REVIEW ARTICLE

Drugs 2007; 67 (4): 547-568
0012-6667/07/0004-0547/$49.95/0

Premature Ejaculation
Definition and Drug Treatment

Marcel D. Waldinger[1,2]

1 Department of Psychiatry and Neurosexology, HagaHospital Leyenburg, The Hague, The Netherlands
2 Department of Psychopharmacology, Faculty of Pharmaceutical Sciences and Rudolf Magnus Institute for Neurosciences, Utrecht University, Utrecht, The Netherlands

Contents

Abstract

Premature ejaculation (PE) is a frequent male sexual complaint that is mediated mainly by disturbances of serotonergic neurotransmission and certain serotonin (5-HT) receptors and, to a lesser extent, oxytocinergic neurotransmission in the CNS.

The current Diagnostic Manual of Mental Disorders (fourth edition, revised text) [DSM-IV-TR] definition of PE has a low positive predictive value and is inadequate for clinical, epidemiological and drug treatment research. Categorisation of PE into four well defined syndromes has recently been proposed for the pending DSM (fifth edition) definition of PE.

Over the last decade, an increasing number of studies of drug treatment of PE have been published. A meta-analysis of those studies, conducted in accordance with current standards of evidence-based medicine, demonstrated similar efficacies for daily treatment with the serotonergic antidepressants paroxetine hemihydrate, clomipramine, sertraline and fluoxetine, with paroxetine (hydrochloride) hemihydrate exerting the strongest effect on ejaculation. On the basis of fundamental insights into serotonergic neurotransmission, it has been suggested that on-demand selective serotonin reuptake inhibitor (SSRI) treatment will not lead to similarly impressive delays in ejaculation as has been observed with daily SSRI treatment. Indeed, some on-demand studies with SSRIs and studies with the new SSRI dapoxetine have shown a weak ejaculation-delaying effect after 1–2 hours of drug intake. Apart from daily treatment with SSRIs, PE can be delayed by on-demand use of topical anaesthetics and tramadol. Treatment with phosphodiesterase type 5 inhibitors should not be prescribed to men with PE with normal erectile function, but may be used if PE is accompanied by erectile difficulties. There is no scientific support for treatment of PE with intracavernous injection of vasoactive drugs.

Animal studies have shown that strong immediate ejaculation delay may be induced by administration of a combination of an SSRI with a serotonin 5-HT_{1A} receptor antagonist. The combination of an SSRI and any other compound that immediately and potently raises serotonin neurotransmission and/or use of oxytocin receptor antagonists may form the basis for the development of new on-demand and/or daily drugs for the treatment of PE.

In this article the latest proposal for a new Diagnostic Manual of Mental Disorders (fifth edition) [DSM-V] and International Classification of Diseases (11th edition) [ICD-11] definition of premature ejaculation (PE) is outlined. In addition, the current evidence-based knowledge of drug treatment and underlying neuropsychopharmacology of PE is presented.

1. Definition of Premature Ejaculation (PE)

Variability of ejaculatory time and PE is a common and normal phenomenon among men.[1,2] However, when the ejaculatory time is consistently and objectively short at every coitus, the early ejaculations may be due to neurobiological, medical and/or

psychological pathology.[1,2] Throughout the previous century and up to the present day, PE has been the focus of various and sometimes highly contrasting theories, approaches and treatments among physicians and sexologists.[3,4] Both medical and psychological treatments have been described; however, most have not been supported by evidence-based research.[3,4]

At the core of the seemingly everlasting debate to find a consensus on its definition are the different meanings of the term 'premature ejaculation' itself. In order to integrate both neurobiological and psychological approaches into a new definition of PE, Waldinger and Schweitzer[2] recently emphasised the relevance of distinguishing PE as a 'complaint' versus PE as a 'syndrome'. PE as a complaint may belong to the normal variation of ejaculatory performance in a certain number of men, but may also be the manifestation of medically or psychologically determined pathological ejaculatory performance. This distinction has consequences for treatment. For example, men who report having PE but only occasionally should be diagnosed as 'natural variable PE'.[2] When PE is consistently present from the first sexual encounter and occurs within seconds after penetration, men should be diagnosed as having 'lifelong PE'. However, men who report having PE but ejaculate after 5–10 minutes should be diagnosed as having 'premature-like ejaculatory dysfunction'.[5] As psychological and/or relationship problems may underlie the latter complaint, these men should not be treated with ejaculation-delaying drugs but with counselling, psycho-education and sometimes psychotherapy.[5] On the other hand, men who have lifelong PE and consistently have very short ejaculation times, usually within 30–60 seconds, should be treated with medication.

1.1 Diagnostic Manual of Mental Disorders (Fourth Edition, Revised Text) and International Classification of Diseases (10th Edition) Definitions of PE

Currently, there are two official definitions of PE. In the DSM (fourth edition, revised text) [DSM-IV-TR], which is issued by the American Psychiatric Association, PE is defined as a "persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it. The clinician must take into account factors that affect duration of the excitement phase, such as age, novelty of the sexual partner or situation, and recent frequency of sexual activity".[6] By this definition, PE can only be diagnosed when "the disturbance causes marked distress or interpersonal difficulty".[6] According to the ICD (10th edition) [ICD-10], which is issued by the WHO, PE is defined as "the inability to delay ejaculation sufficiently to enjoy lovemaking, which is manifested by either an occurrence of ejaculation before or very soon after the beginning of intercourse (if a time limit is required: before or within 15 seconds of the beginning of intercourse) or ejaculation occurs in the absence of sufficient erection to make intercourse possible".[7]

Interestingly, in contrast to the DSM-IV-TR definition, the ICD-10 definition uses a cut-off point for the ejaculation time of 15 seconds, but does not provide literature on which this quantification is based. Conversely, and in contrast to the ICD-10, the DSM-IV-TR states that PE needs to cause marked distress and/or interpersonal difficulty before it can be classified as the sexual disorder PE. However, the distress and/or interpersonal difficulty requirement for the diagnosis of PE is not based on evidence-based studies but on the subjective idea of the DSM-IV Task Force that any mental disorder in the DSM should cause distress and/or interpersonal difficulty.[1]

It should be noted that both the DSM-IV-TR and ICD-10 definitions of PE are based on authority-based opinions and not on the findings of well controlled clinical and epidemiological studies.[1] Recently, it has been shown that the DSM-IV-TR definition of PE has a low positive predictive value when used as a diagnostic test.[1] This low positive predictive value is most likely to be related to the absence in the DSM-IV-TR definition of a quantified cut-off point for the intravaginal ejaculation latency time (IELT), which is the time between vaginal intromission and intravaginal ejacula-

tion.[8,9] This means that according to the DSM-IV-TR definition, men with long IELT values, for example, 10–20 minutes, may be diagnosed as having PE if they perceive themselves as having PE. The existence of men who complain of PE despite having normal and even long durations of IELT became evident in the study by Patrick et al.,[10] in which experienced clinicians diagnosed PE according to the DSM-IV-TR criteria of PE. Obviously, because of the low positive predictive value of the DSM-IV-TR definition, a diagnosis of PE according to this definition hampers clinical practice and epidemiological and drug treatment research.[1,2]

1.2 Proposal for New Definition of PE

The current DSM-IV-TR definition of PE is a descriptive definition that emphasises 'complaints' of PE. Moreover, this definition is hampered by the use of terms that are not well defined and multi-interpretable.

Recently, a new proposal for the pending DSM (fifth edition) and ICD (11th edition) definitions of PE has been put forward.[2,5] According to this proposal, PE should be classified according to a 'syndromal' approach incorporating well controlled clinical and epidemiological stopwatch studies.[2] PE as a clinical entity or a syndrome was described first by Bernard Schapiro in 1943.[11] He distinguished types A and B that were later termed 'lifelong' and 'acquired' PE by Godpodinoff.[12] Both types have been mentioned but not further operationalised in the DSM-IV-TR definition of PE. Recently, as noted in section 1, Waldinger and Schweitzer[2] proposed the existence of a third PE syndrome, which has been called 'natural variable PE'. In this form, PE is regarded as a normally occurring phenomenon and sometimes an ejaculatory complaint. Both authors have suggested that the high prevalence of PE of 20–40%, which has repeatedly been found in population surveys, mainly reflects the high prevalence of PE 'complaints' of men with natural variable PE[2] and premature-like ejaculatory dysfunction.[5] It is likely that the prevalence of the two PE syndromes, lifelong and acquired PE, which are the manifestations of underlying medical and/or psychological pathology, is much lower than 20–40%. Indeed, their prevalence is estimated to be around 1–8%.[2] Based on epidemiological data, Waldinger[5] also recently proposed the existence of a fourth PE syndrome, which, again as noted in section 1, has been called 'premature-like ejaculatory dysfunction'. Men with this syndrome experience and/or complain of PE while having objective long IELT durations of 5–20 minutes[5] (table I).

1.3 Lifelong PE, Acquired PE, Natural Variable PE and Premature-Like Ejaculatory Dysfunction

1.3.1 Lifelong PE

In daily clinical practice it is not difficult to make the diagnosis of lifelong PE.[13,14] Lifelong PE is a syndrome characterised by the cluster of the following core symptoms:

- ejaculation occurs too early at nearly every intercourse;

Table I. The four premature ejaculation (PE) syndromes as proposed for a new definition of PE

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
Aetiology	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 (?)

IELT = intravaginal ejaculation latency time; **?** indicates that prevalence provided in this table is assumed but not known exactly because of the lack of epidemiological research.

- the problem occurs with (nearly) every woman;
- it occurs from about the first sexual encounter onwards;
- ejaculation occurs within 30–60 seconds in the majority of individuals (80%) or between 1–2 minutes (20%);
- ejaculation remains rapid throughout life (70%) and may become more rapid with aging (30%).

