Advances in Treatment for Premature Ejaculation

a report by
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Not every complaint of ejaculation is the result of an ejaculatory 'disorder'. For example, a man may believe himself to be ejaculating prematurely, even though he is doing so within a normal ejaculation time. On the other hand, some men regularly complain of early ejaculation occurring very soon after penetration. Both examples are part of a debate on the definition of premature ejaculation (PE) that has existed since the 1970s, and which has given rise to sometimes fierce debate.

History of Premature Ejaculation

Since the beginning of the last century, PE has been regarded as an expression of an unconscious psychological conflict. It has also been attributed to urological disturbances, and many different treatments have been recommended over the years.[1] A clearer understanding of the differences in aetiology and treatment has resulted from the classification, introduced in 1943 by the German endocrinologist Bernhard Schapiro, of two types of PE: A and B.[2] Later, the types became known as primary (lifelong) PE and secondary (acquired) PE, respectively,[3] and were included in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (Text Revision) (DSM-IV-TR), which is the American Psychiatric Association (APA) classification system of mental disorders.[4]

The *Diagnostic and Statistical Manual of Mental Disorders Fourth Edition* (Text Revision) Definition

Until 1980, the year in which the DSM-III was published by the APA, there was no official definition of PE. In the first part of the 20th century, psychoanalysts considered a man to be suffering from PE when ejaculation occurred so quickly after vaginal penetration that a woman had little chance of getting sexually aroused. In the absence of any official definition, it was a loosely accepted idea that a man suffered from PE when he consistently ejaculated within one minute after penetration. In 1970, William Masters and Virginia Johnson rejected this idea by stating that a man has PE when he is unable to control his ejaculation to satisfy his female partner in more than 50% of intercourses.[5] Masters and Johnson strongly refuted a short ejaculation time as a criterion for the definition of PE. Their view influenced the first official definition of PE, made in the DSM-III in 1980. According to the DSM-III, a man is defined as having PE when "ejaculation occurs before the individual wishes it, because of recurrent and persistent absence of reasonable voluntary control of ejaculation and orgasm during sexual activity."[6] It is clear that the DSM-III defined PE solely in terms of an absence of voluntary 'control', without paying attention to the time that passes before a man actually ejaculates (the ejaculation time). After its publication, the DSM-III definition of PE has given rise to debate among psychiatrists about the meaning of the word 'control'. The result of this debate was that in the next version, the DSM-III-R, published in 1987, the word control was no longer mentioned in the definition. Instead, PE was defined as "persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it."[7] The new defining criterion 'short ejaculation time' remained in the two other DSM editions: the DSM-IV (1994) and the DSM-IV-TR (2000).[4] However, as little evidence-based research into ejaculation time had been conducted in the 1980s, a quantification of the 'short' ejaculation time was not mentioned in the DSM-IV definition. In contrast, the definition of PE in the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10), which is the classification system of the World Health Organization (WHO), does mention a cut-off point for the ejaculation time.[8] According to the ICD-10, a man has PE when he ejaculates within 15 seconds after penetration. However, the ICD-10 makes no reference to any study where this figure had been reported as outcome data.[9]

Research into Ejaculation Time

In the mid-1990s, Waldinger et al. postulated that in the general male population there is variability in the intravaginal ejaculation latency time (IELT), which is defined as the time between vaginal penetration and intravaginal ejaculation.[10] However, it was only in 2005 that such variability was demonstrated in men.[11] In a stopwatch study, financed by Pfizer International, the IELT was measured in a random cohort of men in the general population of five countries – The Netherlands, UK, Spain, Turkey and the US – during a one-month period.[11] The study demonstrated for the first time that in the general male population the IELT has a skewed distribution, with a median IELT of 5.4 minutes (confidence interval [CI] 0.55–44.1 minutes). However, such a continuum of the ejaculation time had previously also been observed using various cohorts of laboratory male Wistar rats.[12,13] Based on this

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continuum, a new animal model for PE was presented. In addition, it was postulated that there are three endophenotypes of male rats: rats that always ejaculate after a short time of copulatory behaviour, i.e. rapid ejaculating rats; rats that ejaculate after a normal ejaculation latency time, i.e. normal ejaculating rats; and rats that ejaculate after a long ejaculation latency time, i.e. sluggish ejaculating rats. It was also postulated that lifelong PE in men represents a specific phenotype and is characterised by specific symptomatology.[14]

