues that treatment of PE aimed at multiple levels of functioning will be self-enhancing and ultimately more effective in producing positive therapeutic outcomes than strategies relying solely on either psychological or biological approaches [32].

### **24.3.2.1 Standard Behavioral Therapy for PE**

In 1956, Semans reported one of the first contemporary behavioral interventions for PE using a “stop-and-start” technique involving extravaginal stimulation of the penis until premonitory sensations of ejaculation occur. At the point of ejaculatory premonition, stimulation was stopped until the sensation resolved. In this fashion it was thought that the man would become conditioned to recognize and control signs of impending ejaculation during penetrative coitus [33]. It was reported that this intervention led to successful results in eight couples but these robust findings have not been convincingly replicated.

Masters and Johnson (1970) reported on the “squeeze” technique for PE; in this methodology the glans penis is withdrawn and forcefully compressed at high states



**Table 24.1** Studies of PDE5 Inhibitors for management of Premature Ejaculation

	Study design	Study size	Placebo?	Medication	Baseline IELT (mins)	Post treatment IELT (mins)	IELT increase
Abdel-Hamid et al. [13]	prospective, blinded, randomized, crossover study	31	No	clomipramine 25 mg sertraline 50 mg paroxetine 20 mg sildenafil 50 mg “squeeze” technique	1	4 3 4 15 3	3 2 3 14 2
Mathers et al. [23]	randomized prospective crossover study	49	No	sertraline 50 mg varденаfil 10 mg	0.59	3.12 5.01	2.53 4.42
Wang et al. [24]	prospective, randomized, non-blinded trial	180	No	50 mg sildenafil 20 mg paroxetine squeeze technique	1.09 1.11 1.06	6.2 4.9 2.8	5.11 3.79 1.74
Aversa et al. [25]	prospective, double-blind, placebo-controlled, cross-over study	42	Yes	varденаfil 10 mg placebo	0.6 0.7	4.5 0.9	3.9 0.2
McMahon et al. [14]	double-blind, placebo-controlled, parallel group, flexible-dose study	157	Yes	sildenafil 50–100 mg placebo	0.96 1.04	2.6 1.63	1.6 0.6
Salonia et al. [28]	prospective, randomized, non-blinded trial	80	No	paroxetine 10 mg (on demand 20 mg) paroxetine 10 mg (on demand sildenafil 50 mg)	0.33 0.35	3.7 and 4.2 (3 & 6 months) 4.5 and 5.3 (3 & 6 months)	3.37 & 3.87 4.15 & 4.95

(continued)

Table 24.1 (continued)

	Study design	Study size	Placebo?	Medication	Baseline IELT (mins)	post treatment IELT (mins)	IELT increase
Mattos et al. [28]	prospective randomized double blind placebo controlled trial	60	Yes	tadalafil 20 mg + fluoxetine 90 mg fluoxetine 90 mg + placebo tadalafil 20 mg + placebo double placebo capsules	0.83 0.94 0.82 0.83	5.6 3.89 3.1 1.13	4.77 2.95 2.28 0.3
Hosseini et al. [30]	prospective randomized	91	No	20 mg fluoxetine +20 mg fluoxetine on demand 20 mg fluoxetine + 50 mg sildenafil on demand	0.5 0.55	3.4, and 4.3 (2 & 4 month) 4.2 and 5.1 (2 & 4 month)	2.9 & 3.8 3.65 & 4.55

of sexual arousal so as to “reset” arousal and permit continued penetrative intercourse after squeezing is complete. Masters and Johnson reported a 97.8 % cure rate for their clients but these results have not been replicated [34].

The behavioral techniques of Semans and Masters and Johnson for management of PE have been incorporated (with and without modifications) into the treatment lexicon of contemporary sexual therapists despite a general lack of published replication of results and long-term follow-up. More contemporary authors have advanced a number of novel interventions/modalities as adjunctive behavioral treatments.

#### **24.3.2.2 Virtual Reality**

Optale studied the efficiency of a 1-year program combining psychodynamic therapy and virtual reality for the treatment of PE (described as “primary”) in 50 men. Therapy included a cycle of 12 psychodynamic sessions over a 25 week period integrating an audio CD and helmet with miniature television screens. Projected on these screens was a specially designed program about the development of sexual identity using a virtual pathway through a forest and nonerotic film clips. Clinical followup was done after 6 and 12 months after the cycle. After 6 months, partial (IELT greater than 2 min on 2/3rds of intercourse episodes) and complete (IELT consistently greater than 2 min) positive response was 8 and 48 %, respectively. This improved to a 54 % rate of complete response at 1 year with no partial responders at that time point. Of note, 26 % of patients dropped out of therapy [35]. The duration and likely expense of this prolonged therapy make the cure rate disappointing; furthermore, the outcome measures are subjective and nonvalidated, the inclusion criteria are vague, and there is no control group. While psychotherapy is likely to be of benefit it is not clear from this study that inclusion of the virtual reality experience improved results.

#### **24.3.2.3 Internet-Based Sex Therapy**

Internet-based sex therapy for men with ED has been advocated as an easily accessible and cost-effective treatment. van LankVeld et al. tested whether internet-based sex therapy is superior to a waiting list in 40 men with self-diagnosed PE. Treatment was based on the sensate-focus model of Masters and Johnson, and supplemented with cognitive restructuring techniques. Internet-based treatment was not superior to waiting list for PE in latency to ejaculation and sexual desire [36]. These data are limited by lack of a genuine control group; however it is suggested that a personal relationship with the therapist is important in realizing benefit from psychotherapy.

#### **24.3.2.4 Functional-Sexological Approach**

Carufela hypothesized that the ejaculatory reflex as such cannot be controlled but sexual excitement can via reduction in muscular tension. In a prospective study of 36 couples with PE (reported IELT <2 min), a functional-sexological curriculum designed to teach men ( $n = 18$ ) how to control sexual excitement was compared to

standard behavioral treatment (including the squeeze and stop-and-start techniques as described above). Nine random couples from each arm of the study were kept on a waiting list and served as a “control group”. This functional-sexological approach relies on focused attention to “temporal, spatial, and energetic dimensions movements”, to variable muscular contractions, and speed of sexual activity before and during intercourse, and to use of sexual positions that require less muscular tension. Stopwatch IELT was 57, 472, and 491 s pre-intervention, post-intervention, and at three-month followup, respectively, in the behavioral treatment arm. Stopwatch IELT was 43, 467, and 413 s pre-intervention, post-intervention, and at three-month followup, respectively, in the functional-sexological arm. Differences in IELT were statistically significant from baseline for both groups with no significant differences between the two treatment arms at followup [37]. Limitations of this method include difficulty mastering physical skills, which may require more effort and time than the traditional methods, as well as lack of clarity regarding presence of comorbid sexual concerns at baseline. Furthermore, the wait list group does not represent a true control.

#### **24.3.2.5 Yoga**

Yoga is a collection of physical and mental disciplines originating in India that have become a popular form of exercise and/or spiritual practice around the world [38]. Yoga has been purported as useful in the management of a number of health concerns including problems pertaining to sex. Dhikav et al. conducted a prospective, nonrandomized study of daily yoga or fluoxetine daily dose in 68 patients with PE. In these men, PE was diagnosed based on DSM-IV criteria, which stipulate only that ejaculation occurs before it is desired with no specific time criteria. *Asanas* (yoga positions) for this study were selected for their general putative health benefits with a focus on postures thought to improve muscle tone and plasticity of the pelvic and perineal muscles. Both groups had significant ( $p < 0.001$ ) improvement in IELT 8 weeks after initiation of treatment although the degree of increase was greater in the fluoxetine group (30 s at baseline increased to 64 s at followup in the yoga arm vs. 33 s at baseline increased to 113 s at followup in the fluoxetine arm) [38]. This patient population was recruited from an outpatient psychiatric clinic which could limit its applicability; furthermore, the lack of placebo control and randomization complicates interpretation of results.

#### **24.3.2.6 Physical Therapy**

La Pera proposed pelvic floor rehabilitation as a therapeutic modality for PE; his program involved physiokinesitherapy, electrostimulation of the external sphincter to induce hypertrophy, and biofeedback to control the ejaculatory reflex which reinforces and tones muscles thought to inhibit the reflex contractions of ejaculation. The trio of interventions is suggested to increase the closing pressure of the external urethral sphincter and possibly delay ejaculation. A prospective study of eighteen patients with PE (defined as ejaculation within 1 min or 15 vaginal

strokes) and normal penile nocturnal tumescence testing evaluated the effects of 15–20 sessions of this program of pelvic floor rehabilitation for PE. Of the eighteen patients, eleven were cured by learning to “control the reflex”, although the precise definition of cure was not reported [39]. The lack of clearly defined endpoints and failure of replication, tend to detract credibility from this manuscript. Furthermore, 15 patients were reported to have had PE for longer than 5 years but it is unclear how many had lifelong versus acquired PE.

### 24.3.3 Acupuncture

Sunay assessed acupuncture for PE (IELT <2 min) compared to daily paroxetine and sham acupuncture. Ninety men with PE received either 20 mg of daily paroxetine, twice weekly acupuncture (with points chosen based on standard acupuncture practice), or twice weekly sham acupuncture (placement of a needle at the same point as the treatment group without skin penetration to produce a “pricking” sensation) for 4 weeks ( $n = 30$  each arm). Men with primary PE made up about 2/3rds of the study cohort and were evenly distributed between treatment arms. IELT was measured for each individual man and mean rank IELT was determined. Paroxetine produced the longest mean-rank increase in IELT at 83 s compared to 66 s in the acupuncture arm and 33 s in the sham arm. The difference between both paroxetine and acupuncture arms was significantly greater than what was observed in the control arm [40]. This manuscript is limited in that men with both secondary and primary PE were enrolled. However, these data suggest that acupuncture may exert an effect on IELT but this effect appears to be less than what is observed with medical therapy. Further investigations of this modality may be warranted.

### 24.3.4 Herbal Medications

Herbal therapies are an increasingly popular treatment for a variety of health concerns, including issues pertaining to sexuality [41]. These treatments may be preferred by individuals who cannot afford prescription medications, individuals who prefer a naturopathic approach to health, and individuals who are mistrustful of prescribed pharmaceuticals. Herbals and nutraceuticals are not regulated by the FDA or other international regulatory agencies and there has been substantial concern about irregularities (contamination, counterfeiting, intentional or accidental mislabeling) of over-the-counter herbal drugs [41]. Nevertheless, these compounds may in some cases have utility in the management of sexual concerns including PE.

*Satureja montana* (winter savory) is a medicinal plant traditionally used to treat disorders including male sexual dysfunction. Zavattia et al. evaluated the effect of the plant’s hydroalcoholic extract, given acutely and subacutely, on copulatory

behavior of sexually potent male rats. Groups of 5–7 animals were given 0 mg, 25 or 50 mg/kg of the extract acutely (testing 45 min post-dose) and subacutely (testing after eight once daily treatments) for: mount latency; intromission latency; ejaculation latency; postejaculatory interval; mount frequency; intromission frequency. Acute administration of *Satureja montana* extract significantly increased ejaculation latency and reduced the number of intromissions before ejaculation without affecting the percentage of animals achieving ejaculation (100 % in all experimental groups) [42]. While the results are interesting it is not clear that these findings are applicable to the human condition of PE; further human studies are required. Gu-jing-mai-si-ha is an herbal compound consisting of *Radix anacycli pyrethri*, *Mastiche*, *Fructus Cardamomi*, *Rhizoma Cyperi*, *Stigma Croci*, *Semen Myristicae*, *Radix Curcumae*, *Folium Syringae oblatae*, *Radix et Rhizoma Nardostachyos*, *Fructus Tsaoko*, and *Flos Rosae rugosae*. It has been hypothesized that this decoction may treat PE by modulation of smooth muscle necessary for ejaculation. Song investigated the effect of gu-jing-mai-si-ha tablets (administered as 4 tablets of unspecified dose twice daily for 15 days) for treatment of primary and secondary PE (IELT <2 min, no specifics on how many primary vs. secondary) in a randomized prospective trial of 69 patients. A comparison group of patients who were not treated with any intervention was included. Evaluation of response was conducted at baseline and “at the end of the treatment period” although it is not clarified if this was on the day of the last dose. Mean IELT improved from 1.27 to 2.73 min in the treatment group compared to a change of mean IELT from 1.25 to 1.16 min in the untreated group. Serum level of NO and PGF2 $\alpha$  increased significantly in the treated group; the authors speculate that this effect may be responsible for the change in IELT [43]. Limitations of this study include unclear enrollment criteria and clinical endpoints, lack of a true placebo control group, unclear means of calculating IELT, and difficulty in determination of the active moiety of this complex herbal extract.

### 24.3.5 Surgical Approaches

It has been speculated that enhanced sensitivity of the glans penis may account for some cases of PE [44]. Indeed, modulation of penile sensitivity is the underlying principle for topical anesthetics in the management of PE [6, 8]. While reversible modulation of penile sensitivity is within the bounds of standard of care, some authors have investigated surgical approaches to permanently decrease glanular sensitivity and in so doing prolong ejaculatory latency.

#### 24.3.5.1 Circumcision

The role of human foreskin on sexual sensitivity and satisfaction is a topic of vociferous debate despite the absence of convincing data that the foreskin is either essential or nonessential for optimal sexual satisfaction, specifically as it pertains

to ejaculatory latency [45–51]. Both removal and/or restoration of the foreskin and frenulum have been touted as potential solutions to disorders of ejaculation.

Waldinger conducted a prospective study of 491 heterosexual couples recruited from the United States, the Netherlands, the United Kingdom, Spain, and Turkey to determine the stopwatch-assessed IELT over a 4-week period in a random cohort of men who had not presented nor been diagnosed with a sexual problem. The overall median value was 5.4 min but with differences between countries; interestingly and contrary to popular belief about early ejaculation as a young men's sexual problem, IELT was lower in progressively older age cohorts. The median IELT did not differ significantly based on circumcision status when subjects from Turkey ( $n = 130$ , all of whom had been circumcised) were excluded (6.7 min in circumcised vs. 6.0 min in uncircumcised European and American men) [45]. While this study was not a prospective analysis of circumcision and its' influence on ejaculatory function, it is suggested that presence or absence of the foreskin does not substantially influence ejaculatory latency.

In a retrospective study, Masood assessed the effect of circumcision for benign disease (most commonly Balanitis xerotica obliterans, nonspecific inflammation, or phimosis) on sexually active men without ED as determined by the abridged, five item version of the International Index of Erectile Function (IIEF-5). Of 150 men who had undergone circumcision, 84 (59 %) responded. Fifty-four of these subjects (64 %) did not report PE (in response to a single- item nonvalidated question about presence or absence of PE) at any time point. Of the remaining 30 patients, 16 (53 %) reported no change in ejaculation, 4 (13 %) reported improvement in PE, and = 10 (33 %) reported worsening of PE after circumcision [47]. This study is limited by the lack of a uniform definition of what constitutes PE as well as potential for recall bias regarding ejaculatory function. All of these men had a benign condition of the penis, most often inflammatory, and the influence of that condition on sexual and ejaculation function may have strongly influenced outcomes. The followup interval is not made clear in this report.

