History of Premature Ejaculation

2

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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.

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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E. A. Jannini et al. (eds.), *Premature Ejaculation*,
DOI: 10.1007/978-88-470-2646-9_2, © Springer-Verlag Italia 2013

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 monobormata, 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 inhition 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 (EMEA) for the treatment of PE [18] and that other companies show interest in drug treatment of PE.

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.

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].

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 α_1 and α_2 adrenergic blocker phenoxybenzamine [65–67] or the selective α_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

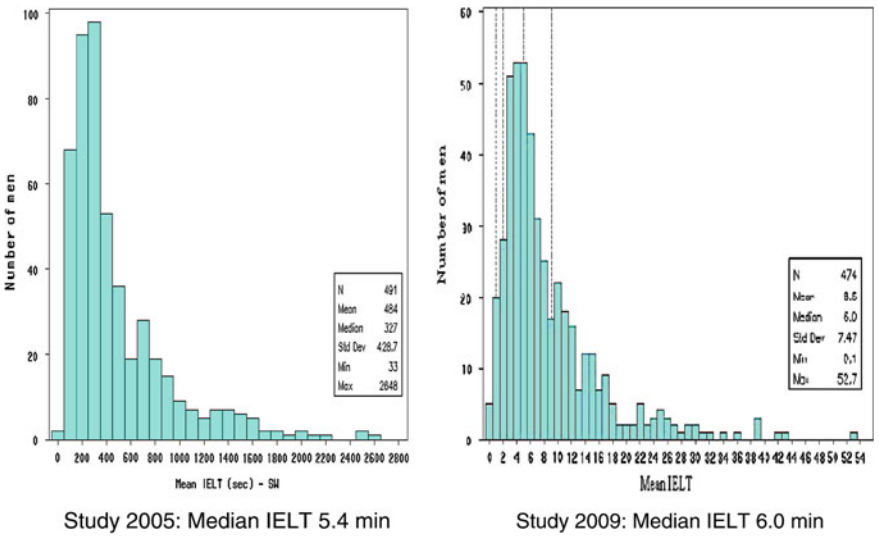

Fig. 2.1 Two epidemiological stopwatch studies of the IELT in random sample of the general male population in five countries [99,100]

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 (EMEA) 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.

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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