Some men ejaculate during foreplay, before penetration or as soon as their penis touches the vagina (*ejaculatio ante portas*). There are no indications that lifelong PE can be cured, either by drug treatment or psychotherapy. In other words, lifelong PE is a chronic ejaculatory dysfunction.[15]

1.3.2 Acquired PE

Acquired PE has a different pattern. The complaint differs in relation to the underlying somatic or psychological problem, and is characterised by the following symptoms:

- early ejaculation occurs at some point in a man's life;
- the man has usually had normal ejaculation experiences before the start of complaints;
- there is either a sudden or gradual onset.
- the dysfunction may be secondary to urological dysfunction (e.g. erectile dysfunction or prostatitis),[16] thyroid dysfunction,[17] or psychological or relationship problems;[18-20]

In contrast to lifelong PE, the acquired form of PE can be cured by treatment of the underlying cause. A physical, blood and/or urine examination is always necessary.

1.3.3 Natural Variable PE

In natural variable PE, the ejaculation time is not consistently rapid and the problem instead occurs coincidentally or situationally. This type of PE should not be regarded as a symptom or manifestation of true pathology, but rather as a normal variation in sexual performance.[2] The syndrome is characterised by the following symptoms:

- early ejaculations are inconsistent and occur irregularly;
- the ability to control ejaculation, i.e. to withhold ejaculation at the moment of imminent ejaculation, may be diminished or lacking, but this is not obligatory for the diagnosis;
- episodes of diminished control of ejaculation are associated with either a short or normal ejaculation time, i.e. an ejaculation of <1.5 minutes.

Men with natural variable PE usually cope well with their coincidental rapid ejaculations, but when seeking advice or information they need to regain their confidence, which can be achieved by therapists explaining to them that their complaint relates to situational problems and reversible factors.[2] Because of the incidental nature of early ejaculations in men with this form of PE, one should not *a priori* treat these men with ejaculation-delaying drugs, which have the potential to cause adverse effects.

1.3.4 Premature-Like Ejaculatory Dysfunction

Men with premature-like ejaculatory dysfunction experience or complain of PE despite the fact that their ejaculation time is within the normal range, i.e. around 3–6 minutes, and may even be of very long duration, i.e. between 5 and 20 minutes.[5] This type of PE should not be regarded as a symptom or manifestation of true medical pathology. Psychological and/or relationship problems may underlie the complaint.[5] The syndrome is characterised by the following symptoms:

- subjective perception of consistent or inconsistent rapid ejaculation during intercourse;
- preoccupation with an imagined early ejaculation or lack of control of ejaculation;
- the actual IELT is in the normal range or may even be of longer duration (i.e. an ejaculation that occurs between 5 and 20 minutes);
- the ability to control ejaculation, i.e. to withhold ejaculation at the moment of imminent ejaculation, may be diminished or lacking, but this is not obligatory for the diagnosis;
- the preoccupation is not better accounted for by another mental disorder.

When seeking advice or information, men with premature-like ejaculatory dysfunction need to be informed by therapists that their actual ejaculation time is within the normal range but that psychological or relationship factors are likely to contribute to their complaint. As a result of the psychological and

relationship nature of the complaints, one should not *a priori* treat these men with ejaculation-delaying drugs, which have the potential to cause adverse effects. Counseling, psycho-education and/or psychotherapy should be considered as first-line treatment.

2. Diagnosis of PE Syndromes

Lifelong, acquired, natural variable PE and premature-like ejaculatory dysfunction are recognisable by taking a brief medical and sexual history with special attention to the duration of the ejaculation time and the course since the first sexual encounter. In daily clinical practice, diagnosis of the four PE syndromes is not difficult and evaluation with questionnaires or the use of a stopwatch is not required.

Conversely, for drug treatment trials and epidemiological research, stopwatch assessment and questionnaires on satisfaction and quality of (sexual) life are prerequisites.[21,22]

3. Drug Treatment

3.1 Evidence-Based Drug Treatment Research

In addition to using randomised, double-blind, controlled study designs, studies of PE drug treatments should include a baseline and a drug treatment period in which the IELT is measured prospectively at each coitus using a stopwatch handled by the female partner.[21,23] The IELT is expressed in seconds or minutes and in cases where ejaculation occurs outside the vagina (*ejaculatio ante portas*), the IELT is by definition equal to zero. As the IELT distribution is positively skewed, IELT values should be logarithmically transformed and results should be reported as geometric mean IELT or median IELT.[24] In addition, ejaculation delay should be expressed as a percentage or fold increase from baseline with 95% confidence intervals (CIs).[24] Adverse effects should be assessed using a validated questionnaire. Moreover, adverse effects of on-demand treatment should be assessed on both the day of drug intake and the following day.

3.2 Systematic Review and Meta-Analysis

A systematic review and meta-analysis[23] revealed that since the first publication describing drug treatment of PE in 1943,[11] there had been 79 publications on drug treatment, involving 3034 men, as at 2003.[23] These studies documented the use of anaesthetic ointments, antipsychotics, monoamine oxidase inhibitors, sympatholytic drugs, antibacterials and other miscellaneous agents. Although some studies of antipsychotics,[25-31] monoamine oxidase inhibitors,[32,33] sympatholytic drugs[34-38] and other miscellaneous agents demonstrated their efficacy in delaying ejaculation, the often disturbing and even dangerous adverse effects of these agents have hampered generalisation of their use.[39]

Currently, daily use of selective serotonin reuptake inhibitors (SSRIs), on-demand use of the tricyclic antidepressant clomipramine and topical use of anaesthetics have become the most popular treatments for PE.[39] Their use has been recognised and supported by results from evidence-based studies.[23,40] The serotonergic antidepressants modify the course of PE by modulating the central serotonergic system and the anaesthetics suppress the sensitivity of the glans penis. A number of studies have also reported efficacy for on-demand use of phosphodiesterase type 5 (PDE-5) inhibitors but their role in the treatment of PE without erectile dysfunction is disputable.[41] Recently, a single study reported ejaculation-delaying effects of the on-demand use of tramadol.[42]

In general, there are two major strategies for the medical treatment of PE: daily and on-demand.

3.3 Daily Treatment

3.3.1 Clomipramine

In 1973, Eaton[43] published the first report on the efficacy of clomipramine, the tricyclic antidepressant with the greatest effect on the serotonergic system, in the treatment of PE. Particularly in the 1970–80s, various studies demonstrated the efficacy of clomipramine in delaying ejaculation.[44-47] However, its use was not very popular in those years, when it was still generally believed that genuine

treatment of PE should consist of merely behavioural psychotherapy. Over the last decade, a number of studies have repeatedly confirmed that daily treatment with clomipramine at dosages ranging from 20 to 50 mg/day is efficacious in the treatment of PE.[48-52]

3.3.2 Selective Serotonin Reuptake Inhibitors (SSRIs)

The introduction of SSRIs in psychiatry led to a revolutionary change in the understanding and treatment of PE. After the first publication in 1994[8] on the efficacy of daily treatment with paroxetine (hydrochloride) hemihydrate, various studies confirmed its strong ejaculation-delaying effects at doses of 20–40 mg/day.[24,53-59] Moreover, it appeared that nearly all SSRIs, with the exception of fluvoxamine,[24,60] exerted a clinically relevant, ejaculation-delaying effect.[61-77] Currently, daily treatment with SSRIs or combined daily treatment with on-demand use has become the first-line treatment of PE.[78] However, although daily use, particularly of paroxetine (hydrochloride) hemihydrate, sertraline and clomipramine and, to a lesser extent, fluoxetine and citalopram, has been shown to be very effective in delaying ejaculation, these drugs have not been approved by the US FDA for the treatment of PE. This has mainly been due to the decision taken by pharmaceutical companies manufacturing SSRIs not to market them as treatments of PE because of concerns that focusing on an ejaculation-delaying effect of these drugs would highlight their potent sexual adverse effects and thereby hamper marketing strategies for use of these agents for depressive disorders.[78]

As the various studies on drug treatment of PE differed greatly in design and methodology, a systematic review and meta-analysis appeared to be imperative to obtain an objective view of the evidence to support their general use. Accordingly, in 2004, Waldinger et al.[23] published a systematic review and meta-analysis of all PE drug treatment studies published between 1943 and 2003. Of the 79 studies identified, only 35 daily clomipramine and SSRI treatment studies conducted between 1973 and 2003 were considered suitable for meta-analysis.[23] Outcome data from the few SSRI treatment studies published between 2003 and 2006 have little effect on the findings of the systematic review and meta-analysis and, therefore, its conclusions are still valid now. One of the major findings was that the majority of the studies were not conducted according to all current standards of evidence-based research. Therefore, all 35 daily clomipramine and SSRI treatment studies were included in a meta-analysis and compared with a separate meta-analysis of eight studies that, in contrast, were conducted according to all current criteria of evidence-based research. The 8-study meta-analysis revealed a placebo effect of a geometric mean 1.4-fold increase in IELT (95% CI 1.2, 1.7). Furthermore, it was demonstrated that the rank order of efficacy (geometric mean fold increase in IELT) was: (i) paroxetine (hydrochloride) hemihydrate (8.8; 95% CI 5.9, 13.2); (ii) clomipramine (4.6; 95% CI 3, 7.4); (iii) sertraline (4.1; 95% CI 2.6, 7); and (iv) fluoxetine (3.9; 95% CI 3, 5.4). Thus, in general, daily SSRI treatment studies reported a 2.6–13.2 geometric mean fold increase in IELT, depending on the type of SSRI. The meta-analysis also demonstrated that open-label and single-blind studies report exaggerated effects and that retrospective assessment of ejaculation time by a questionnaire or subjective report leads to far greater variability in clinical outcomes.[23]

Daily SSRI treatment for PE can consist of paroxetine (hydrochloride) hemihydrate 20–40mg, clomipramine 10–50mg, sertraline 50–100mg, fluoxetine 20–40mg or citalopram 20–40mg.[39] Ejaculation delay usually starts a few days after first intake. However, a clinically relevant effect occurs only gradually after 1–3 weeks. In most cases, the delay continues for years, but sometimes may diminish after 6–12 months. The cause of this tachyphylaxis with SSRIs has not yet been clarified.