#### **24.3.5.2 Frenulectomy**

Gallo et al. hypothesized that the presence of a short frenulum is associated with primary PE and that treatment of this condition may improve ejaculatory latency. In a cohort study of 137 patients with primary PE (defined here as “ejaculation which always or nearly always occurs prior to or within about 1 min of vaginal penetration, and the inability to delay ejaculation”), 59 (43 %) were found to have a “short frenulum”. The authors defined a short frenulum as “every case in which, applying a gentle pressure, the length of the frenulum restricted the movement of the prepuce, causing, during its complete retraction, a ventral curvature of the glans major of 20 °.” Forty patients with short frenulum and PE underwent total excision of the frenulum and coagulation of the proximal stump. Mean IELT was 1.6 min at baseline and 4.1 min at a mean followup time of  $7 \pm 3$  months [52]. Limitations of this study include use of arithmetic rather than geometric mean IELT, short followup of only 7 months, lack of a control group, and somewhat arbitrary definition as to

what constitutes a short frenulum. Surgical intervention for PE may pose significant risks and should be undertaken with extreme caution [53].

### 24.3.5.3 Glans Injections

Glanular injection of bulking agents with the intention of partially disrupting sensation of the glans penis has been advanced as a treatment for PE. The concept is similar in principle to on-demand use of topical anesthetics although in this circumstance the desire is to permanently decrease the density and/or responsiveness of nerve innervations to the glans.

Hyaluronan (HA) is a naturally occurring polysaccharide that is ubiquitous in the extracellular matrix of many animal species including humans. Kim et al. investigated the effects of partial dorsal neurotomy (transection of the dorsal component of the glanular innervations and the ventral and lateral component of the contralateral glanular innervations through a circumcising incision,  $n = 25$ ), glanular augmentation with injectable HA (subcutaneous injection of 2 ml of HA near the corona of the glans in a fanned-out fashion with supplemental HA injections to smooth out undulations,  $n = 65$ ), and dorsal neurotomy with glanular augmentation ( $n = 49$ ) in nonrandomized patients with lifelong PE. Criteria for enrollment were not clearly specified but mean IELT (method of ascertainment not specified) for all groups was less than 2 min (mean baseline range 25–210 min). Six months after treatment, mean IELT was significantly increased in all three groups (89–236 s in the dorsal neurotomy group, 97–282 s in the glans augmentation group, and 102–324 s in the combination treatment group). There was no significant difference in mean IELT between treatment groups although there was a higher rate of adverse events (numbness, paresthesias) in patients who underwent dorsal neurotomy as single or combination therapy. Patient and partner satisfaction was relatively similar between treatment groups [54].

In a subsequent publication by these same authors, Kwak et al. followed up the 5-year outcome of HA injection in 38 of the initial cohort of 65 patients treated with HA injection monotherapy. Followup mean IELT (measured by stopwatch) was high at 352 s (range 220–410 s) compared to baseline mean IELT (84 s with range 45–170 s). The mean IELT was slightly but significantly less at 5 years compared to 6 months; however, the absolute difference was small at 25 s [55].

These studies are limited in that PE is not clearly defined, there is no control group, and it is not specified how patients were assigned to treatment groups. Furthermore, it is not clear whether the patients without 5-year followup data were lost or had simply not reached the 5 year point. A randomized controlled trial with more precisely defined inclusion criteria and endpoints is required before this treatment can be considered anything but experimental.

### 24.3.5.4 Radiofrequency Ablation of the Dorsal Penile Nerves

Basal et al. investigated bilateral neuromodulation of the dorsal penile nerves by pulsed radio frequency in 15 men with lifelong PE (IELT <1 min) refractory to medical management and no ED based on the IIEF-EF (no specifics given).



Neuromodulation of this sort is intended to apply high voltage adjacent to a nerve without inducing injury and has been utilized in pain management. Baseline mean geometric IELT was 19 s; at followup 3 weeks later mean IELT was 140 s. During extended follow-up (mean of  $8.3 \pm 1.9$  months) “none of the patients or their wives reported any treatment failure” but no additional IELT measurements were obtained and the definition of treatment failure is not provided. The procedure was by report painless [56]. The study is limited by small cohort size, lack of a control group and very short follow-up using the gold standard of IELT assessment. The potential for long-term damage to sensory capacity must also be considered.

#### **24.3.5.5 Summary Statement on Surgical Approaches for PE**

While it is difficult to conduct controlled and randomized studies of surgical interventions for PE, the lack thereof constitutes a serious limitation of current studies. The relatively permanent nature of this sort of intervention makes careful patient counseling and further studies essential to determine if there is any utility from these approaches. At the present time, there are insufficient data to justify surgical management of PE.

### **24.3.6 Miscellaneous Medications**

#### **24.3.6.1 Beta Blockers**

Anxiety (either generalized or specific to sexual behaviors) has been linked to PE as a co-morbid or potentially causative condition for decades [34]. Although ejaculation is mediated predominantly by  $\alpha$ -adrenergic receptors, beta-blockers have been shown to improve somatic manifestations of anxiety such as tremor, excessive sweating and muscle tension. Cooper et al. extrapolated from this that beta blockers may be of utility in management of PE. In a prospective, 20 week, double-blind, placebo-controlled crossover trial, the beta-blocker propranolol was evaluated in 12 men with anxiety and PE (IELT <2 min). Mean IELT increased from 1.5 to 1.7 min with both treatments; there was no significant difference between treatment arms and from baseline. However, a beta-blockade effect was noted with a mean decrease in pulse rate in the treatment arm [57]. Although this study is limited by small sample size there is little evidence to suggest that further evaluation of beta-blockade as monotherapy for PE is warranted.

The beta-blocker pindolol is known to block 5-HT<sub>1A</sub> autoreceptors in the dorsal raphe nuclei and thereby potentiate the increase in synaptic serotonin activity induced by SSRIs. In a 6-week randomized controlled study, Safarinejad evaluated pindolol 7.5 mg daily as an adjunctive therapy in 86 men with PE (IELT <2 min) who had failed management with paroxetine 20 mg daily for 2 or more months. Seventy-seven patients (89.5 %) completed the study. Mean IELT in the paroxetine-pindolol arm increased from 48 s at baseline to 188 s at follow up; this was significantly greater than the change observed in the paroxetine-placebo arm (41 s at baseline to 58 s at followup). Upon discontinuing pindolol, all outcome measures

returned to baseline values rapidly [58]. While generally encouraging, several experts have questioned the design of this study. These results will require replication in other centers to determine the true efficacy of this therapeutic adjunct.

#### 24.3.6.2 Antibiotics

Prostatic and lower urinary tract inflammation/infection have been posited as a potential cause of ejaculatory dysfunction [59, 60]. Screponi surveyed the incidence of chronic prostatitis in a cohort of 46 patients with primary ( $n = 21$ ) and secondary ( $n = 25$ ) PE (IELT  $< 2$  min) compared to 30 age-matched healthy controls [59]. Urethral urine, midstream bladder urine, expressed prostatic secretions by prostate massage, and postmassage urine samples were collected and examined according to the protocol of Meares and Stamey [61]. Prostatic secretions were culture positive in 13 of 21 (62 %) of primary PE patients and 9 of 25 (36 %) of secondary PE patients compared to 2 of 30 (7 %) of the non-PE control group. Additionally, four patients with secondary PE had greater than 10 leukocytes per high-powered field in prostate secretions in the absence of culture positivity. In this same paper these authors also report a 61.5 % prevalence of incidental PE in a population of 26 men referred for evaluation of prostatitis [59]. A similar rate of prostatitis was reported by Shamloul in a cohort study of 153 men with PE [60]. These studies do suggest a relationship between prostate inflammation and ejaculation but the correlation does not of necessity establish causation.

In a case report, Brown reported resolution of PE (self-reported IELT 1–2 min) of 3 years duration in a 31-year-old man who was treated with ciprofloxacin for bacterial prostatitis. After a 30-day treatment course self-reported IELT improved to 6–15 min and remained within this range at an unspecified followup time [62]. This study is limited by the entirely subjective description of pre- and posttreatment ejaculation parameters and a lack of clarity regarding the temporal association between prostatitis symptoms and clinical PE.

El-Nashaar and Shamloul reported a 65 % prevalence of chronic prostatitis (defined as 10 or more leukocytes per high powered field in expressed prostatic secretions) in a population of 145 men with secondary PE (IELT  $< 2$  min). The authors state that 20 of these 94 patients were “randomly selected...and considered...as a control group” and that “74 out of 94 patients with PE and chronic prostatitis were further treated with antibiotics, while the control group patients were left untreated.” Antibiotics were given for 1 month and were selected based on culture results; in the absence of culture, selection was made based on patient allergies and prostatic penetration. At 4-month followup, 62 (84 %) of patients reported subjective improvement in ejaculatory latency; in this group mean IELT increased from a baseline of 1.1 to 2.9 min at 1 month and 2.8 min at 4 months posttreatment. The remaining 12 treated patients and the entire control population reported no significant change in IELT or ejaculatory control [63]. Limitations of this study include lack of a placebo control arm and treatment blinding. Furthermore, the rationale for the method of randomization is not made clear; as stated it appears that the authors arbitrarily elected to completely avoid treatment of a

“random” segment of 20 men. While this random-control segment was similar with respect to age, duration of PE, and IELT it is concerning that other variables not disclosed in this report may be present between the control and treatment groups.

There is no controversy that treatment of clinical prostatitis is warranted irrespective of questions pertaining to ejaculation [7]. Treatment with appropriate antibiotics may alter ejaculatory latency but this should not be the primary purpose of antimicrobial therapy. There is currently no evidence supporting the use of antibiotics in isolated lifelong PE [7]. There is insufficient evidence to support routine screening for, and treatment of, asymptomatic prostate inflammation in men with secondary PE. Caution must be exercised when considering use of potent antimicrobials in the absence of clinical infection [7].

### **24.3.6.3 Aromatase Inhibitors**

The androgen testosterone plays a number of important functions pertaining to sexual function, including modulation of libido and possible erectile function. Holbrook conducted a prospective study of 10 men with primary PE (defined as persistent or recurrent ejaculation with minimal sexual stimulation or shortly after penetration and before the person wishes it) treated with the aromatase inhibitor anastrozole (1 mg/d orally), which inhibits the conversion of testosterone to estrogen in adipose tissue. Serum levels of luteinizing hormone, testosterone, and estradiol were assessed at baseline and after 2 weeks of daily treatment. The mean testosterone level at baseline in this study population was 400 ng/dl, within the range that is currently considered normal for serum testosterone concentration in adult men. After 2 weeks of treatment, testosterone and luteinizing hormone increased and estradiol level decreased, as would be expected with this therapy. There was no self-reported improvement in PE at 2- and 4-week followup [64]. Substantial limitations of this study include lack of placebo control, vague criteria for the diagnosis of PE at baseline and at followup, erroneous diagnostic criteria for idiopathic hypogonadotropic hypogonadism, and small cohort size. The fact that no clinical benefit was noted makes it clear that there is no rationale for use of aromatase inhibitors in the management of PE.

## **24.3.7 Central Nervous System Medications**

### **24.3.7.1 Gabapentin**

While serotonin plays an important role in modulation of ejaculation it is evident that other neurotransmitters such as dopamine may have important influences [65]. Chue reported that gabapentin 300–600 mg, taken 1 to 2 h prior to intercourse, improved ejaculatory latency in a single patient with lifelong PE (IELT not specified) refractory to management with SSRI and topical anesthetics. The 300-mg dose led to “satisfactory” ejaculatory delay with no loss of erectile capacity whereas the 600 mg dose was associated with somnolence [66]. Modulation of the

neurotransmitter gamma-aminobutyric acid (GABA) is thought to be the primary mechanism of gabapentin but its role in ejaculation has not been extensively studied. Further research of GABA modulation may be warranted but this case report alone does not justify clinical use of gabapentin for PE.

#### **24.3.7.2 Tramadol**

Tramadol is an opioid receptor agonist with inhibitory activity against serotonin and norepinephrine reuptake. Safarinejad and Hosseini conducted a double-blind, placebo-controlled, fixed-dose, randomized 8-week study to evaluate the efficacy and safety of tramadol 50 mg on demand in delaying ejaculation in 64 patients with PE (IELT <2 min, roughly evenly split between primary and secondary). Men in the tramadol group had an increase in IELT from 19 to 243 s compared to a change of 21 to 34 s in the placebo arm [67]. This study is limited by heterogeneity in the nature of PE amongst the study cohort, relatively small cohort size, and some lingering questions regarding study design.

A single-blind, placebo-controlled, crossover study on the use of tramadol for PE was reported by Salem et al. Sixty men with lifelong PE (IELT of <2 min) were randomized to either tramadol 25 mg or placebo on demand 1–2 h before sexual activity; after an 8-week trial there was a 1-week drug-free washout followed by crossover to the alternate treatment for an additional 8 weeks. Baseline mean IELT was 1.17 min; this increased to a mean-IELT of 7.37 min in the tramadol-treated group compared to 2.01 min in the placebo group [68]. This study is limited by single blinding and small cohort size.

These two studies suggest that tramadol may have efficacy in the management of PE. However, no subsequent trials have reported long-term outcomes and tolerability of this treatment and it must still be considered experimental as of this time. Concern also exists about the addiction/abuse potential of this opioid agonist.

#### **24.3.7.3 d-Modafinil**

Marson et al. studied the sexual effects of d-modafinil, a wakefulness-promoting agent used to treat narcolepsy, in a cross-over randomized controlled trial in rats. This medication is thought to enhance dopamine and serotonin signaling in the CNS and there is hence a rationale for its potential efficacy. Rat subjects were given vehicle (0.25 % methylcellulose in normal saline), 10, 30, or 100 mg/kg of d-modafinil 15 min prior to introduction of a receptive estrous female and then observed for 50 min. Treatment with modafinil at the 30 and 100 mg/kg of the drug led to significantly longer mean ejaculatory latency (10.4 and 8.7 min, respectively) relative to vehicle treatment (6.1 min) with no change in mount or intromission latency. There was no significant difference in mean ejaculation latency between rats treated with modafinil 10 mg/kg and vehicle [69]. These results are intriguing but caution must be exercised when extrapolating the results of animal studies of ejaculation to the human condition of PE. Human trials with careful attention to safety and side-effect profile are warranted before consideration of modafinil as a potential treatment for PE.