Normal and Abnormal Intravaginal Ejaculation Latency Time

What exactly is a normal IELT? This question is frequently asked by patients with lifelong PE of their treating physician. This question, to which there was no evidence-based answer for many years, was finally answered in 2005 – obviously with some reservation – on the basis of the five-nation stopwatch study. According to statistics, any figure under the 2.5 or 0.5 percentile, in a skewed distribution, may be regarded as abnormal or dysfunctional. In the five-nation study it appeared that men under the 2.5 percentile had an IELT of less than one minute.[15] In other words, men with an ejaculation time of less than one minute have, according to the statistics, an abnormal IELT compared with the IELT of the rest of the men in the general population.[15] This IELT of one minute or less was already known from a study in which a clinical cohort of Dutch men with lifelong PE had measured their IELT with a stopwatch over a one-month period at every intercourse: 80% of these men ejaculated within 40 seconds and 90% of these men ejaculated within one minute after vaginal penetration.[16] On the basis of the aforementioned findings in both human and animal research, Waldinger and colleagues postulated that lifelong PE is mainly a neurobiological ejaculation disorder, and probably also a genetically determined one that is related to disturbances of serotonergic (5-hydroxytryptamine [5-HT]) neurotransmission in the central nervous system.[14] They defined lifelong PE in terms of an ejaculation that occurs within one minute after vaginal penetration.[14,16]

Lifelong Premature Ejaculation

Men with lifelong PE suffer from early ejaculations from their first sexual contacts. At almost each coitus and with every woman or sexual partner, they experience an early ejaculation. In the aforementioned stopwatch studies, as well as studies in which PE was self-reported, it has been demonstrated that 90% of men with lifelong PE ejaculate within one minute and that another 10% ejaculate within one to two minutes.[16,17] It is intriguing that many years after the times when men with PE were mainly treated by psychoanalysts, current evidence-based research has demonstrated that their definition in terms of one minute after penetration had actually been correct. In 2007, the International Society for Sexual Medicine (ISSM), in a meeting in Amsterdam, reached a consensus on a new definition of lifelong PE. This definition contains the one minute criterion and is as follows: PE is a male sexual dysfunction characterised by ejaculation that always or nearly always occurs prior to or within about one minute of vaginal penetration; an 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.[18] Throughout their life, men with lifelong PE usually ejaculate within the same short ejaculation time. However, it has been shown that about 20–30% of these men at some point in life experience an even shorter ejaculation time, generally after they reach around 30 years of age.[16,17]

Acquired Premature Ejaculation

Men who start suffering early ejaculations at a certain age after never having had this complaint previously and who had been easily able to delay ejaculation may be diagnosed as having acquired PE. The characteristics of acquired PE have not been investigated and described as well as those of lifelong PE. Men with acquired PE are rather more heterogeneous as a group compared with those with lifelong PE. This is most probably due to the different factors and dysfunctions that may lead to acquired PE. It is not only psychological and relationship factors that may give rise to PE, but also hyperthyroidism, erectile difficulties and urological problems such as prostatitis that may be the cause of this PE subtype.[19–22] In contrast with lifelong PE, which has been well documented, little has been published regarding IELT quantification and patient-reported outcomes (PROs) – such as feelings of satisfaction – in cohorts of men with acquired PE. Most studies on acquired PE used inclusion and exclusion criteria, which resulted in the characteristics of a whole cohort of these men not being completely investigated. This lack of knowledge currently impairs the formulation of an evidence-based definition for this PE subtype. Consequently, the Expert Panel Acquired PE meeting under the auspices of the ISSM, which convened in Hamburg in 2008, has agreed on the following interim position statement on acquired PE: acquired PE is a subtype of PE characterised by a substantial decrease in time to ejaculation compared with a man's previous sexual experience; the inability to delay ejaculation on all or nearly all vaginal penetrations; and negative personal consequences, such as distress, worry, frustration and/or the avoidance of sexual intimacy. The Expert Panel meeting agreed that further clinical research is required to obtain IELT data, as well as PRO data, for men with acquired PE.

Natural Variable Premature Ejaculation and Premature-like Ejaculatory Dysfunction

Based on data obtained from large-scale surveys on the prevalence of PE in the general population,[23] Waldinger and Schweitzer postulated that in addition to lifelong PE and acquired PE, there are two other PE subtypes: natural variable PE and premature-like ejaculatory dysfunction.[24–27] In natural variable PE, an early ejaculation only incidentally and occasionally occurs. This incidentally occurring early ejaculation should not be regarded as a symptom of underlying psychopathology, but rather as a manifestation of normal variation of the ejaculation time. Treatment consists of psychoeducation and reassuring that there is no pathology involved. Men with premature-like ejaculatory dysfunction complain about PE, while from an objective point of view the ejaculation time is just normal or even prolonged, e.g. four to 20 minutes. Treatment should consist of counselling, psychoeducation and sometimes psychotherapy. However, it should be noted that currently there are no evidence-based outcome data available on these treatments in this PE subgroup.