Daily SSRI treatment is usually, but not always, effective in delaying ejaculation. The reason that SSRIs sometimes fail to delay ejaculation has not yet been clarified. Patients should be informed about the short- and long-term adverse effects of SSRIs. In the short term, fatigue, yawning, mild nausea, loose stools or perspiration may occur. These adverse

effects are usually mild, start in the first 1–2 weeks of treatment and most often gradually disappear within 2–3 weeks. Although a head-to-head comparative study has not yet been performed, drug-treatment studies seem to indicate that in contrast to the adverse effects of SSRIs experienced by depressed patients, diminished libido and erectile dysfunction are reported less frequently by healthy non-depressed men with lifelong PE. Waldinger and Schweitzer[2,3] have hypothesised that this may relate to increased oxytocin release in men with lifelong PE. Obviously, further controlled research to confirm and elucidate this phenomenon is needed.

A rather rare adverse effect of SSRIs is the risk of bleeding.[79] Clinicians should caution patients about combining SSRIs with aspirin (acetylsalicylic acid) or NSAIDs as this may further increase the risk of bleeding. A very rare adverse effect is priapism.[80,81] Notwithstanding its rarity, all patients using SSRIs should be advised about the risk of priapism and the need for immediate medical treatment should it occur. SSRIs should not be prescribed to men aged <18 years or men known to have a depressive disorder, particularly when associated with suicidal thoughts. In such cases, referral to a psychiatrist is indicated. With long-term use of SSRIs, weight gain may occur with an associated risk of type 2 diabetes mellitus.[82] Patients taking an SSRI should be advised not to stop taking the medication abruptly in order to prevent the occurrence of an SSRI discontinuation syndrome, which is characterised by symptoms such as tremor, shock-like sensations when turning the head, nausea and dizziness.[83,84]

Clearly, the currently available daily SSRI treatment options are efficacious and safe for the treatment of PE, but their use is hampered by an absence of approval for this indication by the US FDA.

3.3.3 Generic versus Brand-Name SSRIs

A special note should be made about the use of generic SSRIs. The most relevant studies of SSRI treatment of PE were conducted in the early and mid-1990s using brand-name SSRIs, simply because at that time generic SSRIs were not available on the market. However, generic SSRIs are now frequently prescribed. A generic drug and its corresponding brand-name drug are supposed to be interchangeable in accordance with the criterion of 'essential similarity', which requires that the generic drug has the same amount and type of active principal, the same route of administration and the same therapeutic effectiveness as the original drug, as demonstrated by bioequivalence studies. However, the bioequivalence and therapeutic effectiveness of brand-name and generic drugs are not necessarily the same.[85] In a review of the few publications comparing the bioequivalence and efficacy of brand-name and generic psychoactive drugs, it was shown that there are differences between generic drugs and brand-name drugs that had not been noted in the original bioequivalence studies.[85] This issue has consequences for the drug treatment of PE.

Paroxetine (Hydrochloride) Hemihydrate

Particularly in the context of daily SSRI treatment for PE, it is important to note that the efficacy of drug treatment trials with paroxetine has been investigated only with the original brand-name paroxetine (hydrochloride) hemihydrate (Paxil®; Seroxat®)[1] and not with the generic versions of paroxetine (hydrochloride) hemihydrate and/or paroxetine mesylate. The ejaculation-delaying efficacy and relatively mild adverse effect profile of paroxetine (hydrochloride) hemihydrate have been repeatedly demonstrated in well controlled studies.[23] On the basis of the results of these studies, there are no contraindications to the use of the generic paroxetine (hydrochloride) hemihydrate for the treatment of PE.

Paroxetine Mesylate

It is important to note that PE drug treatment studies using paroxetine mesylate have not yet been performed. Moreover, there are some indications that the adverse effect profile of the generic paroxetine mesylate in particular is different from paroxetine (hydrochloride) hemihydrate. The preparation of paroxetine mesylate involves a different type of

1 The use of trade names is for product identification purposes only and does not imply endorsement.

salification process from that used in the preparation of paroxetine (hydrochloride) hemihydrate, creating a number of potential problems with respect to the efficacy, tolerability and toxicity of paroxetine mesylate.[85] No systematic comparative studies of the efficacy of paroxetine mesylate or its bioequivalence to paroxetine (hydrochloride) hemihydrate have yet been conducted. However, several case reports have been published suggesting problems with efficacy and tolerability following a switch from brand-name paroxetine (hydrochloride) hemihydrate to the generic formulation of paroxetine mesylate.[85] For example, Vergouwen and Bakker[86] reported a case of a man who after several years of successful treatment with paroxetine (hydrochloride) hemihydrate, experienced generalised itching and a depressed mood shortly after switching to paroxetine mesylate. These symptoms disappeared after paroxetine (hydrochloride) hemihydrate was reinstated. However, during a rechallenge period of 3 weeks, the itching returned after 2 days and the patient's mood deteriorated once again. These symptoms once again resolved within 3 days of resumption of paroxetine (hydrochloride) hemihydrate treatment. Although this is only a single case report, its publication may reflect a clinically relevant phenomenon. Therefore, and because of the lack of placebo-controlled comparative studies investigating the efficacy and adverse effect profile of both generic paroxetine (hydrochloride) hemihydrate and paroxetine mesylate in the treatment of PE, it is advisable to prescribe only paroxetine (hydrochloride) hemihydrate to men with lifelong PE and not paroxetine mesylate.

3.3.4 α_1-Adrenoceptor Antagonists

Ejaculation is peripherally controlled by the sympathetic nervous system. Blocking the sympathetic system using α_1-adrenoceptor antagonists (α_1-blockers) may theoretically delay ejaculation. Terazosin and alfuzosin are two selective α_1-adrenoceptor antagonists with potential ejaculation-delaying effects that have been investigated in men with PE.[87,88] Both drugs are registered as medications for improving voiding function in men with benign prostatic hyperplasia. However, they are not registered for the treatment of PE.

In a placebo-controlled study of 91 men with PE, both terazosin 5 mg/day and alfuzosin 6 mg/day proved effective in approximately 50% of patients.[87] In another placebo-controlled study in 90 men with PE and lower urinary tract symptoms without chronic prostatitis or benign prostatic hyperplasia, daily use of terazosin 5–10mg was associated with a clinically significant improvement.[88] However, the methodology of both studies was rather weak. Efficacy was measured by merely qualitative measures such as satisfaction and subjective feelings of improvement. Prolongation of the IELT was not assessed by a stopwatch. Furthermore, although α_1-adrenoceptor antagonists may affect ejaculatory performance, they do not always delay ejaculation. This may be concluded from the results of a randomised, double-blind study comparing alfuzosin and tamsulosin in men with lower urinary tract symptoms without PE.[89] Both drugs induced similarly low rates of delayed ejaculation and were not statistically significantly different from each other in this respect.[89]

Despite the aforementioned limitations of methodology and the rather low rate of clinically relevant ejaculation-delaying effects, α_1-adrenoceptor antagonists, and particularly terazosin 5–10 mg/day may be a good alternative for the treatment of men with PE who also have urinary tract dysfunction. However, further well designed studies are pivotal to evaluating the place of α_1-adrenoceptor antagonists in the armamentarium of drugs for the treatment of PE (table II).

3.4 On-Demand Drug Treatment

The aim of on-demand treatment strategies is to delay ejaculation preferably within 1–2 hours after drug intake. Despite the lack of existence of any study investigating patient preferences, it has recently become rather fashionable to state that on-demand treatment of PE would be more favourable than daily treatment. It is not unlikely that this optimistic but suggestive view of on-demand treatment derives from marketing messages from some

Table II. Different classes of drugs for the daily treatment of premature ejaculation

Daily treatment	Drug	Efficacy	Major adverse effects	Evidence for efficacy
SSRIs	Paroxetine	Very strong	Fatigue, yawning, loose stools	+++
	Sertraline	Strong	Fatigue, yawning, loose stools	+++
	Fluoxetine	Strong	Fatigue, yawning, loose stools	+++
	Citalopram	Moderate–strong	Fatigue, yawning, loose stools	+++
	Escitalopram	Moderate–strong	Fatigue, yawning, loose stools	+++
TCA	Clomipramine	Moderate–strong	Nausea, dry mouth	+++

SSRI = selective serotonin reuptake inhibitor; **TCA** = tricyclic antidepressant; **+++** indicates very strong.

pharmaceutical companies that have become interested in producing new on-demand drugs for PE. Currently, it would be more realistic to question whether on-demand use of drugs is indeed generally preferred over daily treatment strategies, as contrary to daily treatment, on-demand strategies may quite negatively interfere with the spontaneity of making love. To investigate this question, studies specifically designed to investigate the preference of men with PE for both treatment strategies are needed.

Despite this lack of preferential studies, on-demand treatment of PE with various drugs has been investigated throughout the years. However, only a few on-demand drug treatment studies have been conducted. These studies have evaluated on-demand treatment with topical anaesthetics, clomipramine, SSRIs, dapoxetine, tramadol and PDE-5 inhibitors. Because of differences in methodology and design, a meta-analysis comparing the efficacy of these on-demand treatments has not yet been feasible.

3.4.1 Topical Anaesthetics

Use of topical local anaesthetics such as lidocaine and/or prilocaine in the form of a cream, gel or spray is the oldest drug treatment strategy and is still practised today.[90,91] The topical anaesthetics delay ejaculation by reducing the sensitivity of the glans penis. However, only a few studies have been conducted to show their efficacy.[90,91] Although application of these agents is rather simple, they may still cause adverse effects such as complete anaesthesia of the penis, which may lead to erectile difficulties. Patients should be informed that use of topical anaesthetics may also lead to vaginal numbness. This may be prevented by use of a condom.

3.4.2 Clomipramine

On-demand use of clomipramine 20–40mg can effectively delay ejaculation after 3–5 hours.[92-96] However, this treatment approach might also give rise to nausea on the day of intercourse and the following day.[96]

3.4.3 SSRIs

In the systematic review conducted in 2003,[23] only eight studies of on-demand treatment with SSRIs and clomipramine were reported.[92-95,97-100] These eight on-demand studies greatly differed in methodology. Indeed, a meta-analysis of the published on-demand SSRI studies could not be performed because the studies were unbalanced with respect to the antidepressants used, baseline IELT values, study design (double-blind vs open-label) and assessment techniques used (questionnaire vs stopwatch).[23] Even without a meta-analysis of on-demand SSRI treatment studies, however, there were indications that on-demand use of SSRIs, such as paroxetine 20mg, did not strongly delay ejaculation after 3–5 hours of intake.[96]

Furthermore, the long interval between intake of the drug and coitus is often a reason for men and perhaps even more so for female partners not wanting to use this on-demand strategy, which negatively interferes with the spontaneity of making love.