#### 24.3.7.4 Antipsychotics

Antipsychotics have been associated with sexual dysfunctions including decreased libido, decreased intensity of orgasms, anorgasmia, painful orgasms, impotence, priapism, retrograde and retarded ejaculations. Gold et al. reported on sexual function outcomes in two patients treated with the older generation antipsychotic agents. The second patient in this series had baseline PE (ejaculation in three thrusts or less after penetration); treatment with thioridazine hydrochloride 50 and 100 mg qpm for bipolar affective disorder and alcohol abuse led to markedly protracted penile erections with concomitant inability to reach orgasm. The patient was by self-report satisfied by this outcome due to satisfaction on the part of his wife [70]. This drug obviously does not represent an actual treatment for PE and this study is extensively limited in its study design and the large number of confounding factors including extensive psychiatric comorbidities and alcohol issues. Use of potent anti-psychotics should not be construed as an appropriate therapy for PE.

#### 24.3.8 Thyroid Metabolism

Anecdotal observations have suggested that thyroid hormone plays a role in modulation of ejaculation [71]. Waldinger conducted a cohort study of 620 men with lifelong PE (IELT <1 min or 1–10 strokes). The geometrical mean TSH concentration was 0.85 mU/l. 14 patients (2.2 %) had TSH levels below the reference range (<0.3 mU/l) and 5 (0.8 %) had TSH levels above the reference range (>4.0 mU/l) but all 620 subjects had free thyroxine concentrations within the reference range [72]. Heterogeneity in serum sampling time and the absence of a control group limits the conclusions that can be derived from these data. However, there does not appear to be support for the hypothesis that lifelong PE is associated with perturbations of thyroid metabolism. Whether thyroid dysfunction predisposes to secondary PE remains uncertain. Currently the ISSM recommends history and physical examination for evidence of thyroid function abnormalities in patients with acquired PE. The ISSM does not recommend serum assays to screen for hyperthyroidism in patients with acquired PE unless there is clinical suspicion for the hyperthyroidism [7].

#### 24.3.9 Penile Constriction Rings

Hosseini treated 42 men with PE (defined as IELT <1 min) prospectively over a 4 week period using a penile constriction ring applied after erection and left on during intercourse. The median IELT was 42 s before treatment and 46 s after treatment; there was no statistically significant difference between groups [73].

### 24.3.10 Conclusions

PE is a frustrating and common sexual problem in men. The lack of basic understanding and effective remedies for the condition is attested to by the lack of a universally approved therapeutic modality for the condition. It is clear that further research into the basic mechanisms of ejaculation biology, epidemiological studies of predictors/associations of clearly defined and clinically troublesome disorders of ejaculation, and development of therapeutic targets must continue so as to improve our ability to care for men with PE and their partners.

In the interim, adherence to expert opinion for the general management of PE is warranted by providers caring for these men. At the present time, erectogenic agents, acupuncture, physical therapy, surgery, beta-blockers, antibiotics, aromatase inhibitors, gabapentin, tramadol, and penile constriction rings cannot be considered effective for the treatment of PE. Current data are insufficient to justify their efficacy or use.

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# From Diagnosis to Treatment: The Office Management of Premature Ejaculation

# 25

Emmanuele A. Jannini and Andrea Lenzi

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## 25.1 Introduction

Which is the role of the physician in the management of PE? Is PE a real medical need? As a matter of evidence (several times described in this Textbook, indeed) PE is a common—if not the most common—sexual dysfunction [1, 2], characterized by reduced ejaculatory latency and a perceived lack of control over ejaculation, generating a distress that can severely compromise the sexual health of the couple. This chapter aims to demonstrate that PE is a true medical need and its treatment is definitively not a recreational issue. In fact, this condition cannot be considered purely a psychological or “lifestyle” problem but rather a multidimensional disorder comprising a biologic dysfunction with psychosocial components [3]. Nevertheless, psychological aspects are an important consideration in PE, as in all sexual dysfunctions [4].

Depending on the definitions, cutoff criteria, study populations and methodologies used to investigate prevalence, PE has been reported to affect 0.5–31 % of men at some point during their life [5–10]. Despite this important prevalence, PE is neglected during the in office practice and often underdiagnosed. This is largely due to patient-related and physician-related barriers [11–14]. For example, patients are often reluctant to initiate conversations about PE because of the stigma and

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embarrassment associated with the condition [12, 14]. Physicians tend not to inquire about PE due to limited awareness of PE as a genuine, common, and treatable sexual dysfunction [14]. Treatment decisions in PE should be based on the physician's assessment of each individual patient's requirements and an accurate diagnosis. In any case, treatment of PE without a careful diagnostic attempt cannot be considered good medical practice and, despite the possible influence of companies interested in selling drugs without a time-intensive diagnostic work up [15], both in the psychosexual and in the medical framework, must be always avoided.

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## 25.2 Diagnosing Premature Ejaculation

A scheme for in-office management of PE is summarized in Fig. 25.1, and is discussed, step by step, in the following sections of this chapter.

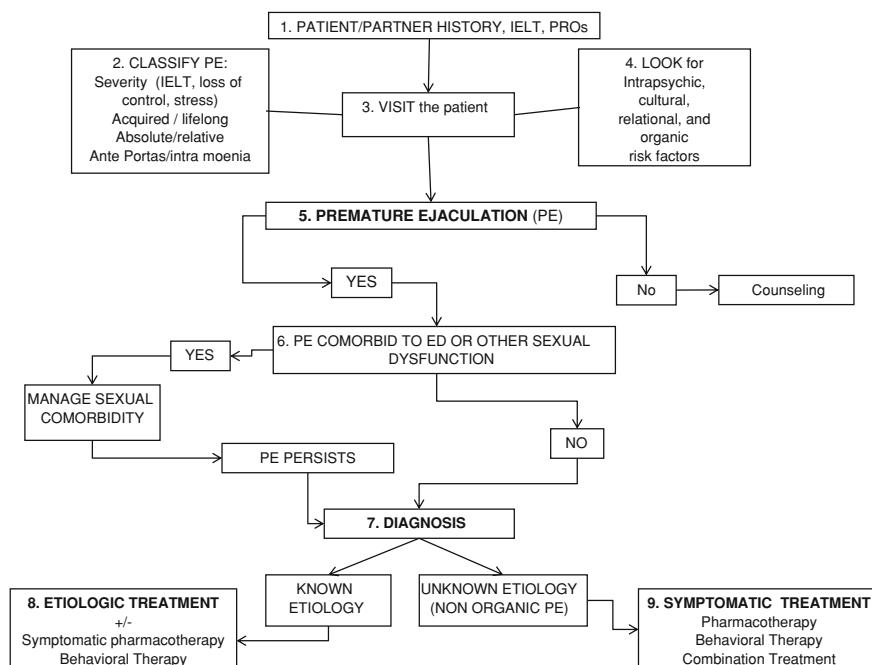
### 25.2.1 Obtain the Patient's History

A primitive and fallacious concept in diagnosing PE is to consider affected patients as a homogenous group (Table 25.1), [16–18]. On the contrary, clinical practice demonstrates that several different subsets of patients can be classified as having PE (Fig. 25.1, step 1).

To start the in office diagnosis of PE, the evaluation of men presenting with self-reported PE should include a full general medical and sexual history to construct a profile of the patient [19]. The profile should be based on demographic factors (e.g., age and education); psychological factors (e.g., level of sexual experience, conditioning, and guilt); relationship factors (e.g., emotional closeness, satisfaction, and amount of sexual activity); and attitudes towards sexuality (e.g., personality, sexual performance anxiety, techniques, and early experiences). Sexual performance anxiety (and other psychosocial factors) can be identified using psychometric tools [20] (see Chap. 16).

Inventories for male and female sexual dysfunctions provide the physician with relevant questions to ask patients and help with interpreting answers [19]. Several tools are available to help assess the patient's history, including the Arabic Index of Premature Ejaculation (AIPE) [21], Premature Ejaculation Profile (PEP) [22], and the Premature Ejaculation Diagnostic Tool (PEDT) [23]. The PEDT is a particularly useful and validated questionnaire to identify men who may have suspected PE. Please note that the PEDT provides a cutoff where the score  $<9$  suggests no PE, the score 9–11 admits the possibility of real PE, while the score  $>11$  is strongly in favor of the presence of a true PE.

At this step it is important to draw the identikit of our patients considering demography (age, culture, education), religion, sexual conditioning (sexual guilt, masturbation rate, sexual experience), the actual and previous relationship(s) (satisfaction, emotional closeness, amount of sexual activity), personal attitudes



**Fig. 25.1** Algorithm of PE diagnosis and management (adapted from Jannini et al., 2010 [79]). Note that the possibility of another comorbid sexual dysfunction should be ruled out first. When risk factors are present, they should be addressed before any symptomatic treatment is considered. However, some patients may require symptomatic treatment in addition to etiologic therapy. Both sexual therapy (e.g., behavioral and cognitive) and pharmacotherapy [selective serotonin reuptake inhibitors (SSRI), dapoxetine] should be considered symptomatic in nature

towards sexuality (performance anxiety, personality, sexual techniques, early sexual experiences).

It is very important to have, when possible, both the partner's point of view and description on the PE, as well the partner's sexual history and attitudes. Premature ejaculation, in fact, not only affects the man, but also has a negative impact on his partner, which can lead to feelings of distress [24], frustration [25], and a breakdown of intimacy [26]. Therefore, it is worthwhile interviewing the partner to determine their view of the situation and how PE is impacting on them and the couple as a whole [24]. This also provides an opportunity to assess the couple's overall relationship and to evaluate whether or not the partner suffers from female sexual dysfunction [27, 28]. It is to be noted, in fact, that female sexual dysfunction (FSD) may be involved in the pathogenesis of PE [e.g., vaginism or hypoactive sexual desire disorder (HSDD)], due to PE (e.g., anorgasmia and HSDD), or casually comorbid. A simple and short screening tool, such as the abridged female sexual function index (FSFI-6), would be clinically useful for this purpose [29].

**Table 25.1** The different *Ejaculation Latency Times* to be evaluated during the in-office management of premature ejaculation

IELT	During vaginal penetration, as measured by stopwatch
PIELT	Perceived IELT (not measured by stopwatch)
PPIELT	Partner Perceived IELT
OELT	Timing of ejaculation during oral stimulation
AELT	Timing of ejaculation during anal penetration
MELT	Timing of ejaculation during masturbation
ELT = 0	Ejaculation before any kind of penetration or stimulation

Even in absence of FSDs, PE can induce distress for the partner, mistrust, frustration, and anger. Typically, and differently to the partner of the patient with ED (where several women believe to be guilty because of the symptom), several partners of PE patients perceive PE as the results of selfishness of the male partner. However, at the best, in the western societies, PE due to selfishness or machismo seems now more rare. Hence, this point should be carefully taken into account when a couple's therapy is prescribed.

In any case, the breakdown of intimacy between partners is a common feature in PE, which should be considered, assessed, and treated.

### 25.2.2 Classify the Symptom

The second step is about the classification of PE. Here the aim is to evaluate the severity of the symptom as measured by the Intravaginal Ejaculation Latency Time (IELT) and clinical characteristics (Fig. 25.1, step 2).

The IELT is an objective measure of time to ejaculation and is commonly used in clinical trials [30]. It is defined as the time from the start of vaginal intromission to the start of intravaginal ejaculation as measured by stopwatch [31]. Each ejaculation after vaginal intromission is measured in seconds or minutes. An ejaculation before intromission (*ante portas*, see later) has an IELT of zero. According to Waldinger's suggestion, the patient's own perception of ejaculatory latency in four different outlets (vaginal, or IELT, oral, or OALT, anal penetration, or AELT, and masturbation, or MELT) should be obtained and compared [32].

The European Association of Urology (EAU) guidelines state that stopwatch-measured IELT is necessary in clinical trials, but the use of self-estimated IELT (perceived IELT, PIELT) is adequate in the practice setting [33]. The presence of the stopwatch, even for short diagnostic purposes, is not frequently accepted. Furthermore, the patent presence (usually the partner is the holder of the stopwatch) of a time-measuring instrument could worsen performance anxiety and, thus, the IELT.

**Table 25.2** The taxonomy of PE (from [59], mod.)

Categories	Symptom	Occurs...
Onset	lifelong (primary) acquired (secondary)	...from the first sexual experience and persists throughout life ...following a period of normal ejaculation experiences
Time	<i>ante-portas</i> <i>intra-moenia</i>	...literally ‘before the gates’, i.e., before vaginal penetration ...literally ‘within the walls of the city’, i.e., during vaginal penetration
Type	absolute (generalized) relative (situational)	...irrespective of partners or context ...in the presence of a particular partner or context
Comorbidities	simple complicated	...in the absence of other sexual symptoms ...in the presence of other sexual symptoms (e.g., erectile dysfunction)

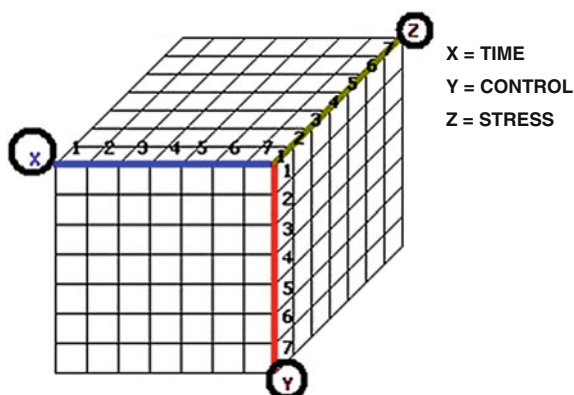
We suggest to ask for the Partner-Perceived IELT (PPIELT), possibly in a separate room, and to compare it with the PIELT. This comparison, both when identical or discordant IELTs are recorded, will provide clinical insights into the couple’s architecture. Furthermore, it is very important to have measurable and initially measured parameters for when, during the follow up, the treatment efficacy is evaluated (Table 25.1).

After assessing the severity, PE should be classified on the basis of onset (e.g., lifelong/primary or acquired/secondary) (Table 25.2), [17]. Lifelong PE is characterized by an onset from the first sexual experience and persists throughout life [34]. Acquired PE is characterized by having a gradual or sudden onset, following a period of normal ejaculation [34]. PE can also be classified on the basis of timing (e.g., *ante portas*—literally ‘before the gates’, i.e., prior to vaginal intercourse—or *intra moenia*—literally ‘within the walls of the city’, i.e., during vaginal intercourse) and type (e.g., absolute/generalized or relative/situational) (Table 25.1) [34].

Note that the classification of PE does not necessarily imply an etiological diagnosis: a situational PE is not necessarily psychogenic in origin; a lifelong PE is not necessarily organic in nature [4]. Current literature has been, unfortunately, quite misleading with this respect, carrying the idea that the simple finding of a symptom present from the first sexual act has always an organic etiology (congenital, genetic). This is nonsense. An intrapsychic risk factor (see Chap. 18) could dramatically modify the ability to control ejaculation from the beginning of the sexual life.