Men with natural variable PE and premature-like ejaculatory dysfunction are rarely seen at urological or sexological outpatient clinics. The existence of these groups of men has mainly been derived from epidemiological surveys. As the prevalence of lifelong PE and acquired PE is probably rather low (about 5–10%), it may well be that the high prevalence rates of 20–30% of PE in the general male population are determined by the large number of males who are dissatisfied with their sexual ejaculatory performance while actually having normal ejaculation times.[27]

Pharmacotherapy of Premature Ejaculation

The pharmacotherapy of PE depends on the PE subtype and the underlying aetiology and pathogenesis.[28] Evidence-based psychopharmacological research has demonstrated that the daily use of some selective serotonin re-uptake inhibitors (SSRIs) in particular, such as 20mg paroxetine, 50–100mg sertraline, 20–40mg citalopram and 10–20mg clomipramine, which is the most serotonergic tricyclic antidepressant, may clinically and statistically significantly delay ejaculation compared with placebo.[29] The daily intake of these serotonergic antidepressants has a number of advantages over the intake of drugs a few hours before intercourse (on-demand intake). By using a daily intake strategy, sexual contact may take place at every moment of the day with about 80% chance of a moderate to strong ejaculation delay.[30] Moreover, the daily use of drugs does not interfere with the desirable spontaneity in having sexual contact on the spur of the moment, since ejaculation will be delayed for nearly all intercourses. In addition, the risk of nausea or other gastrointestinal side effects during sexual contact is diminished after one to three weeks due to habituation of the gastrointestinal tract to the serotonergic component of this group of drugs.[30]

In contrast with daily intake, the on-demand use of serotonergic antidepressants a few hours before intercourse generally leads to less ejaculation delay in men with lifelong PE compared with daily treatment with SSRIs. The on-demand use of these drugs also has an increased risk of gastrointestinal side effects (particularly nausea) a few hours after drug intake. With regard to this time component after intake, the occurrence of nausea may co-occur with the moment of intercourse. Another disadvantage of the on-demand use of drugs is it may have a negative effect on the spontaneity of a couple deciding to have sex. For many men and their partners, it is rather inconvenient to be thinking most of the time whether they dare have sex or not.[17] However, despite these drawbacks the on-demand use of 20–40mg clomipramine about four to six hours prior to coitus may lead to a clinically relevant and satisfactory ejaculation delay. Besides its serotonergic properties, this is probably also due to its sympathicolytic properties. It should be noted that the on-demand use of serotonergic antidepressants may also have advantages over daily treatment. On-demand use of drugs reduces the chance of interactions with other drugs and decreases the chance of interactions with alcohol, and may be prescribed to men who have no steady partner or are content in a relationship with a rather low coitus frequency. It is dubious to advise daily intake of SSRIs to men who have sexual contact perhaps only once or twice per month.

Side Effects of Selective Serotonin Re-uptake Inhibitors and Clomipramine

The side effects of the SSRIs and clomipramine vary in the short and long term.[30] In the short term, SSRIs may give rise to fatigue and yawning, but also to a vague feeling of nausea, flatulence, loose stools and increased perspiration. Usually these side effects diminish and disappear after two to three weeks of daily treatment. However, in the long term SSRIs may give rise to increased weight and sometimes to erectile difficulties and decreased sexual desire. Besides these serotonergic side effects, clomipramine may also give rise to anticholinergic side effects such as dry mouth, blurred vision and constipation. It is of relevance to inform patients about these aforementioned side effects when prescribing the drugs. If the side effects are too disturbing or continue for rather a long time, the patient should be advised to come off the drugs, gradually reducing the daily dosage in order to prevent the occurrence of SSRI discontinuation syndrome. After stopping the drug, one can prescribe another SSRI that may cause fewer side effects.

On-demand Treatment of Tramadol

Recently, two studies have been published on the ejaculation -delaying effect of tramadol 50–100mg.[31,32] The on-demand use of the drug one to three hours prior to coitus may lead to a delayed ejaculation. The precise cause of the induced ejaculation delay is unclear. It may be related to the serotonin re-uptake inhibitory property of the drug as it is unlikely that it is caused by its agonistic effect on the μ-receptor. Due to its opioid affinity, the patient should be informed about the risk of drug dependency when taking the drug on a more regular basis.