Dapoxetine

The SSRI dapoxetine was developed specifically for the purpose of on-demand treatment of PE. However, in 2005, the FDA did not approve dapoxetine for this indication. The reason for this non-approval has not been made public. Nevertheless, it is interesting to consider the pharmacokinetic characteristics of this drug and the outcome data from a large

clinical study.[101] Dapoxetine has a short initial half-life of 1–2 hours and a short time to maximum serum concentration of approximately 1 hour.[101] In addition, the plasma concentration of dapoxetine decreases rapidly within 24 hours. These pharmacokinetic properties are suitable for on-demand treatment of PE. However, ejaculation delay is dependent not only on the pharmacokinetic characteristics but more so on the pharmacodynamic properties of an SSRI.[102] On the basis of the currently available pharmacodynamic knowledge of SSRIs and serotonergic neurotransmission, Waldinger et al.[102], in 2005, predicted that on-demand use of SSRIs, including those with a short half-life, would not lead to a >3-fold increase in the IELT. This prediction appeared to be correct. In a large, placebo-controlled, phase III trial of dapoxetine the fold increase of the mean IELT of the placebo, dapoxetine 30 and 60mg was 1.8, 2.8 and 3.3 minutes, respectively. Regrettably, the authors did not apply the appropriate statistics. As the IELT has a skewed distribution, the median IELT or the geometric mean IELT ought to have been applied. By using the median, the fold increase of placebo and dapoxetine 30mg would have been somewhere between 1–2 minutes, and about 2 minutes for dapoxetine 60mg.[103] These very minor ejaculation-delaying effects of dapoxetine confirm the view that a clinically relevant and strong ejaculation delay is not dependent on pharmacokinetics, but on pharmacodynamic effects of SSRIs on specific serotonergic neurons in the CNS.

3.4.4 Tramadol

A recently published study evaluated the efficacy of the on-demand use of tramadol for the treatment of PE.[42] Tramadol is registered as a centrally acting analgesic agent that combines μ-opioid receptor activation and reuptake inhibition of serotonin and noradrenaline (norepinephrine).[104] In a double-blind, placebo-controlled study,[42] on-demand use of tramadol 50mg, taken 2 hours prior to coitus, was associated with a clinically relevant ejaculation delay in men with PE. Of the tramadol-treated men, 28% reported adverse effects. The most common adverse effects were nausea (15.6%), vomiting (6.2%) and dizziness (6.2%), but these were reported to be mild. Although further studies with different dosages are needed, tramadol seems to be quite an interesting on-demand drug for PE. However, although tramadol has a weak μ-opioid agonistic effect, long-term follow-up studies are also needed to investigate the risk of opioid addiction with this drug.

3.4.5 Phosphodiesterase Type 5 Inhibitors

In recent years, a number of investigators have suggested that on-demand use of PDE-5 inhibitors is effective for the treatment of PE. However, most of these studies have lacked good methodology, which makes their results difficult to interpret. Recently, McMahon et al.[41] published a well designed systematic review of all publications on the use of PDE-5 inhibitors for PE published between 2001 and 2006. This review summarised and analysed 14 studies.[95,99,100,105-115] These studies reported on the use of sildenafil,[95,107-110,115] vardenafil[111] and tadalafil.[112] The majority of these studies did not meet all current criteria for evidence-based medicine; indeed, the only study to do so was that by McMahon et al.[108] Six studies did not include any form of baseline IELT measurement as an inclusion criterion, and most studies did not distinguish lifelong from acquired PE. The small number of publications and the lack of sufficient data precluded any meta-analysis of the results. On the basis of this systematic review it was concluded that there is no convincing evidence of any direct effect of PDE-5 inhibitors on central or peripheral control of ejaculation, or for any role in the treatment of PE, except for men with PE and co-morbid erectile dysfunction.[41]

3.4.6 Intracavernous Vasoactive Drug Injection

A special comment should be made regarding use of intracavernous self-injection treatment for PE. This strategy for treating PE is advocated by a few private institutions. However, it should be noted that there is no evidence-based support for the efficacy of this strategy. Actually, there has only been one study investigating this treatment method.[116] In this open-label study, eight men with PE injected vasoactive drugs into the corpus cavernosum. The

Table III. Different classes of drugs for the on-demand treatment of premature ejaculation

On-demand treatment	Drug	Efficacy	Major adverse effects	Evidence for efficacy
SSRIs	Paroxetine	Weak	Nausea	++
	Sertraline	Weak	Nausea	++
	Fluoxetine	Weak	Nausea	++
	Citalopram	Weak	Nausea	++
	Escitalopram	Weak	Nausea	++
SSRI short t_{max}	Dapoxetine	Weak	Nausea	++
TCA	Clomipramine	Moderate	Nausea	+++
α1-Adrenoceptor	Terazosin (terazosine)	Weak	Dizziness	+
antagonists	Alfuzosin	Weak	Dizziness	+
Anaesthetics	Lidocaine	Weak–moderate (?)	Numb penis	++
	Prilocaine	Weak–moderate (?)	Numb penis	++
μ-Opioid antagonists	Tramadol	Weak–moderate (?)	Dizziness, headache	+
PDE-5 inhibitors	Sildenafil	None	Flushes, headache	+
Intracavernous injection	Papaverine	None	Risk of priapism	–

PDE-5 = phosphodiesterase type 5; **SSRI** = selective serotonin reuptake inhibitor; **TCA** = tricyclic antidepressant; $\mathbf{t_{max}}$ = time to maximum concentration; **+** indicates weak; **++** indicates moderate; **+++** indicates strong; **–** indicates none; **?** indicates may have moderate effect, but not very clear due to lack of controlled studies.

drugs used were a mixture of papaverine 30 mg/mL and phentolamine 1 mg/mL. After receiving instruction on injection technique, the patients practised self-injection at home of 0.2mL unilaterally into the corpus cavernosum base using a 27-gauge needle. Of the eight men, three stated that they were cured and stopped the treatment, while the other five men continued using the medication after 14 months. However, the methodology of this study was very weak. There were no baseline assessments of the IELT, and prolongation of the IELT was not measured with a stopwatch. Moreover, success of treatment was defined by prolongation of erectile function after ejaculation and not by the extent to which ejaculation was delayed. As long as there are no well controlled studies demonstrating the efficacy of injection treatment to delay ejaculation time, PE should not be treated with intracavernosal injection of vasoactive drugs (table III).

4. Neurotransmitters and Ejaculation

The clinically very relevant ejaculation delay induced by daily SSRI treatment, the differences between SSRIs in the extent to which they bring about ejaculation delay and the weak ejaculation delay induced by on-demand SSRI treatment, including SSRIs with a short half-life, can be explained by central serotonin neurotransmission. In addition, increasing knowledge of oxytocin neurotransmission has deepened our understanding of the neurobiology of the ejaculation process.

4.1 Serotonin, Serotonergic Receptors and Serotonergic Neurotransmission

The clinically important ejaculation delay induced by daily treatment with SSRIs and the rather minimal ejaculation delay induced by on-demand SSRI treatment is consistent with our current understanding of serotonin neurotransmission in the CNS.

Serotonergic neurons regulate their own activity using three mechanisms.[102,117,118] One of the basic features of serotonergic neurotransmission is that any short-term increase in serotonin release into the synapse is immediately followed by activity of the neuron to lower the higher serotonin level. Under normal physiological conditions, serotonin activates (presynaptic) serotonin 5-HT_{1A} autoreceptors on the cell bodies of serotonergic neurons. Activation of these 5-HT_{1A} autoreceptors decreases firing of the serotonin neuron and consequently lowers release of serotonin from the presynaptic neuron into the synaptic cleft (mechanism 1). After release of serotonin into the synapse, presynaptic 5-HT_{1B} autoreceptors become activated, and these, in turn, also inhibit

release of serotonin 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 that prevents overstimulation of postsynaptic 5-HT receptors is the immediate removal of serotonin in the synapse back into the presynaptic neurone by serotonin transporters at presynaptic endings and in serotonergic cell bodies (mechanism 3).

This complex feedback mechanism in the central serotonergic system helps to sustain homeostasis.[102] However, it also has consequences for drug treatment of PE, particularly, for on-demand treatment with SSRIs.[102]

4.1.1 Short-Term SSRI Administration

All serotonin transporters are blocked after short-term SSRI administration, resulting in higher serotonin levels in the synaptic cleft and in the space around the cell bodies.[119] The increased serotonin levels activate 5-HT_{1A} autoreceptors and consequently lead to lower serotonin release into the synaptic cleft within minutes. The diminished release of serotonin in the synaptic cleft compensates (completely or partially) for the initially increased serotonin levels as a result of SSRI-induced blockade of serotonin reuptake from the synapse into the presynaptic neuron by transporters. Higher serotonin levels in the synapse increase activation of presynaptic 5-HT_{1B} autoreceptors, which in itself attenuates serotonin release. The net effect of short-term SSRI administration, under physiological conditions, is only a mild or no increase in serotonin neurotransmission and mild or no stimulation of postsynaptic 5-HT receptors.