Premature ejaculation can be considered a tridimensional condition that is defined by a set of constructs (Fig. 25.2), [16, 35]. These include rapidity of ejaculation, lack of perceived control and self-efficacy over ejaculation; and negative personal consequences (e.g., decreased satisfaction, and increased

**Fig. 25.2** Premature ejaculation can be considered a tridimensional condition (adapted from Jannini et al., 2011 [3]). The three main elements are shortened intravaginal ejaculatory latency time (TIME), lack of perceived control (CONTROL), and negative personal consequences related to ejaculation (STRESS)



distress and interpersonal difficulty) related to ejaculation. Thus, the three dimensions of PE are: time, control, and distress. Several definitions of PE exist that incorporate all or most of these constructs [36–38]. Most of these, however, are expert opinion-led, rather than evidence-based. In 2007, the International Society for Sexual Medicine (ISSM) proposed an evidence-based consensus definition of lifelong PE [16]: *A male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within about **one minute** of vaginal penetration, and the **inability** to delay ejaculation on all or nearly all vaginal penetrations, and **negative** personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy.* Note that all three dimensions (time, control, and stress) are embedded in the ISSM definition (in bold text).

Current published definitions of PE do not specify a precise ‘time to ejaculation’ [35]. However, by incorporating the phrase ‘*within about one minute*’, the ISSM definition provides the physician with flexibility to diagnose PE in treatment-seeking men who ejaculate within 1–2 min of penetration without unnecessarily stigmatizing men who also ejaculate within this time frame, but have no complaints of PE. It also minimizes the potential for inclusion and exclusion errors because more restrictive criteria would increase the likelihood of exclusion errors, whereas more lenient criteria would increase the likelihood of inclusion errors [13]. In addition, it allows a multivariate approach to diagnosing PE that considers objective time to ejaculation as well as subjective components associated with this condition [16]. Because PE comprises a defined and measurable set of symptoms, there is an emerging role for using evidence-based multidimensional definitions in the diagnosis and management of lifelong PE in the office-based practice setting.

At present, there is no ISSM evidence-based definition of acquired PE due to insufficient objective data from well-designed and controlled trials [16] (see Chap. 7). Nevertheless, similar Intravaginal Ejaculatory Latency Time (IELT) and levels of control over ejaculation and distress between men with lifelong or acquired PE, indicate the possibility of a single unifying definition of PE [39].

The unit of measurement of the first PE dimension (time) is a shortened IELT (see above).

The second and third dimensions can be measured using psychometric tools such as the PEP [22] and PEDT [23]. Patient-reported outcomes (PROs) assess important subjective components of PE, including control over ejaculation and satisfaction with intercourse, as well as personal distress and interpersonal difficulty related to ejaculation. In clinical trials, PROs are typically evaluated using questionnaires, such as the Index of Premature Ejaculation [40, 41], PEP [22, 42], and tools based on the Diagnostic and Statistical Manual of Mental Disorders (4th edn., Revised text; DSM-IV-TR) criteria, such as the PEDT [23, 43, 44]. The use of questionnaires, such as the PEP [22], to evaluate PROs is important in the diagnosis of PE in clinical practice. Moreover, assessing PROs when the patient initially visits the physician enables treatment outcomes to be monitored at subsequent followup visits [see Appendix].

### 25.2.3 Perform Physical Examination

Recently published EAU guidelines recommend that a simple but complete andrological assessment should be performed at the initial visit on the man presenting with self-reported PE [33]. This includes an examination of the penis, testes and epididymis, prostate and the man's level of virilization, as well as a check of his reflexes (Fig. 25.1, step 3). The aim is to identify underlying medical conditions associated with PE or other sexual dysfunctions, such as chronic illness, endocrinopathy, autonomic neuropathy, Peyronie's disease, urethritis, vesiculitis, or prostatitis. Laboratory or physiological testing should be directed by specific findings from history or physical examination and is not routinely recommended.

The importance of physical examination in PE should be stressed as well in all sexual dysfunctions. In particular, in the patient with PE, although LUTS and prostatic diseases are not very frequent in the clinical practice with PE patients (see Chaps. 7 and 13), the symptom of inadequate control over ejaculation must be considered by the physician as a great occasion for urological prevention and to evaluate prostatic health.

### 25.2.4 Identify Underlying Risk Factors

Together with the previous step 3, it is now time to identify the possible risk factors that can cause, contribute to, or be comorbid with PE (Fig. 25.1, step 4).

We stress here again that the suggestion to look exclusively for etiologies other than genetic in patients with acquired PE is not evidence- nor logic-based. All chronic etiologies or risk factors present in a patient with acquired PE could be present also in a patient with lifelong PE. The unique exception is a severe disease, such as hyperthyroidism, which is in fact present only in acquired PE [45] and, obviously, not in lifelong PE [46]. It is also potentially possible that a genetic



predisposition to PE could be symptomatic only later in life, when relational or other epigenetic factors may become effective, and not from the beginning of sexual life.

There are a number of potential causative factors of PE, including those that are organic (e.g., genetic, neurobiological, urological, hormonal, or pharmacological) and those that are non-organic or idiopathic [e.g., functional (experience and education), constitutive (intra-psychological), stress-induced, relational, or psychosexual] [4, 20]. Several etiologies and risk factors of PE are discussed in detail in [Chap. 7](#) and followings.

As a first fundamental message, it is important to diagnose the underlying primary cause of PE and any associated comorbidities, because these should be treated first [34]. Examination should be extended to assess endocrine, urological, and psychorelational/psychosocial risk factors, in order to identify possible underlying medical conditions associated with PE.

#### **25.2.4.1 Endocrine Risk Factors**

Symptomatic hyperthyroidism can be simply diagnosed at the clinical visit, by evaluating heart frequency, and signs of hyperreflexia and psychic hyperactivity (e.g., agitation, irritability, mood disturbances and anxiousness) [47], and other factors, such as fatigue, tremors, sweating and muscle aches. Thyroid dysfunction (i.e., hyperthyroidism) can be detected by a test that analyzes levels of thyroid stimulating hormone (TSH) and/or thyroxine (T4) in the blood (see [Chap. 12](#)). However, because the clinical picture of hyperthyroidism is often self-evident and in agreement with the ISSM guidelines on diagnosis of PE [48], we do not suggest TSH screening in all PE patients. A patient with thyroid dysfunction should be referred to an endocrinologist for thyrostatic pharmacology, radioiodine or thyroidectomy (see [Chap. 23](#)).

Because altered levels of the hormones testosterone [49], leptin [50, 51] and prolactin [52] are likely to be a consequence of PE, rather than a cause of PE, laboratory screening of their levels would be useful for research purposes but not for normal clinical practice.

#### **25.2.4.2 Urological Risk Factors**

Evaluation of prostatic health should be considered mandatory during the andrological visit, and not only in cases of PE (see [Chap. 13](#)). When a prostatitis is suspected, the diagnostic workup should include prostate evaluation by transrectal ultrasonography and standardized Meares and Stamey protocol [53]. Urethral and midstream bladder urine, expressed prostate secretions by prostate massage, and postmassage urine samples are collected, examined microscopically, and cultured bacteriologically. Prostate inflammation is diagnosed if 10 or more white blood cells per high power field are present in the expressed prostate secretions. Nonbacterial prostatitis is defined by evidence of prostate inflammation together with negative urine and prostate fluid cultures. Prostate infection is defined by a colony count 10 times greater in the expressed prostate secretion or post-massage urine sample than in the urethral urine sample. The presence of *Chlamydia trachomatis*, *Trichomonas vaginalis*, *Mycoplasma hominis*, *Candida* species, and *Ureaplasma urealyticum* should be carefully checked for. Hence, it is critical to have a competent

microbiology laboratory: the large majority of negative findings in the Meares and Stamey test is due to an inadequate expertise of the according operator, to errors in storing samples or, perhaps more frequently, to an inadequate laboratory.

### 25.2.4.3 Psychorelational/Psychosocial Risk Factors

Premature ejaculation has long been viewed as a psychological condition [54], associated with a number of psychorelational comorbidities [8], such as emotional distress [26], anxiety [8, 26], depression [8, 14], and social phobia [55, 56]. All these psychological symptoms may be cause, rather than caused, by PE [25]. Several Chapters (Chaps. 8, 11, 15, 16) highlight the role of psychological and relational derangements involved in PE. However, as a matter of evidence, we cannot recommend a specific psychometric tool for the assessment of a possible psychological derangement comorbid with PE.

## 25.2.5 Is the Patient Really Affected by PE?

At the end of this part of the in-office management of PE, the physician should be able to define if the patient is really affected by PE (Fig. 25.1, step 5). Premature ejaculation is, in fact, a self-diagnosis, carrying the risks of inadequate and incorrect ideas about what is pathological and what is to be considered normal. In some subjects of both sexes, an IELT equal to 10 min could be considered pathological. However, although potentially affecting the sexual health of a given couple, this timing could be hardly considered pathological.

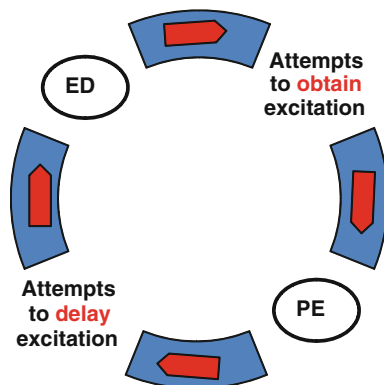
As assessed in Chap. 4, cases other than lifelong and acquired PE have been described. Natural variable PE [57] is a symptom occurring sometimes and not characterizing the sexual life of the patient. It could be better considered a 'situational PE'. (i.e., the psychological factors that result in PE with the wife and not with the mistress are significantly affecting the control over ejaculation and likely to reflect considerable psychological distress). It is probably a frequent condition, which could be different from chronic PE.

Premature-like ejaculatory dysfunction [57] is a PE complaint grounding on essentially unrealistic expectations, ignorance and sexual myth. The patient fulfilling the latter definition cannot be considered to be affected by PE. Like in other sexual myths, this subject should be treated with counselling [58] and possibly with cognitive reconstruction, and not necessarily going through the following steps.

## 25.2.6 Identify Sexual Comorbidities

In presence of a real PE at this step, it is clinically mandatory to define whether PE is simple (occurring in the absence of other sexual dysfunctions) or complicated (occurring in the presence of other sexual symptoms, such as erectile dysfunction) (Fig. 25.1, step 6), [59]. Evidence indicates a high prevalence of comorbid PE and erectile dysfunction [60]. Results from the Premature Ejaculation Prevalence and

**Fig. 25.3** The possible correlation between premature ejaculation and erectile dysfunction (from Jannini et al. 2005 [60], mod.)



Attitudes (PEPA) survey showed that approx. a third (32 %) of men with PE also reported erectile dysfunction [8]. The possible correlation between these two sexual dysfunctions may be due, at least in part, to a shared vicious cycle. For example, in trying to control his ejaculation, the man instinctively reduces his level of excitation, which results in erectile dysfunction. Conversely, in trying to achieve an erection, the man instinctively increases his level of excitation, which results in PE (Fig. 25.3) [60].

Even the self-diagnosis can be misleading. In fact, in some patients PE can be a conscious or unconscious ‘bed trick’. These patients may consider it easier and less humiliating to admit to PE caused by “enthusiasm” than to other sexual dysfunctions, such as the socially worst, the ED. For this reason, the possibility that other sexual problems coexist with PE should always be investigated.

Erectile dysfunction can be assessed using the International Index of Erectile Dysfunction (IIEF) and/or Sexual Health Inventory for Men (SHIM) [8, 61, 62]. However, evidence suggests that some men with PE, but normal erectile function, record contradictory responses to the SHIM, and may be incorrectly categorized as having erectile dysfunction [63]. Findings from a study demonstrated that the SHIM generated false-positive results in approx. a third of cases [63]; therefore, the SHIM has limited reliability when used to discriminate ED from PE. Erectile dysfunction is typically treated with phosphodiesterase type 5 (PDE5) inhibitors, such as sildenafil, tadalafil, or vardenafil [33]. Finally, it has been recommended that men with ED be screened for PE [64].

Several therapeutic dropouts in patients with PE are probably due to the lack of ability to recognize the condition of complicated PE. All therapies for PE, both pharmacological and psychological, attempt to reduce excitation. Hence, a patient with weak or unstable erection [such as the subclinical erectile dysfunction [65]], the therapy of PE may exacerbate the erectile failure. As a universal rule, any therapy for PE must be prescribed only after any weakness of erection is fixed.

Finally, as stated earlier in this chapter, the presence of other sexual dysfunctions such as HSDD should be addressed before any other PE treatment. In particular, low desire can be present in the partner and being involved in the

shortening of the copulatory time. It is also possible that vaginism in the partner results in the male's PE [28]. Again, it does not make sense to treat PE in a couple where an important *primum movens*, such as vaginism, is present.

### 25.2.7 Diagnosis

Only at this step (Fig. 25.1, step 7) the physician is able to perform the final diagnosis of the possible risk factors (frequently present) or causes (not frequently recognizable) of a given case of PE.

The final diagnosis of PE should not distinguish between organic etiologies vs psychogenic etiologies. The interpretation of PE (as well as erectile dysfunction, HSDD or FSDs) as a possible psychogenic symptom is mainly due to the founders of modern sexology, Masters and Johnson [66]. In reality, anxiety and depression almost always accompany PE [67], and can invalidate, if not assessed and treated, an exclusively “medical” therapy. In fact, every patient whose PE is mainly due to an organic disorder, especially if it is longstanding (as, unfortunately, is often the case), builds his own world of fear, anxiety, worry, depression and distress around his disorder [68], a world reinforced by the partner. Furthermore, anyone who has treated a patient with a sexual dysfunction of any origin will know that even the most organic PE—such as that caused by hyperthyroidism [69]—is *also* psychogenic [70]. In fact, when a sexual encounter results in frustration and stress rather than gratification, it is all but impossible not to construct a psychoneuroendocrine [71] vicious cycle of distress and depression, spectator syndrome and performance anxiety. All PEs and other sexual dysfunctions of organic origin therefore also have a psychogenic aspect (or is “mixed”, as it is classified by some [72]). **All**, not just some. So whatever the cause, all sexual dysfunction is, at least partly, psychogenic. Thus, if this reasoning is correct, the term psychogenic and that of “mixed” are therefore at the very least, unhelpful, and essentially redundant.

There is another reason to delete the term “psychogenic” from the clinical vocabulary of PE. As it is therefore impossible to objectively demonstrate, with instrumental, psychometric or psychological means, that a given event or existential condition is “**the**” cause of the sexual dysfunction (as *S. pneumoniae* in pneumonia), the definition “psycho-genic”, with the meaning of “generated by the psyche”, seems obtrusive and is probably unjustifiable [73]. An obtrusive definition which is perceived by the patient, though erroneously, is a stigma of madness, a damnation into the hell of psychotherapy from which to envy the paradise of pharmacotherapy.

Conventional algorithms in the textbooks teach that PE and other sexual dysfunctions are diagnosed by “exclusion” [74]. This is another conceptual mistake. No one, in fact, can be sure to have “excluded” all possible etiologies when studying a patient. We have no proof that we now know every technique necessary to make a diagnosis, nor that we have perfected our pathophysiological knowledge of sexual dysfunctions. A recent example is the thyroidal etiology of acquired PE: only in 2006 was it discovered that thyroid diseases could cause PE [45].