On-demand Treatment with Phosphodiesterase V Inhibitors

Phosphodiesterase V (PDE-V) inhibitors, such as sildenafil, cialis and vardenafil, may effectively treat the cause of PE, particularly in the case of acquired PE that is the result of erectile difficulties. These drugs facilitate erectile function and because of this the drugs diminish the chance that a man decides to (prematurely) ejaculate as a way to mask his difficulty to maintain his erection. As the PDE-V inhibitors have no effect on the actual ejaculation time, these drugs are not useful in men with lifelong PE and no erectile difficulties. However, there have been some publications in which PDE-V inhibitors are recommended for men with lifelong PE. However, the methodology of these studies is rather weak.[33]

On-demand Treatment with Local Anaesthetic Cream

The use of anaesthetising creams and sprays to delay ejaculation is the oldest known pharmacological method of treating PE.[2] A few studies have demonstrated that lidocain- and prilocain-containing creams, such as local anaesthetic (EMLA) cream, may delay ejaculation. However, few men with lifelong PE report much success using EMLA creams, and there have been few studies on these negative treatment results.

New Drugs Against Premature Ejaculation

Since the 1990s, the SSRIs and clomipramine have become the most popular drugs to treat PE. However, they have not been officially registered with the US Food and Drug Administration (FDA) or the European Medicines Agency (EMEA) for the treatment of PE. This is related to the fact that the pharmaceutical companies that have produced these drugs have never been interested in drug treatment of PE for marketing reasons. Also, the companies producing tramadol and PDE-V inhibitors have never been interested in PE. However, there are two pharmaceutical companies who are currently interested in the registration of their drugs to treat PE.

Dapoxetine

At the time of writing the producer of dapoxetine, Johnson & Johnson, is waiting for a decision from the EMEA as to whether their drug will become registered for the on-demand treatment of PE in Europe. Dapoxetine is an SSRI and was originally developed by Eli Lilly as an antidepressant with a short half-life,[34] and the application of the drug as a potential treatment for PE was subsequently investigated by Alza and

Johnson & Johnson. The drug is suitable for on-demand use to treat PE particularly due to its pharmacokinetic properties, for example its short half-life. Two placebo-controlled trials have shown that when taken one to three hours before intercourse, dapoxetine statistically significantly delays ejaculation compared with placebo.[35] However, the extent of ejaculation delay seems to be rather weak, which may also be derived from the reported drug-induced normal IELT distribution.[36]

Topical Eutectic Mixture for Premature Ejaculation

Topical eutectic mixture for premature ejaculation (TEMPE), a eutectic anaesthesising topical spray containing lidocain and prilocain, has been developed by Plethora specifically to treat PE.[37] The spray immediately penetrates the skin of the glans penis, and this property distinguishes it from creams and sprays containing lidocaine and prilocaine that penetrate the skin at a much slower rate. The first study demonstrated that the spray delays ejaculation without clinically relevant side effects.[37] As the induced geometrical mean IELT is shorter than the induced mean IELT, it may be inferred that the drug shows an interesting potential for delaying ejaculation.[36]

Conclusion

Since the mid-1990s, there has been an increasing interest in drug treatments of PE. Research has been conducted by clinicians and neuroscientists, and has remarkably been performed with little financial support from pharmaceutical companies. In a considerable number of studies, it has been shown that daily use of some SSRIs and clomipramine delays ejaculation most effectively, and that the initial side effects diminish and even disappear after about three weeks. Since 2000, studies on the on-demand use of PDE-V inhibitors have also been published. Their application is particularly useful in men who have PE on the basis of erectile difficulties. The recent interest of the pharmaceutical industry is welcomed, but the registration of a new drug, whether it effectively or inadequately delays ejaculation, may lead to new hype that goes along with information on PE that presumably will be strongly determined by the marketing strategies of the pharmaceutical producing companies. A well-known marketing strategy in this respect is to criticise current effective and safe treatment strategies that have been accepted by the medical community;[38] therefore, it is essential that prescribing physicians remain informed through independent studies, i.e. studies conducted and written by authors other than those of the pharmaceutical company, their advisers or medical writers.[39]

Apart from the developments in drug treatment of PE, important progress has been made in the research of a better and more appropriate classification of PE. Research into the recently proposed new classification of four PE subtypes, genetic research, pharmacogenetic and animal research will probably contribute to a better understanding of their aetiology, pathogenesis and treatments in the next decade. ■

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