In other words, based on these data, it can be predicted that on-demand SSRI treatment will not lead to any relevant stimulation of 5-HT postsynaptic receptors in the short-term (i.e. within 1–2 hours), because there is very little serotonin increase in the synapse and hardly any stimulation of postsynaptic 5-HT receptors. If postsynaptic 5-HT receptors are not or almost not activated at all, clinically relevant ejaculation delay will not occur.[102]

Indeed, animal studies have shown that short-term administration of the five SSRIs (fluoxetine, paroxetine [hydrochloride] hemihydrate, sertraline, fluvoxamine and citalopram) has no significant effect on IELT and the number of ejaculations.[120] Human studies also indicate that on-demand use of SSRIs does not lead to the substantial delay in ejaculation as induced by daily treatment with SSRIs.[96]

4.1.2 Long-Term SSRI Administration

In contrast to short-term administration, long-term administration of SSRIs results in a number of adaptations that are pivotal for inducing relevant ejaculation delay. The ongoing blockade of serotonin transporters results in a persistent increase in serotonin levels in the synapse and in the space around the cell bodies. This leads to desensitisation of 5-HT_{1A} autoreceptors over the course of a few weeks,[121] possibly also to desensitisation of 5-HT_{1B} autoreceptors,[122] and, consequently, to less inhibition on serotonin release into the synapse. The net effect of long-term SSRI administration is more serotonin release into the synapse, stronger enhancement of serotonin neurotransmission and consequently stronger activation of postsynaptic 5-HT receptors compared with short-term SSRI administration.[123]

In other words, based on these insights into serotonergic neurotransmission, it can be predicted that daily SSRI treatment will lead to very relevant stimulation of serotonin postsynaptic receptors and, as a consequence, clinically very relevant ejaculation delay after 1–2 weeks of continuous intake.[102] Indeed, animal studies have shown that long-term administration of fluoxetine and paroxetine results in increased IELT values.[60,124,125] Moreover, human studies have repeatedly shown the clinically very relevant ejaculation delay induced by daily treatment with paroxetine (hydrochloride) hemihydrate, sertraline and clomipramine.[23]

4.2 Oxytocin and Oxytocinergic Neurons

Two oxytocinergic neuronal systems in the CNS can be distinguished: the magnocellular and the parvocellular neurons.[126] Magnocellular oxytocin-

containing cells are located in the hypothalamic supraoptic nucleus (SON) and in the anterior and posterior paraventricular hypothalamic nucleus (PVH). Magnocellular neurons release oxytocin into the bloodstream via axons terminating in the posterior pituitary. The dorsal and lateral PVH contain parvocellular neurons that project to several brain and spinal cord areas.[127,128]

4.2.1 Oxytocin and Sexual Behaviour

Oxytocin is known to facilitate sexual reproduction in mammals.[129] The role of oxytocin in female reproductive behaviour is well known: oxytocin is released during sexual behaviour, parturition and suckling, and is involved in uterine smooth muscle contraction and milk ejection.[130] However, the influence of oxytocin on the reproductive behaviour of male mammals is less clear.

In men, plasma oxytocin levels are elevated during sexual arousal, erection and at the time of orgasm,[131-134] although the degree of the elevation differs between with each of these settings. After ejaculation, oxytocin levels were increased in the blood plasma in rabbits[135] and in the cerebrospinal fluid in rats.[136] Electrical stimulation of the dorsal penile nerve, which relays sensory information from the genitals to the spinal cord, as well as tactile stimulation of the glans penis, produced excitation in about half of the oxytocin cells in the PVH and SON of rats.[137,138]

Although the copulation-induced release of oxytocin is well established, the exact role of oxytocin in male sexual behaviour is less clear. The effects of oxytocin on male sexual behaviour are generally divided into a central pathway involved in erection, mediated via oxytocinergic neurons projecting from the PVH to the spinal cord, and a peripheral pathway involved in ejaculation, mediated via oxytocin release in the bloodstream.

4.2.2 Oxytocin and Ejaculation

The role of peripheral oxytocin in ejaculation is supported by several findings. Systematic administration of oxytocin reduced the number of intromissions required for ejaculation in young adult rats,[135] whereas it shortened the mount, intromission and ejaculation latencies and post-ejaculation intervals in old rats, especially in sexually sluggish rats.[139] Since oxytocin is a peptide and cannot readily penetrate the blood-brain barrier, the effects of peripherally injected oxytocin on ejaculation are probably exerted predominantly through peripheral oxytocin receptors that have been found in the testis, epididymis, ductus deferens, prostate and penis of rats and humans, where they mediate the contractility of smooth muscle cells.[140,141] However, some effects of systematically injected oxytocin on ejaculation might be mediated by central oxytocin receptors, since a small proportion of subcutaneously injected oxytocin does cross the blood-brain barrier.[142]

4.2.3 Serotonin, Oxytocin and Lifelong PE

In addition to their roles in normal male sexual behaviour, Waldinger et al.[3,117,143,144] postulated that both serotonin and oxytocin might be involved in the aetiology of lifelong PE (*ejaculatio praecox*) and that lifelong PE is a genetically determined sexual dysfunction. These investigators further postulated that this genetic vulnerability will lead to a biological variability of the IELT in men. Indeed, a biological continuum of the IELT in men was found in 2005 in a stopwatch study of a large randomised sample of 491 men in the general male population of five countries (The Netherlands, Spain, Turkey, UK and the US).[145] This study demonstrated a positively skewed IELT distribution with a median IELT of 5.4 minutes (range 0.55–44.1 minutes). According to these researchers, lifelong PE is the clinical manifestation of the extreme left part of the IELT curve.[144,146] Since the 0.5 percentile equated to an IELT of 0.9 minutes and the 2.5 percentile to an IELT of 1.3 minutes, IELTs of <1 minute may be considered dysfunctional.[144-146] Using this dynamic approach of endophenotypes, lifelong PE ought to be defined in terms of the duration of the IELT.[1,2,144]

In 1998, Waldinger et al.[117] proposed that the genetic component of PE could involve dysfunction of the serotonergic receptor system, for example, hyposensitivity of the 5-HT_{2C} receptor and/or hypersensitivity of the 5-HT_{1A} receptor. In addition, PE might be associated with increased oxytocin release during intercourse.[3] This hypothesis was

based on a rather unknown, and in the literature highly neglected, but clinically very relevant phenomenon. Originally described by Schapiro[11] in 1943, Waldinger[3] emphasised that many men with lifelong PE report also report having rapidly occurring erections (*erectio praecox*). Since oxytocin strongly facilitates erection, *erectio praecox* in the context of lifelong *ejaculatio praecox* may be associated with increased oxytocin release during coitus.[2,3]

5. New Drugs

Daily treatment with the currently available SSRIs has repeatedly been demonstrated to be very efficacious in delaying ejaculation in men with PE. However, as pharmaceutical companies producing these SSRIs have never been interested in registration of these medications for PE, the use of SSRIs to treat PE has remained off-label. In contrast, in recent years some other pharmaceutical companies have become interested in the on-demand treatment of PE by SSRIs with a short half-life and a short time to maximum concentration. An example of such a drug is dapoxetine.

However, based on current knowledge of central serotonin neurotransmission, it seems rather unlikely that SSRIs with a short half-life can increase ejaculation delay above a 3-fold increase of the logarithmic mean IELT.[102] Because of pharmacodynamic considerations, SSRIs with a short half-life, such as dapoxetine, will probably always have a much lower ejaculation-delaying effect than that achieved with daily use of conventional SSRIs such as paroxetine (hydrochloride) hemihydrate and sertraline.[102] On-demand use of SSRIs with a short half-life (if ever approved) will probably represent only a transition phase towards the use of new and more powerful on-demand drugs for the treatment of PE.[15]

5.1 Serotonin 5-HT_{1A} Receptor Antagonists and Oxytocin Receptor Antagonists

On the basis of our current understanding of the pharmacological processes involved in ejaculation, short-term delay of ejaculation might be possible with combinations of 5-HT_{1A} receptor antagonists and/or oxytocin receptor antagonists. There have been no reports as yet on the short-term effects of oxytocin receptor antagonists. However, animal studies have shown that on-demand treatment with SSRIs can be highly improved by simultaneous use of 5-HT_{1A} receptor antagonists.[147,148] This combination of serotonin reuptake inhibition and 5-HT_{1A} receptor antagonism, and probably any drug that significantly increases serotonin neurotransmission, may become the basis for the development of new on-demand drugs that truly delay ejaculation to an important degree within 1 hour after intake.

5.2 Requirements for Clinically Effective On-Demand SSRI Treatment

Assuming that relevant ejaculation delay is defined as at least ≥1-minute delay compared with baseline values, it may be argued that, particularly for men with an IELT of <1 minute, on-demand drugs against PE should induce at least ≥5- to 6-fold or 400–500% IELT delay within 1–2 hours. Currently, such persistent and potent on-demand SSRIs are not available. However, animal studies have provided data indicating that short-term ejaculation delay of this magnitude is in principle feasible with an on-demand SSRI, at least when the SSRI is combined with a 5-HT_{1A} receptor antagonist.

5.3 Short-Term Enhancement of Serotonin Neurotransmission

In order to overcome the pharmacological limitations of short-term SSRI treatment, that is, low initial serotonin neurotransmission and postsynaptic 5-HT_{2C} receptor activation, enhancement of serotonin neurotransmission is needed at the very start of treatment. One way to achieve this is by selectively blocking the presynaptic 5-HT_{1A} autoreceptor. The resulting increase in serotonin release into the synapse will rapidly lead to increased activation of postsynaptic 5-HT_{2C} receptors. In studies of male rats[147] it has been shown that combined short-term treatment of a 5-HT_{1A} receptor antagonist with an SSRI (which, administered separately, did not affect

sexual activities) had powerful effects on copulatory behaviour and delay of ejaculation latency.