Before, a hyperkinetic man with some tachycardia, anxiety, and PE was considered hysterical and his PE psychogenic in nature.

We suggest that the diagnosis by PE cannot be as an exclusion, but rather as a probability. A negative medical diagnosis does not mean, in fact, that the cause is psychogenic, but simply that it is unknown. This is to be understood in the same way as the diagnosis of the most common medical symptom, hypertension (= high blood pressure with no identifiable cause) despite the impossibility to find an organic cause it is considered a psychosomatic disorder with an ascertained organic etiology and known risk factors, cured by behavioral therapy and counseling aimed to change the lifestyle (such as work addiction, weight loss, regular exercise, low fat diet, limits in sodium intake) as well by drugs. For this reason, the classification of PE and other sexual dysfunctions into organic/psychogenic should be abandoned, in favor of organic/non-organic or idiopathic, recognizing that whatever the cause, the psychogenic component is inseparable in the case of a symptom like PE, so easily capable of unhinging a couple's relationship [4].

While it is mandatory to perform any reasonable effort to have a complete diagnosis in any PE case, the best treatment approach is always the integration of psychosexual considerations with the power of drugs [75]. A number of specific treatments for PE exist [33], which are discussed in detail elsewhere in this textbook (see [Chaps. 17–27](#)).

### 25.2.8 Etiological Therapies

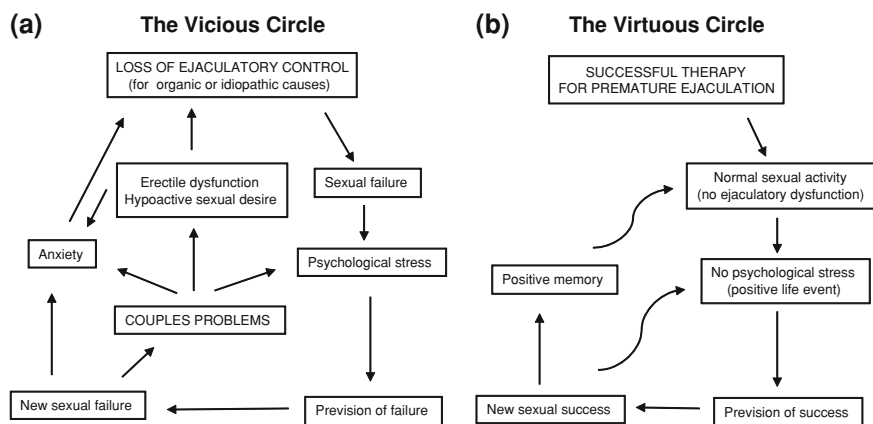
On the basis of the collected data, a patient may be classified as having an organic PE or (better) a PE with organic contribution or risk factors. In this case, and when possible, treatment is etiological (Fig. 25.1, step 8).

Unfortunately, not always the full recovery for a PE cause or risk factor means a complete healing from PE. Clinical experience demonstrates that not all patients successfully treated for prostatitis or hyperthyroidism (see [Chaps. 12 and 23](#)) achieve good ejaculatory control. Many of them develop a secondary psychological concern regarding their ability to delay ejaculation, which needs counselling and, frequently, pharmacological treatment with a Selective Serotonin Reuptake Inhibitor (SSRI) [76], even after removal of the primitive cause.

It is also well known that a PE, *bona fide* due to psychosocial etiologies, is often refractory to psychosexual approaches [77]. Again, integration of treatments is to be considered the best approach also when a possible PE etiology is determined.

### 25.2.9 Symptomatic Therapies

As with all sexual disorders, PE is a symptom rather than a disease. From a clinical point of view this suggests that, in all cases of PE, the disease (physical and/or psychological) behind the symptom must be carefully researched and, possibly, cured. This definition also implies that therapies can be etiologic, as long as the



**Fig. 25.4** The final aim of a symptomatic therapy may go beyond the simple management of the symptom. A successful therapy may generate a positive memory which can disrupt the vicious cycle depicted in panel (a) always present in PE as well as in other sexual dysfunctions

disease is cured. For example, bibliotherapy is an etiologic therapy for PE caused by ignorance, and propylthiouracil is an etiologic therapy of hyperthyroidism-induced PE (Fig. 25.1, step 9). On the other hand, a drug that delays (such as antidepressants) the ejaculatory reflex is a symptomatic therapy, as the majority of psychological and medical therapies for PE that are currently available. It is important, in fact, to realize that all available therapies for PE are symptomatic, perhaps with the unique exception of psychoanalysis, which supposes to be able to address the remote causes of PE [78].

This chapter is not devoted to specify the characteristics of psychological and medical therapies for PE. The former is described in Chaps. 17 and 18 and the latter in Chaps. 19–24. However, we would like to stress here again a few possibly useful suggestions for the in-office management of PE.

The cognitive feedback from PE can lead to a ‘performance anxiety’, which may combine with other conditions to further impair ejaculatory control. Performance anxiety acts as a positive feedback in a vicious cycle described in Fig. 25.4, panel A. For these reasons, a psychological approach is always useful in PE treatment. The aim of any therapy is, in fact, to transform the clinical history of the patient according to Fig. 25.4, panel B.

While pharmacological treatment of PE has been demonstrated to be reliable and efficacious, its therapeutic window is frequently localized to the exact period of drug administration. In fact, once therapy is ceased, PE once more affects most patients who obtained good ejaculatory control. This is in keeping with the evidence that SSRIs as dapoxetine and other antidepressants are, basically, a symptomatic therapy. The best outcome is obtained when drugs are used for a period during which sexual therapy with the couple is also performed. The pharmacological aid, delaying the emission phase, allows the patient to understand

what is happening in his body before the point of no return. In this way, the ability to control ejaculation creates a “positive memory” of sexual success, which will help the patient to overcome the problem (Fig. 25.4, panel B).

In prescribing symptomatic therapies it is important to remember that drug association should be used after the prescription of a single treatment. For example, an effective and well-tolerated treatment, such as dapoxetine, should be used alone for at least 8 times in a comfortable and erotically adequate setting (see Chap. 20). Unsatisfied patients who did not experience serious side effects, should be then titrated to the highest dose (60 mg on demand, 1–2 h before the sexual attempt) and re-evaluated, as before, after 8 administrations. Only at this point, the unsatisfied patients could be prescribed another SSRI or dapoxetine in association with a topical anesthetic treatment.

Where dapoxetine is not yet available, it is possible to start the therapeutic procedures with an anesthetic drug applied locally on the glans. At this moment, a lidocaine-based spray in a metered dose is marketed in North America under FDA monograph 21 CFR 348. Patients are instructed to apply 3–10 sprays to the glans and shaft of the penis, rub the product in thoroughly, and wait 10 min prior to sexual activity. It is recommended that the product be washed off with a damp wash cloth prior to sexual activity, especially if oral intercourse is anticipated. Also in this case it seems important to wait again for eight administrations before titrating to higher doses or shifting to another treatment, such as an SSRI alone (see Chap. 19).

Refractory patients are usually treated very successfully with dapoxetine or another SSRI, in association with counseling and/or psychotherapy and with a topical anesthetic treatment.

Finally, it is important to remember here that, for obvious legal reasons, approved treatments, where available, should be considered the first therapeutic choice. On the other hand, informed consent should be obtained when drugs are prescribed off-label.

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### 25.3 Conclusions

The development of clinical definitions [16], diagnostic algorithms [27, 48, 79], and treatment guidelines [34] for PE has helped to improve how this multidimensional condition is managed. Nevertheless, the potential for cure could be further improved by increasing physicians' understanding of how best to diagnose PE, based on the following decalogue: (i) obtaining the patient's general medical and sexual history; (ii) classifying the symptom on the basis of onset (e.g., lifelong or acquired PE), (iii) timing (e.g., prior to or during intercourse), and (iv) type (e.g., absolute/generalized or relative/situational); (v) involving the partner to determine their view of the situation and the impact of PE on the couple as a whole; (vi) Identifying sexual comorbidities (e.g., erectile dysfunction) to define whether PE is simple (occurring in the absence of other sexual dysfunctions) or complicated (occurring in the presence of other sexual dysfunctions); (vii) performing physical

examination to check the man's sexual organs and reflexes; (viii) identifying underlying aetiologies and risk factors (e.g., endocrine-, urological- or psychorelational/psychosexual-related) to determine the primary cause of PE and any associated comorbidities; (ix) discussing treatment options to find the most suitable intervention, according to the needs of the man and his partner; (x) prescribing a treatment. The widespread application of practical and structured diagnostic approaches for PE would help inform treatment decisions and ensure that patients and their partners are managed appropriately, according to their individual needs and as a couple.

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# Clinical Trial Designs for Premature Ejaculation: Observational, Intervention and Intervention Preference Studies

# 26

Jacques Buvat

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## 26.1 Introduction

Within the past two decades, the objective knowledge about premature ejaculation (PE) has substantially increased thanks to the enforcement of an evidence based approach to sexual medicine. In this chapter we will review the main PE clinical trial (CT) designs that have been used for developing this evidence based approach, and recommendations for future trials. The following incorporates elements of various recently published comprehensive review papers or chapters that address this topic [1–4].

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## 26.2 Main Types of Clinical Trials Applied to PE Research

These include three types of studies [2, 4].

- **Observational studies**, that consist in observing subjects with PE without any therapeutic intervention. These included only case–control trials, used to identify factors that characterize or may contribute to the dysfunction, by comparing a group of men with PE with a control group of non-PE subjects. No longitudinal cohort trials have yet been reported.
- **Interventional studies** may assess the effects of any intervention on PE. They have mainly be used for testing the effects of drugs and have included:
  - Preclinical trials: in vitro or animal studies,

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- Phase 0 trials: exploratory, first-in-human, mainly consisting insert of pharmacokinetics (PK) trials.
- Phase 1 trials that assess the safety, tolerability, PK and pharmacodynamics in dose-escalation trials involving small groups of healthy volunteers.
- Phase 2 trials that investigate safety and efficacy of different doses of the interventional drug in randomized controlled trials (RCTs) including larger groups of patients. Their results condition the phase III trials implementation.
- Phase 3 trials that explore efficacy, safety, and drug interactions in larger RCTs that may include special populations. They are the “pivotal” studies that provide the evidence requested by the regulatory agencies for approval of a drug. Parallel designs, with fixed doses are preferred by regulatory authorities.
- Phase 4 trials that include the setting-up of pharmaco-vigilance databases, drug interaction studies, and special population studies (i.e men with both PE and Erectile Dysfunction-ED), are presently run.
- **Preference studies** have still scarcely been used in PE research. They attempt to identify which intervention a subject prefers, and to establish the subject characteristics and the intervention features that condition this preference. Their results may be easily biased by improper design [2] and their methodology is dependent upon an understanding of the unique factors that can influence the results [5].

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## 26.3 Clinical Trial Methodology Used in PE Studies

The basis of ideal PE CT design involves adequately defining the trial population, a cohort or case–control observational trial design, a double-blind, placebo-controlled RCT design, and the use of sensitive, validated, and reproducible outcome measures [2].

### 26.3.1 Defining the Trial Population

#### 26.3.1.1 The Main Inclusion Criteria

The main inclusion criteria that have been used in the best designed evidence based trials and should be recommended for future studies are [2]:

- age  $\geq 18$  years for the man
- signature of a written informed consent
- stable, monogamous sexual relationship with the same partner for at least 6 months
- subjects with the same sexual orientation and partner gender preference
- acceptance to attempt intercourse on a regular basis and at least once a week
- non pregnant partners
- subject meets criteria for PE diagnosis using a multivariate definition of PE and a baseline threshold ejaculatory latency time

### 26.3.1.2 The Main Exclusion Criteria in the Same Trials Are

- use of any investigational drug within the past month, or within a period of <5 times the drug half-life if it is longer
- any significant somatic disorder
- any potential neurological, urological, or endocrine cause of PE
- any current or past history of psychiatric disorder
- current or past history of alcohol or psychoactive substance abuse or dependence
- use of any medication that may cause sexual dysfunction
- any other sexual dysfunction including ED
- untreated hypogonadism, hyperprolactinemia, hyper or hypothyroidism
- clinically significant female sexual dysfunction (FSD) of the partner

### 26.3.1.3 Definitions of PE

Up to 2008, many different definitions of PE were used. They were based on author opinion rather than on evidence [2, 4]. Based on an extensive literature review and on the results of several recent epidemiological studies using stop-watch-measured intravaginal ejaculation latency time (IELT), the International Society for Sexual Medicine (ISSM) published in 2008 the first evidence-based definition for lifelong PE [6] (see Chaps. 4 and 5). This new definition set a strict criterion for lifelong PE. Its use is strongly recommended as the basis of diagnosis of PE for all PE CTs.

In the absence of IELT and Patient Reported Outcomes (PRO) data for acquired PE, it has not been possible until now to propose such a strict definition for acquired PE. The provisional definition that is recommended by the ISSM and should be used for CTs is also provided in Chap. 5.

### 26.3.1.4 PE Diagnostic Questionnaires

This topic is developed in Chap. 16. Three short (5–10 items) diagnostic questionnaires have been proposed to screen for PE: the Arabic and the Chinese Indexes of PE have minimal validation and CT data available, while the PE Diagnostic Tool (PEDT) has a somewhat more elaborate database [7]. A recent Turkish study [8] reported that both the PEDT and the Arabic index of PE had high sensitivities (respectively 89.3 and 89.5 %) but their specificities seemed too low (50.5 and 39.1 %) so that they are used as diagnostic tools in PE CTs.

## 26.3.2 Trial Outcome Measures

### 26.3.2.1 Efficacy Outcome Measures

#### Ejaculatory Latency Time

IELT, which is the length of time between vaginal penetration and ejaculation, has been until now the only Ejaculatory Latency Time (ELT) used as an efficacy outcome measure in most PE CTs. Several studies found that estimated and stop watch-measured IELT correlate reasonably well and are interchangeable in assigning PE status when

combined with Patient Reported Outcomes (PROs) [2, 9, 10]. Baseline IELT should be determined during a 4-week baseline period during which the man should have at least four intercourses at least 24 h apart. Determination of IELT should be limited to the first intercourse attempt and not to subsequent attempts to avoid the prolonging effect of the refractory period. Condoms, topical anesthetic creams and prior significant alcohol consumption should not be permitted [2].

As IELT is distributed in a positively skewed pattern, reporting baseline and end-point IELTs as arithmetic means overestimates the response to treatment [3, 11]. The use of geometric mean or median IELT is more representative of the response [12]. Lastly, the trial-end fold increase in geometric mean IELT compared with baseline is more representative of the true treatment outcome than is the mean raw trial-end IELT, and should be considered as the standard for reporting IELT [3].

### Patient Reported Outcomes

IELT provides an objective measure of ejaculatory function, but does not give information about the impact of rapid ejaculation on the patient's confidence on his sexual performance, and finally on his well being. Likewise, even if it is prolonged by a treatment, IELT does not provide information on the subjective benefit resulting from this improvement. PROs have been elaborated on request of U.S. FDA to capture these subjective aspects and benefits. They are assessed with single-item diary questions or multi-item domain questionnaires. The main PROs are:

- Perceived ejaculatory control which has been found to be central in men with PE diagnosed with the DSM-IV criteria [12–15]. According to path-analysis, the effects of IELT on three other essential PROs (ejaculation-related personal distress, satisfaction with personal intercourse, and interpersonal difficulty related to ejaculation) are mediated by perceived control over ejaculation [14, 15].
- Sexual satisfaction is decreased in men with PE and its increase is an important parameter when assessing the response to treatment. However such an increase in sexual satisfaction may reflect more than just the objective benefit derived from a pharmacological treatment [3]. This may occur for minimal increase in IELT, and result in fact from subtle psychological changes e.g., linked to improvement in communication with the partner or in intimacy, or, merely, from alleviation of the distress due to medical support.
- Personal distress encompasses different negative psychological reactions that have been found by many studies in men who seek treatment for PE and in their partners [7, 13, 16]: bother, frustration, words that better capture this psychological parameter of PE than the word distress, anxiety, depression, low self-esteem, loss of confidence ... Personal distress may significantly affect the sexual and overall quality of life. It may also result in inappropriate behaviors such as performance anxiety, avoidance of intimacy, that may aggravate the sexual dysfunction and couple disharmony. It probably best defines the severity of PE [3, 17].

Following FDA request, two main instruments have been developed and validated to assess these PROs in interventional trials (see development in [Chap. 16](#)): Index of Premature Ejaculation (IPE) [18], and the Premature Ejaculation Profile (PEP) [19].

Clinical Global Impression of Change (CGIC), a third PRO instrument frequently used in other medical domains, has also been adapted and validated for PE assessment [20].

### **Partner Reported Outcomes**

It is essential to consider the partner in the design of studies that address male sexual dysfunctions [4]. This is especially the case in PE, since men with PE regard fulfilling their partner's needs as the most important factor contributing to their sexual satisfaction [21]. Partner distress has also been found as one of the most influential factors in determining PE status, more important than IELT [10], though female partners generally assess PE as less severe as do their male partner [13]. Accordingly, a female version of the PEP profile has been developed for dapoxetine CTs, but no validation of this questionnaire has been published until now.

#### **26.3.2.2 Safety Measures**

Adverse events are usually reported retrospectively by the patient at the following trial visit and are recorded and rated by the investigator using MedDRA.

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## **26.4 Methodology Used in the First Large CTs Conducted in Men with PE**

### **26.4.1 Observational Trials**

In their 2006 review on definition and prevalence of PE, Carson and Gunn [22] concluded that the epidemiology of PE had many limitations due to the lack of standardization in defining the disorder and in study design. The first evidence-based observational trials on PE epidemiology were published from 2005, and based on stopwatch-measured IELT [11]. Larger trials were subsequently run in the USA [10, 13] and in Europe [14] using a more comprehensive design: multicenter studies each involving over 1,000 men and their female partners, diagnosis of PE based on DSM-IV-TR criteria, partner-measured IELT, subject and partner independently-assessed PROs, assessment of relationships between PEP measures and IELT with path analysis. These studies were pivotal to the realization that PE could not be characterized only by a short IELT, and required also PROs assessment, especially perceived control over ejaculation, also to the new ISSM definition of PE, and to the validation of the PEP questionnaire (see also [Chap. 4](#)).

### **26.4.2 Interventional Trials**

#### **26.4.2.1 Pharmacological Treatments**

Until now, only 2 large CT programs had their design and results published in peer-reviewed literature. They concerned dapoxetine [23] and a topical eutectic mixture for PE (TEMPE-PSD502) [24]). For more details about these programs



see [Chaps. 20](#) and [21](#). Both programs started prior to the publication of the ISSM definition for PE, and the patients were selected according to the more subjective DSM-IV definition, combined with a stopwatch measured IELT of  $\leq 2$  mn (dapoxetine) or 1 mn (TEMPE) in at least respectively 75 and 66 % of the events, and to the absence of relevant ED as assessed by an IIEF-Erectile Function Domain score of  $\geq 21$ . The other inclusion and exclusion criteria were in agreement with those listed above. In addition to these large trials, the literature contains many small RCTs of antidepressant SSRIs or clomipramine since the maiden studies by Waldinger et al. [[25](#)] and Haensel et al. [[26](#)] (see [Chap. 19](#)) and two smaller trials of tramadol [[27](#), [28](#)].

### **Dapoxetine Trials**

These were multicenter, placebo-controlled, double blind, parallel group studies comparing placebo with the doses of 30 and 60 mg of dapoxetine taken on demand. Main outcome measures were partner measured stopwatch IELT, PEP profile, and CGIC. A dose-dependant increase in IELT, all PEP items and CGIC was demonstrated in the dapoxetine groups compared with the placebo group in all four phase three CTs and in the pooled data [[23](#)]. Efficacy was confirmed retrospectively in the subgroup of patients fulfilling the ISSM definition (unpublished data). A responder definition was developed following the third phase three study [[29](#)]. Based upon a post hoc path-analysis of the data, it was a composite of a two category increase in control and a one category decrease in distress from baseline [[15](#)].

### **TEMPE Trials**

These were two multicenter, placebo-controlled, double blind, parallel group studies [[30](#), [31](#)]. Primary end point was the stopwatch IELT, and secondary end points were the IPE and PEP questionnaires, the quality of orgasm on a 5-point scale and rating of study medication on a 4-point scale. All end point measures improved significantly more on TEMPE than on placebo. No systemic adverse events (AEs) were reported.

### **Antidepressant SSRIs and Clomipramine**

A systematic review of 79 drug-treatment studies (3,034 men) published till 2003 with meta-analysis of 43 of them allowed to conclude that the efficacy of paroxetine, clomipramine, sertraline and fluoxetine was comparable, but that paroxetine exerts the strongest ejaculation delay [[32](#)]. Only eight studies (18.5 %) fulfilled all criteria used in evidence-based medicine. Interestingly, retrospective use of a questionnaire, subjective reports, single-blind and open-study designs proved to generate far greater variability of ejaculation time both at baseline and during active treatment than real-time assessment by stop watch, confirming if necessary the importance of a strict methodology.

### **Tramadol Trials**

They include a single-blind, placebo-controlled, crossover, two-8-week treatment period, stopwatch-monitored study in 60 patients with lifelong PE [[27](#)] and a double-blind, placebo-controlled, fixed-dose, randomized study of 64 patients with

undifferentiated PE [28]. Diagnosis was based on IELT which was also used as primary end point and increased significantly more on tramadol compared to placebo in both studies.

#### **26.4.2.2 Non Pharmacological Treatments**

Unfortunately most of the psychological treatment outcome studies are uncontrolled. However, De Carufel and Trudel recently reported an eight fold increase in IELT among men with PE treated with either their new behavioral technique, or the squeeze technique, compared with control men with PE on a waiting list [33]. The efficacy of the squeeze technique has also been compared with that of sildenafil and of antidepressant SSRIs in two randomized and either crossover [34], or parallel group [35] trials. In both studies, compared to baseline, ejaculation latency significantly increased with the squeeze technique but sildenafil obtained significantly better results.

Lastly, three Chinese studies reported on combination therapy with pharmacological and behavioral treatment for PE compared with pharmacotherapy alone [7], and another study reported on treatment with pharmacotherapy followed by behavior therapy. In all studies combination therapy was superior to pharmacotherapy alone on either the IELT or the Chinese Index of PE [7].

Although the methodology of these seven trials was still improvable, they demonstrate that it is possible to apply a more evidence-based methodology to sexological research in PE, and should encourage sex-therapists to try to demonstrate the efficacy of the treatments they are using in controlled studies.

Recently, an interesting randomized, placebo-controlled (sham-acupuncture) CT reported a significant increase of IELT and PEDT score with both daily paroxetine treatment and acupuncture compared with placebo [36]. Extent of ejaculation delay was significantly higher on paroxetine compared with acupuncture.

#### **26.4.3 Intervention Preference Studies**

No large scale preference study has been reported in men with PE. Following a single center observational study of 88 men with lifelong PE who filled out a questionnaire, Waldinger et al. reported that 81 % preferred a drug for daily use, 16 % a drug on demand, and 2 % an anesthetic cream [37]. This interesting finding deserves to be confirmed in a broader, multicenter study. In the already mentioned randomized, unblinded, parallel group study by Wang et al. comparing sildenafil, paroxetine and the squeeze technique, after 6 month respectively 1.7, 18.3 and 36.7 % of the patients withdrew from the study, and 86.7, 60.0 and 45.0 % wanted to continue with the same treatment [35].

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### **26.5 Recommendations**

In 2008 McMahon concluded a comprehensive review of the CT methodology in PE by stressing that data from PE studies are only reliable, interpretable, and capable of being generalized to patients with PE when derived from well-designed observational

studies, or intervention RCTs using ELT and subject/partner reported outcome (PaROs) measures of perceived ejaculatory control and personal/partner/relationship distress as trial outcome measures [3]. These recommendations were recently updated by an expert committee at the 3rd International Consultation of Sexual Medicine [4]:

- Observational studies should make use of the new ISSM definition [6] and the new validated PRO measures developed for investigation of PE [18, 19]. Partner data of PE patients should also be collected by means of validated PROs.
- Regarding interventional studies, future drug trials should follow a prospective, randomized, placebo-controlled, and double-blind design similar to modern ED trials as concerns the duration of the run-in and treatment phases. A more detailed description of the recommended design was summarized as follows: Clinical trials in premature ejaculation should consider the following items:
  1. Key inclusion and endpoint parameter is the stopwatch-measured IELT.
  2. Although the new ISSM definition for lifelong PE sets an IELT cut-off point of about 1 min, the committee recommends also consideration of patients with IELT cut-off points of and between 2 and 5 min provided there is evidence by history taking and/or PROs that the patients/couples show psychological distress.
  3. PE patients should be randomized according to the respective IELT cut-off values considered in the trial.
  4. PE trials should enroll reasonable numbers of both patients with lifelong and acquired PE to ensure collection of reliable data for both patient populations
  5. One trial in a population with ante-portal ejaculation is encouraged.
  6. At least one trial in an investigational drug development program should consider a well-defined population suffering from a combination of ED and PE
  7. Validated PROs specifically developed for PE trials such as IPE or PEP should be used as study endpoints in addition to IELT.
  8. Valuation of validated partner-reported outcomes (available in PEP) is encouraged.

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## 27.1 Introduction

Since the 1990s, off-label daily SSRI treatment, on-demand treatment with clomipramine, combined daily with on-demand SSRI treatment, on-demand dapoxetine treatment, and/or on-demand use of a topical anesthetic have become popular and effective treatments of lifelong and acquired premature ejaculation (PE) [1–3]. These drug treatments are mostly quite effective in delaying ejaculation in the majority of men who complain of PE. However, from daily clinical experience it is known that these drugs are not always effective or become less effective after a certain period of time, a pharmacological phenomenon which is called tachyphylaxis [3]. Although longitudinal SSRI treatment efficacy studies in large cohorts of males with PE have not yet been performed, I estimate that in about 20 % of random samples of males with lifelong PE, the SSRIs do not delay ejaculation at all. In addition, in the remaining 80 % of men who experience an SSRI-induced ejaculation delay, a certain number of men is either not satisfied with the extent of ejaculation delay, or has to stop taking the drug due to SSRI-induced side effects. In other words, there obviously is a need for new drugs that delay ejaculation and are efficacious in men with lifelong PE.

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## 27.2 Ejaculation-Delaying Drugs and Drugs for Premature Ejaculation

One has to distinguish (1) drugs which delay ejaculation and (2) drugs which can be used to treat lifelong PE. This distinction is clinically important as not all drugs which delay ejaculation are automatically efficacious in men who ejaculate within about 1 min. Drugs that delay ejaculation can be very suitable for men who are not satisfied with their ejaculatory performance although they ejaculate within for example 3–4 min or within 5–15 min. According to the classification, proposed by Waldinger et al. [4, 5] these men belong to the PE subtype “Subjective PE” or “Premature-like Ejaculatory Dysfunction”. On the other hand, men with lifelong PE, especially men who ejaculate within seconds, need a pharmacologically powerful drug. Apart from being powerful, such a drug must not have disturbing side effects. With regard to on-demand drug treatment of lifelong PE, a drug should also have a fast effect on ejaculation in order not to intervene with the spontaneity of sexual arousal or pleasure.

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## 27.3 Therapeutic Class Review

Currently there is no information on the percentage of men that use SSRIs to delay ejaculation. For that purpose pharmaco-epidemiological research should be performed. This knowledge may clarify the potential market for drug treatment of PE. In this regard it should be noted that the high prevalence rate of 30 % probably does not reflect the real percentage of men that are in need of PE drug treatment. Certainly, it may be expected that men suffering from lifelong PE, e.g., men with an IELT of less than 1 min, will form a potential market for a drug that exerts a strong ejaculation delay, but men who are not satisfied with their ejaculatory performance but do ejaculate within 2–5 min may not “suffer enough” to be motivated to take a drug, particularly when the drug is not really effective. The real percentage of men suffering from lifelong PE is not really known, but it is roughly estimated as about 3–5 % of the male population. In contrast, a much higher percentage of men may be interested to delay ejaculation for non-medical reasons, for instance, out of feelings of convenience in order to enhance sexual satisfaction. The attractiveness to use a drug is obviously also related to its efficacy, lack of disturbing side effects, and price.

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## 27.4 Palliative and Curative Drugs

The ideal drug for PE is one that will cure the dysfunction [3]. However, with the current available drugs, i.e., the SSRIs, clomipramine, dapoxetine, and topical anesthetics, it has repeatedly been shown that PE returns within a few days after discontinuation of the drug. As long as the core neurobiological mechanisms of PE

have not been elucidated it is questioned whether a curative drug can be developed. Therefore one should attempt to develop new palliative drugs, e.g., drugs that effectively delay ejaculation with a minimum of side effects. Animal research has shown that it is feasible to develop new drugs that very strongly delay ejaculation within 1–2 h.

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## 27.5 Finding New Therapeutic Targets

Developing new pharmacological treatments starts with finding new therapeutic targets [6]. A therapeutic target is a molecular switch, most often a protein, that, when triggered, selectively alleviates disease. A well-known strategy for target discovery is the approach in which the working mechanism of existing, effective drugs is examined. In this way targets in the same pathway can be found that may have higher efficiency or fewer side effects. This approach is only effective when the existing pharmacological treatment is effective in humans and in animal models. Applied to PE, this means that it is pivotal that the efficacy of a drug to delay ejaculation is robust and objectively established. Otherwise, the search for new targets by this method is most likely deemed to fail.