5.4 5-HT$_{1A}$ Receptor Antagonists and SSRIs

Desensitisation of receptors as a result of long-term SSRI exposure can be mimicked in short-term treatment by blocking 5-HT$_{1A}$ autoreceptors instantaneously through coadministration of a 5-HT$_{1A}$ receptor antagonist and an SSRI. In an *in vivo* microdialysis study, in which the selective 5-HT$_{1A}$ receptor antagonist WAY 100635 (Research Biochemicals, Natick, MA, USA) was combined with citalopram, WAY 100635 increased extracellular serotonin levels.[149] In male rats, Williamson et al.[147] combined another 5-HT$_{1A}$ receptor antagonist (robalzotan; also known as NAD-299)[150] with fluoxetine and citalopram, and then evaluated copulatory behaviour 1 day and 11 days after treatment. Neither fluoxetine nor citalopram affected the IELT at day 1, confirming the findings of Mos et al.[120] However, at day 11, fluoxetine significantly increased ejaculation time, while citalopram had no such effect. Interestingly, both at day 1 and at day 11, coadministration of fluoxetine or citalopram with robalzotan 15 minutes prior to the tests significantly delayed ejaculation time without affecting any other copulatory parameter.[147] In an analogous study, de Jong et al.[148] administered citalopram, the 5-HT$_{1A}$ receptor antagonist WAY-100635, or both drugs combined to male rats for 15 days. Copulatory parameters were studied 1 hour after drug administration on days 1, 8 and 15. In this study, WAY-100635 alone had no effect on the ejaculation latency. Long-term treatment with citalopram alone diminished ejaculation frequency, indicating a mildly delayed ejaculation time. However, both short- and long-term coadministration of citalopram and WAY-100635 delayed ejaculation time immediately (within 1 hour). In addition, neuronal activation in brain sites associated with sexual behaviour was lower in rats administered both citalopram and WAY-100635 compared with the other groups.[148] The results of this study may lead to the conclusion that blocking 5-HT$_{1A}$ receptors does not change the ejaculation latency under physiological conditions, but does so during SSRI treatment. The results of this study also suggest that 5-HT$_{1A}$ receptor functioning is an essential element in the effects of SSRIs on ejaculation. It is likely that desensitisation of the 5-HT$_{1A}$ receptor is pivotal for delaying ejaculation. This conclusion could also be drawn from the results of a recent male rat study in which long-term SSRI treatment and particularly paroxetine impaired 5-HT$_{1A}$ receptors involved in ejaculation.[151]

The results of the aforementioned animal studies support the view that serotonin pharmacodynamics are essential for serotonergic drugs to delay ejaculation and provide a scientific basis for the development of new on-demand drugs that result in an immediate strong ejaculation delay. However, clinical studies are needed to provide evidence that such combinations of drugs do indeed induce a strong ejaculation delay and do not lead to potentially dangerous or otherwise bothersome adverse effects.

5.5 New Drugs and Animal Models of PE

Most of our current understanding of the neurobiology of sexual behaviour and ejaculatory function has been derived from animal studies using rats with normal sexual behaviour.[152,153] However, none of these proposed models adequately represents human ejaculatory disorders. On the basis of the 'ejaculation distribution theory', which postulates that the IELT in men is represented by a biological continuum,[3,117,144-146] Olivier et al.[152] and Pattij et al.[154,155] have developed an animal model for research into PE and delayed ejaculation. In this model, a large number of male Wistar rats are investigated over 4–6 weekly sexual behavioural tests. Rapid and sluggish ejaculating rats are distinguished based on the number of ejaculations during 30-minute tests, each representing approximately 10% at both ends of a Gaussian distribution.[154,155] Together with other parameters, such as ejaculation latency time, these rats at either end of the spectrum resemble men with PE and delayed ejaculation, respectively.[154,155] Comparable to the human situation, in which the IELT distribution is positively skewed in the general male population,[145,146] endophenotypes

exist with regard to basal ejaculatory performance in a normal population of rats.

6. Conclusions

The DSM (third edition), DSM (third edition, revised), DSM-IV and DSM-IV-TR definitions of PE have not been based on evidence-based data but rather on an authority-based consensus. Recently, a new categorisation of four PE syndromes, which are based on evidence-based clinical and epidemiological data, has shown that PE cannot be defined in one overall descriptive definition. For the pending DSM (fifth edition), a proposal for four definitions, dependent on the underlying PE syndrome, has been put forward.

Animal and human psychopharmacological studies have supported the hypothesis that PE is a neurobiological dysfunction related to a disturbance in central serotonin neurotransmission and 5-HT postsynaptic receptor functioning. However, although serotonin plays an important role in the motoric output of ejaculation, it is not yet clear whether a disturbance of central serotonin neurotransmission constitutes the core of the syndrome. An increasing number of studies have also indicated involvement of central oxytocinergic neurotransmission in the ejaculatory process. The extent to which PE is related to disturbances in central oxytocinergic neurotransmission needs to be elucidated in future studies.

Currently, there is no information on the percentage of men that use SSRIs to delay ejaculation. For that purpose, pharmacoepidemiological research should be performed. It should be emphasised that, when assessing the potential market for drug treatment of PE, a critical approach is needed in the interpretation of the very high prevalence rates of PE that have been repeatedly found in epidemiological studies. The very high prevalence rates of 20–40% reported probably do not reflect the real percentage of men that are in need of drug treatment. Indeed, it has been argued that probably a very high percentage of these men have natural variable PE and premature-like ejaculatory dysfunction, and thus do not really need drug treatment. Certainly, it may be expected that men with lifelong PE, for example, men with an IELT of <1.5 minutes, will form a potential market. However, although many studies have found very high prevalence rates of PE, it is important to realise that this percentage indicates only the percentage of men who have 'complaints' of PE. The real percentage of men with lifelong or acquired PE syndromes is not known, but is roughly estimated to be (only) about 1–8% of the general male population. In contrast, a much higher percentage of men may be interested in delaying ejaculation for non-medical reasons, for example, to enhance sexual satisfaction. However, it is unknown what percentage of men constitutes this group. Epidemiological research should elucidate this question.

The ideal new drug to treat PE is one that will cure the dysfunction. However, with the currently available drugs, for example, the SSRIs, it has repeatedly been shown that lifelong 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 questionable whether a curative drug can be developed. Therefore, it is important to try to develop new palliative drugs, for example, drugs that effectively delay ejaculation with a minimum of adverse effects. Animal research has shown that it is feasible to develop new drugs that potently delay ejaculation within 1–2 hours of administration.

Daily treatment with SSRIs, particularly paroxetine 20mg and sertraline 50–100mg, has been shown to be a very effective treatment for lifelong PE. Despite the adverse effects of SSRIs, which may contribute to non-compliance in the long term, daily treatment with this class of drugs is currently one of the best options to treat PE. Topical use of anaesthetics is another option but has never gained much popularity among men with lifelong PE. Use of intracavernous injections of vasoactive drugs to delay ejaculation is not based on any well controlled study and as long as there are no well controlled studies supporting this method, it should not be prescribed to men with PE. Although some studies have mentioned the beneficial effects of PDE-5 in-

hibitors, the beneficial effects of these agents for men with lifelong PE without erectile dysfunction remain highly speculative and are not yet supported by hard evidence.

The combination of an SSRI with a 5-HT_{1A} receptor antagonist, contributing to an immediate strong ejaculation delay in male rats, paves the way for the development of exciting new on-demand drugs. Dapoxetine (if approved by the EMEA or the FDA) may add to treatment options, but compared with the very strong ejaculation delay induced by daily treatment with paroxetine 20mg or sertraline 50–100mg, its relative lack of potency (maximum 3-fold delay) will probably become a serious limitation in the treatment of men with lifelong PE, most of whom ejaculate within seconds after penetration.

However, in contrast to the relatively small market of 'medical dysfunction' lifelong PE patients, the potential 'consumer market' for PE is probably large. Any effective drug for the 'medical dysfunction' market should result in a marked ejaculatory delay with minimal adverse effects. However, in contrast, a less potent ejaculation-delaying drug may be appropriate for consumers wanting a 'lifestyle' product. Therefore, it is important that the marketing strategies of pharmaceutical companies do not 'pathologise' and 'medicalise' men with 'normal variable PE' and 'premature-like ejaculatory dysfunction' in order to enlarge their potential commercial market. Hopefully, responsible authorities such as the EMEA and the FDA will remain vigilant about accepting drugs with unacceptable efficacy/toxicity ratios. Ongoing sexual psychopharmacological research will probably lead to new insights into pathways and neurotransmitters that may form the basis for the development of new drugs that will potentially delay ejaculation.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. The author has no conflicts of interest that are directly relevant to the content of this review.

References

1. Waldinger MD, Schweitzer DH. Changing paradigms from an historical DSM-III and DSM-IV view towards an evidence based definition of premature ejaculation: part I. Validity of DSM-IV-TR. J Sex Med 2006; 3: 682-92
2. Waldinger MD, Schweitzer DH. Changing paradigms from an historical DSM-III and DSM-IV view towards an evidence-based definition of premature ejaculation: part II. Proposals for DSM-V and ICD-11. J Sex Med 2006; 3: 693-705
3. Waldinger MD. The neurobiological approach to premature ejaculation. J Urol 2002; 168: 2359-67
4. Waldinger MD. Lifelong premature ejaculation: from authority based to evidence based medicine. Br J Urol Internat Update Series 2004; 93: 201-7
5. Waldinger MD. The need for a revival of psychoanalytic investigations into premature ejaculation. J Mens Health Gender 2006; 3: 390-6
6. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edition. Text revision. Washington, DC: American Psychiatric Association, 2000
7. World Health Organization. The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research. Geneva: World Health Organization, 1993
8. Waldinger MD, Hengeveld MW, Zwinderman AH. Paroxetine treatment of premature ejaculation: a double-blind, randomised, placebo-controlled study. Am J Psychiatry 1994; 151: 1377-9
9. Waldinger MD, Hengeveld MW, Zwinderman AH, et al. An empirical operationalization study of DSM-IV diagnostic criteria for premature ejaculation. Int J Psychiatry Clin Pract 1998; 2: 287-93
10. Patrick DL, Althof SE, Pryor JL, et al. Premature ejaculation: an observational study of men and their partners. J Sex Med 2005; 2: 358-67
11. Schapiro B. Premature ejaculation: a review of 1130 cases. J Urol 1943; 50: 374-9
12. Godpodinoff ML. Premature ejaculation: clinical subgroups and etiology. J Sex Marital Ther 1989; 15: 130-4
13. Waldinger MD. Lifelong premature ejaculation: current debate on definition and treatment. J Mens Health Gender 2005; 2: 333-8
14. Waldinger MD. Overview of premature and retarded ejaculation. Eur Urol Today 2005; 17: 20-2
15. Waldinger MD. Emerging drugs for premature ejaculation. Expert Opin Emerg Drugs 2006; 11: 99-109
16. Screponi E, Carosa E, Stasi SM, et al. Prevalence of chronic prostatitis in men with premature ejaculation. Urology 2001; 58: 198-202
17. Carani C, Isidori AM, Granata A, et al. Multicenter study on the prevalence of sexual symptoms in male hypo- and hyperthyroid patients. J Clin Endocrinol Metabol 2005; 90: 6472-9
18. Lawrence JS, Madakasira S. Evaluation and treatment of premature ejaculation: a critical review. Int J Psychiatr Med 1992; 22: 77-97
19. Althof SE. Psychological treatment strategies for rapid ejaculation: rationale, practical aspects, and outcome. World J Urol 2005; 23: 89-92
20. Hartmann U, Schedlowski M, Kruger THC. Cognitive and partner-related factors in rapid ejaculation: differences between dysfunctional and functional men. World J Urol 2005; 23: 93-101
21. Waldinger MD. Towards evidence-based drug treatment research on premature ejaculation: a critical evaluation of methodology. Int J Impot Res 2003; 15: 309-13