Another strategy for target discovery, in general, is the investigation of the pathophysiology of the disease [6]. However, this strategy may suffer from the difficulty to develop a valid animal model for the disease. In an animal model, the putative targets presumably underlying the effects of a drug can be tested. For this reason, it is pivotal to critically look for a valid animal model for PE. Fortunately, such a model has been found in the last decade [7, 8].

On the other hand, nonpharmacological interventions may be used to aid the discovery of new therapeutic targets. Acquired knowledge of the mechanisms underlying nonpharmacological interventions can point out (molecular) biologically relevant processes. With regard to PE, the question arises whether there are nonpharmacological interventions that effectively delay ejaculation in these men. Unfortunately, there is hardly any evidence that nonpharmacological interventions efficaciously delay ejaculation in men with lifelong PE. Personally, I am not convinced by the publications on the stop-start or squeeze technique, that these strategies lead to minimal durable changes in brain mechanisms involved in delaying ejaculation. Nevertheless, considered as a nonpharmacological intervention, it may be interesting to perform brain-imaging investigations in men in which behavioral treatment has successfully led to a delayed ejaculation. From studying the underlying neurobiological mechanisms of the nonpharmacological interventions that lead to recovery it may be possible to deduce novel therapeutic targets. Obviously, the development of new nonpharmacological interventions to delay ejaculation are encouraged and should be investigated by neuroscientists.



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## 27.6 Four PE Subtypes

For finding new therapeutic targets, it is pivotal to make a clear distinction in the four PE subtypes. By applying such a distinction, the separate four groups of men become more homogenous, and consequently the odds will increase to find therapeutic targets which these men have in common.

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## 27.7 More Research into the Phenotype

The currently available drugs are capable to delay ejaculation in men with lifelong PE, but they do not cure lifelong PE. Actually, there currently is no cure at all for lifelong PE. Even the answers to the current genetic research questions, e.g., the association between genetic polymorphisms of the central serotonergic system and the IELT duration, will probably not lead to a cure of lifelong PE. So what is wrong with our current research that we are not able to cure lifelong PE?

One of the reasons might be that lifelong PE is not completely and well enough described in the details of its symptomatology and that we miss some clinically important characteristic features that are a genuine part of the syndrome. In other words, that the “phenotype” of lifelong PE is not well enough described. Therefore, it remains pivotal to continue clinical research of lifelong PE and to find the very essential features of lifelong PE and also the clinical differences with the other PE subtypes. Consequently, it remains clinically and scientifically relevant to separately define the four PE subtypes.

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## 27.8 Application of the Stopwatch and IELT

Although for daily clinical practice a stopwatch is not required, and although its use for research has been criticized, for drug treatment research and (pharmac) genetic research stopwatch measurement remains the most objective way to assess the IELT. Moreover, although also the IELT has been criticized, for example as it is not suitable for research of homosexual men or men who do not have intercourse, the IELT remains the most studied measure of PE and is essential for objective drug treatment research of PE. Also, despite the criticism of some clinicians, there is no reliable objective alternative tool or measure other than the stopwatch and the IELT for drug treatment research. Therefore, both the application of a stopwatch and IELT should be continued in future drug treatment research.

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## 27.9 On-Demand SSRI Treatment

Off-label daily paroxetine treatment may give rise to a 9-fold increase of the IELT duration [1]. On the other hand, on-demand use of dapoxetine and SSRIs gives rise to a 3–4-fold increase of the IELT compared to its baseline value [3]. Further research

with SSRIs with a short half-life is needed in order to elucidate whether their unique pharmacokinetic profile can increase ejaculation delay above a 3–4-fold increase [9]. So far, however, and based on current knowledge of central serotonergic neurotransmission, it seems unlikely that SSRIs with a short half-life will exert a similar very strong ejaculation delay as exerted by daily use of conventional SSRIs [10]. If drug companies remain interested in PE and its research, we may expect the development of new and more powerful on-demand drugs to treat PE.

Animal studies have shown that on-demand treatment with SSRIs can be highly improved by simultaneous use of 5-HT<sub>1A</sub> receptor antagonists [11, 12]. This combination of serotonin reuptake inhibition and 5-HT<sub>1A</sub> receptor antagonism and probably any drug that acutely significantly increases 5-HT neurotransmission, may become the basis for the development of new on-demand drugs which really strongly delay ejaculation within 1 h after intake [10].

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## 27.10 On-Demand Use of Topical Anesthetics

The use of topical local anesthetics such as lidocaine and/or prilocaine as a cream, gel or spray is the oldest drug treatment strategy and is still practiced today. A real advantage of a topical anesthetics spray is that its use does not lead to systemic side effects. An ideal topical spray to treat PE is a spray that gives rise to a localized hypesthesia of the glans penis within a few minutes after its application. In this area, the development of new effective topical anesthetic sprays are encouraged and may improve the current available armamentarium of drugs for PE.

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## 27.11 New Serotonergic Drugs

Unless future research will discover new or already known neurotransmitter systems that are highly involved in the ejaculation process, the central serotonergic system remains the most important target for delaying ejaculation. For a good understanding of the psychopharmacological possibilities to intervene with this system, I add the following paragraph to this chapter. More details can be found in one of my articles in which I have described these details for the first time (see [9, 10]). It will show that by intervening in some basic mechanisms, new drugs can be produced that may more effectively delay ejaculation.

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## 27.12 Basic Serotonergic Mechanisms

The clinically very relevant ejaculation delay induced by daily SSRI treatment and the rather small ejaculation delay induced by on-demand SSRI treatment is in line with current understanding of serotonin (5-hydroxytryptamine; 5-HT) neurotransmission in the central nervous system.

- *Mechanism I.* Serotonergic neurons regulate their own activity by three mechanisms [10, 13, 14]. One of the basic features of serotonergic neurotransmission is the phenomenon that any acute increase of 5-HT release into the synapse is immediately followed by activity of the neuron to diminish the extra 5-HT level. Under normal physiological conditions, 5-HT activates (presynaptic) 5-HT<sub>1A</sub> autoreceptors on the cell bodies of serotonergic neurons. Activation of these 5-HT<sub>1A</sub> autoreceptors decreases firing of the 5-HT neuron and consequently lowers the 5-HT release from the presynaptic neuron into the synaptic cleft (mechanism I).
- *Mechanism II.* After release of 5-HT in the synapse, presynaptic 5-HT<sub>1B</sub> autoreceptors become activated that in turn inhibit the 5-HT release from the presynaptic neuron into the synaptic cleft (mechanism II). This feedback mechanism of the neuron probably prevents overstimulation of (post)synaptic 5-HT receptors.
- *Mechanism III.* Another automechanism to prevent overstimulation of postsynaptic 5-HT receptors is the immediate removal of 5-HT in the synapse back into the presynaptic neuron by 5-HT transporters (5-HTT) at the presynaptic endings and at the serotonergic cell bodies (mechanism III).

This complex feedback mechanism in the central serotonergic system is meant to sustain homeostasis [10]. However, it has also consequences for drug treatment of PE, particularly, for on-demand treatment with SSRIs [10].

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### 27.13 Acute SSRI Administration

All 5-HT transporters are blocked after acute SSRI administration, leading to higher 5-HT levels in the synaptic cleft and in the space around the cell bodies [15]. The increased 5-HT levels activate 5-HT<sub>1A</sub> autoreceptors and consequently lead to lower 5-HT release into the synaptic cleft within minutes [16]. The diminished release of 5-HT in the synaptic cleft compensates (completely or partially) the initially increased 5-HT concentrations as the result of the SSRI-induced blockade of the 5-HT reuptake by transporters from the synapse into the presynaptic neuron. Higher 5-HT concentrations in the synapse will increase the activation of presynaptic 5-HT<sub>1B</sub> autoreceptors that by itself will attenuate 5-HT release. The net effect of acute SSRI administration, under physiological conditions, is only a mild or no increase of 5-HT neurotransmission and mild or no stimulation of all postsynaptic 5-HT receptors.

In other words, according to these data, on-demand SSRI treatment will acutely (i.e., within 1–2 h) not lead to relevant stimulation of 5-HT postsynaptic receptors, as there is hardly any 5-HT increase in the synapse and hardly any stimulation of postsynaptic 5-HT receptors. If postsynaptic 5-HT receptors are not or hardly activated clinically relevant ejaculation delay will not occur [10].

Indeed, animal studies have shown that acute administration of the 5 SSRIs (fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram) has no significant effects on ejaculation time and number of ejaculations [17]. And also human studies indicate that on-demand use of SSRIs do not lead to similar strong ejaculation delays as can be induced by daily treatment with SSRIs.

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### 27.14 Chronic SSRI Administration

In contrast to acute administration, chronic administration of SSRIs leads to a number of adaptations that are pivotal for inducing relevant ejaculation delay. The ongoing blockade of 5-HTT results in a persistent increase of 5-HT levels in the synapse and in the space around the cell bodies. This leads to desensitization of 5-HT<sub>1A</sub> autoreceptors over the course of a few weeks [18], possibly also to desensitization of 5-HT<sub>1B</sub> autoreceptors [19], and consequently to less inhibition on 5-HT release into the synapse. The net effect of chronic SSRI administration is more 5-HT release into the synapse, stronger enhancement of 5-HT neurotransmission and consequently stronger activation of postsynaptic 5-HT receptors compared with acute SSRI administration [20].

In other words, based on these insights into serotonergic neurotransmission, it is predicted that daily SSRI treatment will lead to very relevant stimulation of 5-HT postsynaptic receptors and, accordingly, clinically very relevant ejaculation delay after 1–2 weeks of continuous intake [10]. Indeed, animal studies have shown that chronic administration of fluoxetine and paroxetine results in increased values of ejaculation latency time [21–23]. Moreover, human studies have repeatedly shown the clinically very relevant ejaculation delay induced by daily treatment of paroxetine, sertraline, and clomipramine.

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### 27.15 Requirements for Clinically Effective On-Demand SSRI Treatment

Assuming that relevant ejaculation delay is defined as at least a 1-minute delay compared to baseline values, it may be argued that, particularly for men with an IELT of less than 1 min, on-demand drugs against premature ejaculation should at least exert a 5- to 6-fold or 400–500 % IELT delay within 1–2 h. Currently, such persistent strong-acting on-demand SSRIs are not available. However, animal studies have provided data indicating that such a strong acute ejaculation delay exerted by SSRIs is in principle feasible, at least when an SSRI is combined with a 5-HT<sub>1A</sub> receptor antagonist.

## 27.16 Acute 5-HT Neurotransmission Enhancement

In order to overcome the pharmacological limitations of acute SSRI treatment, that is, a low initial 5-HT neurotransmission and postsynaptic 5-HT<sub>2C</sub> receptor activation, enhancement of 5-HT neurotransmission is needed at the very start of treatment. One way to achieve this is by blocking selectively the presynaptic 5-HT<sub>1A</sub> autoreceptor. The resulting increased 5-HT release into the synapse will shortly lead to an increased activation of postsynaptic 5-HT<sub>2C</sub> receptors. In studies of male rats it was shown that combined acute treatment of a 5-HT<sub>1A</sub> receptor antagonist with an SSRI (which separately did not affect sexual activities) displayed strong effects on copulatory behavior and enhanced delay of ejaculation latency.

## 27.17 5-HT<sub>1A</sub> Receptor Antagonists

Desensitization of receptors due to chronic SSRI exposure can be mimicked in acute treatment by blocking 5-HT<sub>1A</sub> autoreceptors instantaneously through coadministration of a 5-HT<sub>1A</sub> receptor antagonist and an SSRI. In an *in vivo* microdialysis study, in which the selective 5-HT<sub>1A</sub> receptor antagonist WAY 100635 (Research Biochemicals, Natick, MA, USA) was combined with citalopram, WAY 100635 increased extracellular 5-HT concentrations [24]. In male rats, Williamson et al. [11] combined another 5-HT<sub>1A</sub> receptor antagonist (robalzotan - ROB, also known as NAD-299) [25] with fluoxetine and citalopram and copulatory behaviour was studied at acute and after 11 days of treatment. Neither fluoxetine nor citalopram affected ejaculation latency at day 1, confirming the findings of Mos et al. [17]. However, at day 11 fluoxetine increased ejaculation time significantly while citalopram had no such effect. Interestingly, both acutely and at day 11, coadministration of fluoxetine or citalopram and robalzotan (15 min prior to the tests) significantly delayed ejaculation time without affecting any other copulatory parameter. In analogy to this study, de Jong et al. [12] administered citalopram, the 5-HT<sub>1A</sub> receptor antagonist WAY-100635, and citalopram, together with WAY-100635, to male rats during 15 days, and copulatory parameters were studied 1 h after drug administration on day 1, 8, and 15. In this study WAY-100635 alone had no effect on ejaculation latency. Chronic treatment with citalopram alone diminished ejaculation frequency, indicating a mildly delayed ejaculation time. However, both acute and (sub)chronic coadministration of citalopram and WAY-100635 delayed ejaculation time immediately, within an hour. In addition, neuronal activation in brain sites associated with sexual behavior was lower in rats that received both citalopram and WAY-100635 than in the other groups [12]. The results of this study may lead to the conclusion that blocking 5-HT<sub>1A</sub> receptors does not change ejaculatory latency under physiological conditions, but does so during SSRI treatment. The results of this study suggest also that 5-HT<sub>1A</sub> receptor functioning is essential in the effects of SSRIs on

ejaculation. It is likely that desensitization of the 5-HT<sub>1A</sub> receptor is pivotal for delaying ejaculation. This could also be derived from a recent male rat study in which chronic SSRI treatment and particularly paroxetine impaired 5-HT<sub>1A</sub> receptors involved in ejaculation [26]. The results of the aforementioned animal studies support the view that 5-HT pharmacodynamics is essential for serotonergic drugs to delay ejaculation and provide a scientific basis for the development of new on-demand drugs that immediately lead to strong ejaculation delay. However, human studies need to provide evidence that such combination drugs do indeed exert strong ejaculation delay and do not lead to potentially dangerous or otherwise bothersome side effects.

The combination of an SSRI with a 5-HT<sub>1A</sub> receptor antagonist, contributing to an immediate strong ejaculation delay in male rats, paves the way for the development of exciting new on-demand drugs.

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### **27.18 Medical Dysfunction Versus Consumer Market for Premature Ejaculation**

As the prevalence of lifelong PE and acquired PE is rather low compared to the number of men who do not suffer from these medical disorders, but are not satisfied with their ejaculatory performance, it may be argued that the “medical dysfunction” market is rather low compared to the potential “consumer market” of drugs that delay ejaculation.

It is my personal opinion, that any effective drug for the “medical dysfunction” market should lead to a strong ejaculatory delay with minimal side effects. In contrast, for the “consumer market” a less strong ejaculation delaying drug but also with minimal side effects may be appropriate. Ongoing sexual psychopharmacological animal research will probably lead to new insights into pathways and neurotransmitters that may form the basis for the development of drugs which potently delay ejaculation.

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### **27.19 Conclusion**

Apart from a placebo-controlled and double-blind design, the most appropriate way of objective drug treatment research of PE is the use of a stopwatch to measure the IELT. So far, and although it is known that, for example, dopamine and oxytocine are also involved in the ejaculation process, the central serotonergic system remains the most important system that can be manipulated for delaying ejaculation. Based on animal research, combination of an SSRI with a 5-HT<sub>1A</sub> antagonist may lead to an acute strong ejaculation delay. This may form the basis for the development of new powerful on-demand drugs to treat lifelong PE.

Apart from the aforementioned positive view that there are psychopharmacological possibilities to develop new drugs, it is my personal view that we should wonder why we are still not capable to definitely cure lifelong PE. Currently available drugs can only delay ejaculation in these men. One of the reasons for having no cure for lifelong PE may perhaps be that we still do not know all the characteristic clinical features of lifelong PE, and therefore miss an important link to other central pathways or neurotransmitter systems that are involved in lifelong PE. More research of the “phenotype” lifelong PE is therefore warranted. Relevant to this research is that future research should not only focus on finding more detailed features of lifelong PE but should also focus on finding clinical differences among the four PE subtypes. By applying this strategy, research can focus on more homogenous subgroups of PE. This may increase the odds to find new therapeutic targets, that are essential for psychopharmacological research. However, research on finding new therapeutic targets is not only limited to pharmacological strategies that delay ejaculation. Also nonpharmacological strategies that effectively delay ejaculation should be investigated to find the neurobiological mechanisms by which they intervene with the ejaculation process.

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## Appendix: Psychometric Tools for Premature Ejaculation and Related Erectile Dysfunction

# 28

Emmanuele A. Jannini, Erika Limoncin and Giacomo Ciocca

When patients with premature ejaculation (PE) finally consult their doctors, they are acutely aware of their sexual troubles, but negative feelings such as anxiety and guilt severely hinder the patient–physician relationship and impair effective communication and empathy, that is the first step towards solving the problem. Establishing an interested and warm relationship is the prerequisite for obtaining an informative and thorough history, the cornerstone of an economical investigation, an accurate diagnosis and a successful treatment of PE. The physician needs to consider the background of the sexual problem, in terms not only of the patients themselves, but also within the context of the couple’s relationship and of the family background.

At the beginning of the interview, the physician should obtain information about the patient’s origin, education, job, home, lifestyle, hopes, and fears, to get onto friendly terms with him/her. In listening to the patient’s history, the physician should pay attention even to the slightest details such as the voice inflection, facial expressions and attitude. The physician will then elicit a careful history of the patient’s illness not apparently related to the sexual problem, knowing that any event reported by the patient, even trivial or apparently remote, may be the key to the solution of the sexual problem. It is important to note that most PEs are symptoms of other pathological processes that must be correctly identified and, possibly, treated.

Given the personal, interpersonal, social, and occupational implications of PE, the assessment of sexual history is altogether complex. The underlying philosophy of the patient–physician relationship is the acceptance of each person with PE as unique and valuable. There must be a tension between the physician and the patient,

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a holistic care approach to obtain and use the full range of information to direct the diagnostic and therapeutic intervention. In sexual medicine, this paradigm is not always easy. Finding the correct way to ask questions and to decode answers on sexual health in general and ejaculatory control in particular might be difficult and, in some way, embarrassing. Hence, expert-guided, validated, and standardized sexual inventories (i.e., structured interviews and self-report questionnaires) might help novice and more experienced physicians alike to address PE. In addition, sexual inventories might help to evaluate the outcome of therapies better and more easily. These clinical tools have the advantage of being standardized, easy to administer and score, in that they provide normal values in general and pathological populations, as well as being relatively unobtrusive and substantially inexpensive. However, they carry a risk of oversimplification and are sensitive to language differences (they need to be validated in each language), semantic perception, and to ethnic, religious, education, and cultural factors. Despite this, sexual inventories represent a unique tool in the assessment and therapeutic follow-up of patients with PE. Nonetheless, sexual inventories here presented can be considered a guide, not a substitute for an in-depth sexual history [1].

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## 28.1 Patient-Reported Outcome in Premature Ejaculation

The patient-reported outcome (PRO) measures have been elicited from men and their partners as control over ejaculation and satisfaction with sexual intercourse (0 = very poor to 4 = very good), personal distress and interpersonal difficulty (0 = not at all to 4 = extremely), and severity of PE (0 = none to 3 = severe). An overlap in IELT distributions was observed between the PE and non-PE groups, indicating the need for additional PRO measures to better characterize PE. Hence, lacking a quantitative value, the PRO questions can be used in the clinical practice for qualitative evaluation [2].

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## 28.2 Index of Premature Ejaculation

The Index of Premature Ejaculation (IPE) is a questionnaire developed and validated to measure the overall experience of PE. The 10-item measure explores sexual satisfaction, control, and distress. Reliability is good, both with internal consistency and test–retest reliability. Convergent validity using IELT is excellent: control domain (0.75), sexual satisfaction domain (0.60), and distress domain (0.68). Known-groups validity is very good, all domain mean scores being statistically significantly worse in men with PE compared with the men reporting no PE. The IPE is a reliable and valid questionnaire for the assessment of control over ejaculation, satisfaction with sex life, and distress in men with PE. This tool has the potential to add value to interpretations of improvements in ejaculation latency resulting from new treatments of PE [3]. The IPE can be downloaded from the website of the copyright holder ([www.pfizerpatientreportedoutcomes.com](http://www.pfizerpatientreportedoutcomes.com)).

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### **28.3 The Premature Ejaculation Diagnostic Tool**

This popular psychometric tool is built on the essence of DSM-IV-TR PE definition. The Premature Ejaculation Diagnostic Tool (PEDT) is psychometrically validated in a 5-item, unidimensional measurement of control, frequency, minimal stimulation, distress, and interpersonal difficulty. Sensitivity/specificity analyses suggest a score of  $< \text{ or } = 8$  indicating no-PE, 9 and 10 probable PE, and  $> \text{ or } = 11$  PE. It is a user-friendly, very short self-report questionnaire for use in clinical trials to diagnose PE as well for daily clinical practice [4]. The PEDT can be downloaded from the website of the copyright holder ([www.pfizerpatientreportedoutcomes.com](http://www.pfizerpatientreportedoutcomes.com)).

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### **28.4 The Clinical Global Impression of Change**

The Clinical Global Impression of Change (CGIC) is a PRO measurement which may have high utility both in clinical practice and in research. The validity of the patient-reported CGIC measure in men with PE has been evaluated. Furthermore, the relationship between CGIC ratings and assessments of control, satisfaction, personal distress, and interpersonal difficulty have been examined. The CGIC can provide clinicians in practice with a valid and brief outcome assessment of their patient's condition [5].

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### **28.5 The Chinese Index of Premature Ejaculation (CIPE)**

The CIPE is a questionnaire based on 10 questions, focusing on libido, erectile function, ejaculatory latency, sexual satisfaction and difficulty in delaying ejaculation, self-confidence and depression. Each question is to be responded to on a 5 point Likert-type scale. The CIPE-5 is a useful method for the evaluation of sexual function of patients with PE and can be used as a clinical endpoint for clinical trials studying the efficacy of pharmacological intervention [6].

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### **28.6 The Arabic Index Premature Ejaculation (AIPE)**

The AIPE is a diagnostic tool for designed for PE validated in 71 men complaining of PE and 73 healthy subjects. The seven items selected were based on assessment of erectile function, sexual desire, ejaculation latency, ejaculation control, patient satisfaction, partner satisfaction, and psychological distress [7]. PEDT and AIPE have a comparable ability in diagnosing PE with high sensitivity, especially in patients with lifelong and acquired PE [8].

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## 28.7 The Sexual Quality of Life for Men Instrument

The Sexual Quality of Life for Men (SQOL-M) instrument systematically captures the impact of sexual dysfunction on quality of life (QOL) in men with PE or ED. It consists of an 11-item scale with no overlap between items and good item-total correlations. Factor analysis confirms a one-factor solution. Excellent internal consistency was demonstrated, with a Cronbach's alpha of  $>$  or  $=$  0.82 in all groups. In men reporting no change in their symptoms, the SQOL-M showed excellent test-retest reliability: the intraclass correlation coefficient was 0.77 for men with PE, and 0.79 for men with ED. Convergent validity was also good. In men with PE, the SQOL-M correlated with the satisfaction and distress domains of the Index of PE [9].

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## 28.8 The International Index of Erectile Dysfunction

The International Index of Erectile Function (IIEF) is the most frequently used psychometric tool for the evaluation of male sexual function [10]. It has been widely used for determining the efficacy of treatments in controlled clinical trials. Although IIEF has been widely considered an excellent tool in the evaluation of the efficacy of drug therapies, it could not analyze pathogenetic components underlying erectile dysfunction (ED) and its role in differentiating the various causes of ED has been questioned [11, 12]. Note that Q9 is related to ejaculation, but not to PE. In any case, the IIEF is an well validated instrument to rule out ED in PE patients. However, it should be noted that some men with PE and normal erectile function may record contradictory responses to erection related items of the IIEF and may be incorrectly categorized as suffering from ED [13].

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## 28.9 Sexual Health Inventory for Men

Although the IIEF is a useful instrument, because of its length it is not as well suited for use in clinical practice with impotent patients. Consequently, an abridged 5-item version of the original 15-item IIEF, the IIEF-5 (Sexual Health Inventory for Men, SHIM5) [14, 15] and a 6-item version, the IIEF-6 (the erectile function domain of IIEF) [16] were separately developed and validated to diagnose the presence and severity of ED. Note that it has been demonstrated a 33.3% false positive SHIM diagnosis of ED in men with PE [13]. However, the real clinical risk is to miss the diagnosis of ED in PE, rather than the vice versa.

## 28.10 Structured interview on erectile dysfunction (SIEDY)

SIEDY is a powerful psychometric instrument exploring the specific weight of organic, intrapsychic, and relational factors in men with ED [17]. This structured interview is not designed for EP. However, several articles in the field of PE have been published on cohorts of patients selected using SIEDY [18, 19, 20].

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## 28.11 Female Sexual Function Index-6 (FSFI-6)

Female sexuality is complex and multifaceted. For this reason, psychometry of female sexual function and dysfunction is not easy. However, it is mandatory to study the partner of the patient with PE. One possible instrument is the Female Sexual Function Index in its abridged form (FSFI-6), which seems a valuable tool for screening women that are likely to suffer from female sexual dysfunction (FSD) [21]. In six simple questions, taking no more than 3 minutes, a score of less than 19 indicates the need for further investigations, including the full-length FSFI-19 and a dedicated interview. The use of FSFI-6 in the clinical setting of the couple with PE is strongly encouraged to disclose FSD rapidly and efficiently.

Finally, the ability of PE in affecting sexual health of homosexual couples is scarcely studied [22]. Psychometric tests to assess the involvement of the male partner in the pathogenesis of PE have to be developed.

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## Epilogue: Future Perspectives

The groundbreaking progress made in the professional attention to, and diagnosis and treatment of premature ejaculation (PE) during the last two decades, has been documented throughout this textbook.

This book shows that in the early 1990s, PE was a rather neglected disorder, both in sexology as in general medicine. It also describes the previous almost exclusive psychological view of its etiology and pathogenesis that had prevailed for many decades which has given way to a neurobiological, genetic, and medical view albeit retaining some of the psychological origins and psychosocial and cultural consequences of PE. It should also be noted how the internet has become an important source of information for patients attempting to inform themselves about the various available treatments of PE.

Despite these remarkable developments—many of them during the 1990s—now 12 years into the new century, we are already experiencing a number of continuing and also new emerging issues, challenges, opportunities, but also concerns that demand our attention.

The three editors of this textbook and some of the contributing authors have been active in the research and/or clinical management of PE since the early 1990s. We witnessed how PE developed from a rather obscure and unusual disorder into a recognized and well-known one. A number of years ago, the International Society for Sexual Medicine (ISSM) acknowledged the importance of PE and actively contributed to two important historical events: reaching a consensus on a new definition of lifelong PE and then laying down a guideline for the treatment of PE.

Another remarkable historical fact is that the research into the most appropriate methodology and design of drug treatment studies of PE by SSRIs and anesthetic creams, was developed in the 1990s by independent clinicians and researchers without the involvement of pharmaceutical companies—which is clearly contrary to the belief by some that the increasing attention given to PE is only the result of pharmaceutical companies' interests!

While attention being paid to PE has resulted from independent researchers and the stimulus given through the ISSM in recent years, it has also been stimulated by Johnson & Johnson, the pharmaceutical company, that has produced dapoxetine for the on-demand treatment of PE. Their financial support has enabled large epidemiological studies on PE to be performed, and it should be recognized that without their support this could have never been achieved.

In the 1990s, only a handful of researchers investigated and wrote about PE, and they were well-acquainted with nearly all published articles and specific views on PE. Today we are confronted with an abundance of articles and an increasing number of authors writing about PE. This is a positive development but a caution should be issued—that this does not lead to a dilution of knowledge. We are already seeing articles that fail to mention important new information in this field. Hopefully, this textbook will help potential authors update themselves quickly with the most relevant and recent knowledge on the subject of PE.

The title “Future Perspectives” given to this epilogue obviously pertains to a look into the future regarding new approaches to treat PE. In this regard, we hopefully look ahead to innovative approaches that may change and/or even replace the currently available treatments of PE, and even lead to a definitive cure for lifelong PE.

In order for this to happen, continuing animal and sexual psychopharmacological research into new pathways and targets is needed. As I argued in Chap. 29, one reason for the lack of cures for lifelong PE may possibly lie in our not knowing all the characteristic clinical features of lifelong PE. We therefore miss an important link to other central pathways or neurotransmitter systems that are involved in lifelong PE. In other words, we should not only rely on established clinical and pharmacological facts, but further examine, crucially, the “phenotype” lifelong PE. This can only be performed by close examination of the clinical differences between the four PE subtypes. In other words, clinical research should focus on delineating the four PE subtypes in more homogenous subgroups. This strategy will increase the odds to find (new) essential clinical characteristics of the four PE subtypes. This may be crucial if we are ever to find new therapeutic targets essential for future psychopharmacological research.

However, research aimed at finding new therapeutic targets is not only limited to innovative pharmacological strategies that delay ejaculation; nonpharmacological strategies that effectively delay ejaculation should also be investigated in order to find the underlying neurobiological mechanisms by which they intervene with the ejaculation process. In this respect, it is argued that the effect of psychotherapy or any other nonpharmacological strategy is based on underlying neurobiological mechanisms.

Last but not least financial support for new research is needed. Sadly it is becoming increasingly more difficult to obtain this support. Official scientific institutions prefer to finance nonsexual research projects. Therefore, we should welcome any new pharmaceutical company that is willing to finance basic and clinical research in the field of PE, obviously with their respect for the independence of the researcher but also with an open eye of the researcher for the business interests of the company. In this way independent scientific research into premature ejaculation will be secured.

Marcel D. Waldinger



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