22. Waldinger MD. Relevance of an evidence-based ejaculation time cutoff point for neurobiological research of premature ejaculation. J Comp Neurol 2005; 493: 46-50
23. Waldinger MD, Zwinderman AH, Schweitzer DH, et al. Relevance of methodological design for the interpretation of efficacy of drug treatment of premature ejaculation: a systematic review and meta-analysis. Int J Impotence Res 2004; 16: 369-81
24. Waldinger MD, Hengeveld MW, Zwinderman AH, et al. Effect of SSRI antidepressants on ejaculation: a double-blind, randomized, placebo-controlled study with fluoxetine, fluvoxamine, paroxetine and sertraline. J Clin Psychopharmacol 1998; 18: 274-81
25. Pico Costero J, Abreu de la Torre C, Roque Banos YL. Eyaculacion precoz: tratamiento con tioridacina. Revista del Hospital Psiquiatrico de la Habana 1986; 27: 277-80
26. Hronek J, Kolomaznik M. Farmakoterapie prekotneho prubehu pohlavniho styku. Ceskoslovenska Psychiatrie 1986; 82: 303-6
27. Bartova D, Bouchal M. Thioridazine treatment of ejaculatio praecox. Act Nerv Super [Praha] 1965; 7: 244-5
28. Mellgren A. Treatment of ejaculatio praecox with thioridazine. Psychother Psychosom 1967; 15: 454-60
29. Falaschi P, Rocco A, De Giorgio G, et al. Brain dopamine and premature ejaculation: results of treatment with dopamine antagonists. In: Gessa GL, Corsini GU, editors. Apomorphine and other dopaminomimetics. Vol. 1. Basic pharmacology. New York: Raven Press, 1981: 117-21
30. Wabrek AJ. Effect of metoclopramine on ejaculatory threshold in a group of premature ejaculators. Neurourol Urodyn 1984; 3: 155-61
31. Greco E, Polonio-Balbi P, Speranza JC. Levosulpiride: a new solution for premature ejaculation. Int J Impot Res 2002; 14: 308-9
32. Nielsen NP. L'ejaculazione precoce e il suo trattamento: nota preliminare sull'attivita' del caroxazone. Rassegna di Studi Psichiatrici 1981; 70: 1065-80
33. Bennett D. Treatment of ejaculatio praecox with monoamine-oxidase inhibitors [letter]. Lancet 1961 Dec; 9: 1309
34. Beretta G, Chelo E, Catanzaro F, et al. Trattamento con un alfa-bloccante (fenossibenzamina) della eiaculazione precoce. Minerva Urologica e Nefrologica 1988; 40: 29-32
35. Martinez Hurtado M, Gonzales Menendez R, Idelfonso Alavarez E, et al. La eyaculacion precoz: caracteristicas clinicas y respuesta al tratamiento con guanetidina. Revista del Hospital Psiquiatrico de la Habana 1981; 22: 105-16
36. Shilon M, Paz GF, Hommonai ZT. The use of phenoxybenzamine treatment in premature ejaculation. Fertil Steril 1984; 42: 659-61
37. Beretta G, Chelo E, Fanciullacci F, et al. Effect of an alpha-blocking agent (phenoxybenzamine) in the management of premature ejaculation. Acta Europaea Fertilitatis 1986; 17: 43-5
38. Cavallini G. Alpha-1 blockade pharmacotherapy in primitive psychogenic premature ejaculation resistant to psychotherapy. Eur Urol 1995; 28: 126-30
39. Waldinger MD, Olivier B. Utility of selective serotonin reuptake inhibitors in premature ejaculation. Curr Opin Investig Drugs 2004; 5: 743-7
40. Montague DK, Jarow J, Boderick GA, et al. AUA guidelines on the pharmacologic management of premature ejaculation. J Urol 2004; 172: 290-4
41. McMahon CG, McMahon CN, Liang JL, et al. Efficacy of type-5 phosphodiesterase inhibitors in the drug treatment of premature ejaculation: a systematic review. BJU Int 2006; 98: 259-72
42. Safarinejad MR, Hosseini SY. Safety and efficacy of tramadol in the treatment of premature ejaculation. J Clin Psychopharmacol 2006; 26: 27-31
43. Eaton H. Clomipramine in the treatment of premature ejaculation. J Int Med Res 1973; 1: 432-4
44. Goodman RE. An assessment of clomipramine (Anafranil) in the treatment of premature ejaculation. J Int Med Res 1980; 3 Suppl.: 53-9
45. Porto R. Essai en double aveugle de la clomipramine dans l'ejaculation prematuree. Med Hyg 1981; 39: 1249-53
46. Girgis SM, El-Haggen S, El-Hermouzy S. A double-blind trial of clomipramine in premature ejaculation. Andrologia 1982; 14: 364-8
47. Assalian P. Clomipramine in the treatment of premature ejaculation. J Sex Res 1988; 24: 213-5
48. Althof SE, Levine SB, Corty EW, et al. A double-blind cross-over trial of clomipramine for rapid ejaculation in 15 couples. J Clin Psychiatry 1995; 56: 402-7
49. Montorsi F, Guazzoni G, Trimboli F, et al. Clomipramine for premature ejaculation: a randomized, double blind, placebo controlled study. Acta Urol Ital 1995; 1: 5-6
50. Kim SC, Seo KK. Efficacy and safety of fluoxetine, sertraline and clomipramine in patients with premature ejaculation: a double-blind, placebo controlled study. J Urol 1998; 159: 425-7
51. Kolomaznik M, Hronek J, Kolomaznik J, et al. Sertralin v leche ejaculatio praecox: Intermitentne nebo kontinualne? Psychiatrie C'slo 1998; 2: 244-6
52. Rowland DL, De Gouveia Brazao CA, Slob AK. Effective daily treatment with clomipramine in men with premature ejaculation when 25mg (as required) is ineffective. BJU Int 2001; 87: 357-60
53. Ludovico GM, Corvase A, Pagliarulo G, et al. Paroxetine in the treatment of premature ejaculation. Br J Urol 1996, 2
54. Waldinger MD, Hengeveld MW, Zwinderman AH. Ejaculation retarding properties of paroxetine in patients with primary premature ejaculation: a double-blind, randomised, dose-response study. Br J Urol 1997; 79: 592-5
55. Giammusso B, Morgia G, Spampinato A, et al. La paroxetina nel trattamento dell'eiaculazione precoce. Arch Ital Urol Androl 1997; 69: 11-3
56. McMahon CG, Touma K. Treatment of premature ejaculation with paroxetine hydrochloride. Int J Impot Res 1999; 11: 241-5
57. Waldinger MD, Zwinderman AH, Olivier B. Antidepressants and ejaculation: a double-blind, randomized, placebo-controlled, fixed-dose study with paroxetine, sertraline, and nefazodone. J Clin Psychopharmacol 2001; 21: 293-7
58. Waldinger MD, Zwinderman AH, Olivier B. SSRIs and ejaculation: a double-blind, randomised, fixed-dose study with paroxetine and citalopram. J Clin Psychopharmacol 2001; 21: 556-60
59. Waldinger MD, Zwinderman AH, Olivier B. Antidepressants and ejaculation: a double-blind, randomised, fixed-dose study with mirtazapine and paroxetine. J Clin Psychopharmacol 2003; 23: 467-70
60. Waldinger MD, van De Plas A, Pattij T, et al. The SSRIs fluvoxamine and paroxetine differ in sexual inhibitory effects after chronic treatment. Psychopharmacology 2001; 160: 283-9

61. Mendels J, Camera A, Sikes C. Sertraline treatment for premature ejaculation. J Clin Psychopharmacol 1995; 15: 341-6
62. Kery S, Kozma A. Ejaculatio praecox citalopram kezelese. Magyar Urologia 1995; 7: 359-64
63. Kara H, Aydin S, Agargun Y, et al. The efficacy of fluoxetine in the treatment of premature ejaculation: a double-blind, placebo controlled study. J Urol 1996; 156: 1631-2
64. Lee HS, Song DH, Kim CH, et al. An open clinical trial of fluoxetine in the treatment of premature ejaculation. J Clin Psychopharmacol 1996; 16: 379-82
65. Raju GAR, Rani PU, Naidu MUR, et al. Evaluation of fluoxetine in premature ejaculation. Indian J Pharmacol 1997; 29: 204-5
66. Haensel SM, Klem TMAL, Hop WCJ, et al. Fluoxetine and premature ejaculation: a double-blind, crossover, placebo-controlled study. J Clin Psychopharmacol 1998; 18: 72-7
67. Biri H, Isen K, Sinik Z, et al. Sertraline in the treatment of premature ejaculation: a double-blind placebo controlled study. Int Urol Nephrol 1998; 30: 611-5
68. McMahon CG. Treatment of premature ejaculation with sertraline hydrochloride: a single-blind placebo controlled crossover study. J Urol 1998; 159: 1935-8
69. McMahon CG. Treatment of premature ejaculation with sertraline hydrochloride. Int J Impot Res 1998; 10: 181-4
70. Balbay MD, Yildiz M, Salvarci A, et al. Treatment of premature ejaculation with sertralin. Int Urol Nephrol 1998; 30: 81-3
71. Basar MM, Atan A, Yildiz M, et al. Comparison of sertraline to fluoxetine with regard to their efficacy and side effects in the treatment of premature ejaculation. Arch Esp de Urol 1999; 52: 1008-11
72. Yilmaz U, Tatlisen A, Turan H, et al. The effects of fluoxetine on several neurophysiological variables in patients with premature ejaculation. J Urol 1999; 161: 107-11
73. Atan A, Basar MM, Aydoganli L. Comparison of the efficacy of fluoxetine alone vs. fluoxetine plus local lidocaine ointment in the treatment of premature ejaculation. Arch Esp de Urol 2000; 53: 856-8
74. Kolomaznik M, Cervinka L, Kutilek S, et al. Fluoxetin v lecbe ejaculatio praecox. Psychiatrie 2002; 6: 6-9
75. Novaretti JPT, Pompeo ACL, Arap S. Selective serotonin uptake inhibitor in the treatment of premature ejaculation. Braz J Urol 2002; 28: 116-22
76. Atmaca M, Kuloglu M, Tezcan E, et al. The efficacy of citalopram in the treatment of premature ejaculation: a placebo-controlled study. Int J Impot Res 2002; 14: 502-5
77. Safarinejad MR, Hosseini SY. Safety and efficacy of citalopram in the treatment of premature ejaculation: a double-blind, placebo-controlled, fixed dose, randomized study. Int J Impot Res 2006; 18: 164-9
78. Waldinger MD. Drug treatment of premature ejaculation: pharmacodynamic and pharmacokinetic paradigms. Drug Discov Today 2005; 2: 37-40
79. Weinrieb RM, Auriacombe M, Lynch KG, et al. Selective serotonin re-uptake inhibitors and the risk of bleeding. Expert Opin Drug Saf 2005; 4: 337-44
80. Ahmad S. Paroxetine-induced priapism [letter]. Arch Intern Med 1995; 155: 645
81. Rand EH. Priapism in a patient taking sertraline [letter]. J Clin Psychiatry 1998; 59: 538
82. Fava M, Judge R, Hoog SL, et al. Fluoxetine versus sertraline and paroxetine in major depressive disorder: changes in weight with long-term treatment. J Clin Psychiatry 2000; 61: 863-7
83. Ditto KE. SSRI discontinuation syndrome; awareness as an approach to prevention. Postgrad Med 2003; 114: 79-84
84. Black K, Shea C, Dursun S, et al. Selective serotonin reuptake inhibitor discontinuation syndrome; proposed diagnostic criteria. J Psychiatry Neurosci 2000; 25: 255-61
85. Borgherini G. The bioequivalence and therapeutic efficacy of generic versus brand-name psychoactive drugs. Clin Ther 2003; 25: 1578-92
86. Vergouwen AC, Bakker A. Adverse effects after switching to a different generic form of paroxetine: paroxetine mesylate instead of paroxetine HCl hemihydrate [in Dutch]. Ned Tijdschr Geneesk 2002; 146: 811-2
87. Cavallini G. Alpha-1 blockade pharmacotherapy in primitive psychogenic premature ejaculation resistant to psychotherapy. Eur Urol 1995; 28: 126-30
88. Basar MM, Yilmaz E, Ferhat M, et al. Terazosin in the treatment of premature ejaculation: a short-term follow-up. Int Urol Nephrol 2005; 37: 773-7
89. Buzelin JM, Fonteyne E, Kontturi MJ, et al. Comparison of tamsulosin with alfuzosin in the treatment of patients with lower urinary tract symptoms suggestive of bladder outlet obstruction (symptomatic benign prostatic hyperplasia). Br J Urol 1997; 80: 597-605
90. Berkovitch M, Keresteci AG, Koren G. Efficacy of prilocaine-lidocaine cream in the treatment of premature ejaculation. J Urol 1995; 154: 1360-1
91. Busato W, Galindo CC. Topical anaesthetic use for treating premature ejaculation: a double-blind, randomized, placebo-controlled study. BJU Int 2004; 93: 1018-21
92. Segraves RT, Saran A, Segraves K, et al. Clomipramine vs placebo in the treatment of premature ejaculation: a pilot study. J Sex Marital Ther 1993; 19: 198-200
93. Haensel SM, Rowland DL, Kallan KTHK, et al. Clomipramine and sexual function in men with premature ejaculation and controls. J Urol 1996; 156: 1310-5
94. Strassberg DS, de Gouveia Brazao CA, Rowland DL, et al. Clomipramine in the treatment of rapid (premature) ejaculation. J Sex Marital Ther 1999; 25: 89-101
95. Abdel-Hamid IA, El Naggar EA, El Gilany AH. Assessment of as needed use of pharmacotherapy and the pause-squeeze technique in premature ejaculation. Int J Impot Res 2001; 13: 41-5
96. Waldinger MD, Zwinderman AH, Olivier B. On-demand treatment of premature ejaculation with clomipramine and paroxetine: a randomized, double-blind fixed-dose study with stopwatch assessment. Eur Urol 2004; 46: 510-6
97. Kim SW, Paick JS. Short-term analysis of the effects of as needed use of sertraline at 5 PM for the treatment of premature ejaculation. Urology 1999; 54: 544-7
98. McMahon C, Touma K. Treatment of premature ejaculation with paroxetine hydrochloride as needed: 2 single-blind, placebo-controlled, crossover studies. J Urol 1999; 161: 1826-30
99. Chia SJ. Management of premature ejaculation: a comparison of treatment outcomes in patients with and without erectile dysfunction. Int J Androl 2002; 25: 301-5
100. Salonia A, Maga T, Colombo R, et al. A prospective study comparing paroxetine alone versus paroxetine plus sildenafil in patients with premature ejaculation. J Urol 2002; 168: 2486-9
101. Pryor JL, Althof SE, Steidle C, et al. Efficacy and tolerability of dapoxetine in treatment of premature ejaculation: an integrated analysis of two double-blind, randomised controlled trials. Lancet 2006; 368: 929-37

102. Waldinger MD, Schweitzer DH, Olivier B. On-demand SSRI treatment of premature ejaculation: pharmacodynamic limitations for relevant ejaculation delay and consequent solutions. J Sex Med 2005; 2: 120-30
103. Waldinger MD, Schweitzer DH, Olivier B. Dapoxetine treatment of premature ejaculation. Lancet. 2006; 368: 1869-70
104. Frink MC, Hennies HH, Engelberger W, et al. Influence of tramadol on neurotransmitter systems of the rat brain. Arzneimittelforschung 1996; 46: 1029-36
105. Zhang XS, Wang YX, Huang XY, et al. Comparison between sildenafil plus sertraline and sertraline alone in the treatment of premature ejaculation. Zhanghua Nan Ke Xue 2005; 11: 520-2, 525
106. Chen J, Mabjeesh NJ, Matzkin H, et al. Efficacy of sildenafil as adjuvant therapy to selective serotonin reuptake inhibitor in alleviating premature ejaculation. Urology 2003; 61: 197-200
107. Tang W, Ma L, Zhao L, et al. Clinical efficacy of Viagra with behaviour therapy against premature ejaculation. Zhanghua Nan Ke Xue 2004; 10: 366-7, 370
108. McMahon CG, Stuckey B, Andersen ML, et al. Efficacy of Viagra sildenafil citrate in men with premature ejaculation. J Sex Med 2005; 2: 368-75
109. Li X, Zhang SX, Cheng HM, et al. Clinical study of sildenafil in the treatment of premature ejaculation complicated by erectile dysfunction. Zhanghua Nan Ke Xue 2003; 9: 266-9
110. Lozano AF. Premature ejaculation: pharmacological treatment. Three years after [abstract no. MP-2-6]. Int J Imp Res 2003; 15 Suppl. 6: S11
111. Sommer F, Klotz T, Mathers MJ. Treatment of premature ejaculation: a comparative vardenafil and SSRI crossover study [abstract no. 741]. J Urol 2005; 173 Suppl.: 202
112. Mattos RM, Lucon AM. Tadalafil and slow-release fluoxetine in premature ejaculation: a prospective study [abstract no. 880]. J Urol 2005; 173 Suppl.: 239
113. Erenpreiss J, Zalkalns J. Premature ejaculation: comparison of paroxetine alone, paroxetine plus local lidocaine and paroxetine plus sildenafil [abstract no. PS-7-4]. Int J Imp Res 2002; 14 Suppl. 4: S33
114. Linn R, Ginesin Y, Hardak S, et al. Treatment of sildenafil as part of the treatment in premature ejaculation [abstract no. P-168]. Int J Imp Res 2002; 14 Suppl. 4: S39
115. Atan A, Basar MM, Tuncel A, et al. Comparison of efficacy of sildenafil-only, sildenafil plus topical EMLA cream, and topical EMLA-cream-only in treatment of premature ejaculation. Urology 2006; 67: 388-91
116. Fein RL. Intracavernous medication for treatment of premature ejaculation. Urology 1990; 35: 301-3
117. Waldinger MD, Berendsen HHG, Blok BFM, et al. Premature ejaculation and SSRI-induced delayed ejaculation: the involvement of the serotonergic system. Behav Brain Res 1998; 92: 111-8
118. Olivier B, van Oorschot R, Waldinger MD. Serotonin, serotonergic receptors, selective serotonin reuptake inhibitors and sexual behaviour. Int Clin Psychopharmacol 1998; 13 Suppl. 6: S9-14
119. Fuller RW. Uptake inhibitors increase extracellular serotonin concentration measured by brain microdialysis. Life Sci 1994; 55: 163-7
120. Mos J, Mollet I, Tolboom JT, et al. A comparison of the effects of different serotonin reuptake blockers on the sexual behaviour of the male rat. Eur Neuropsychopharmacol 1999; 9: 123-35
121. Blier P, de Montigny C. Electrophysiological investigations on the effect of repeated zimelidine administration on serotonergic neurotransmission in the rat. J Neurosci 1983; 3: 1270-8
122. Chaput Y, Blier P, de Montigny C. In vivo electrophysiological evidence for the regulatory role of autoreceptors on serotoninergic terminals. J Neurosci 1986; 6: 2796-801
123. Blier P, Chaput Y, de Montigny C. Long-term 5-HT reuptake blockade, but not monoamine oxidase inhibition, decreases the function of terminal 5-HT autoreceptors: an electrophysiological study in the rat brain. Naunyn Schmiedeberg's Arch Pharmacol 1988; 337: 246-54
124. Cantor J, Binik I, Pfaus JG. Chronic fluoxetine inhibits sexual behaviour in the male rat: reversal with oxytocin. Psychopharmacology 1999; 144: 355-62
125. Frank JL, Hendricks SE, Olson CH. Multiple ejaculations and chronic fluoxetine: effects on male rat copulatory behaviour. Pharmacol Biochem Behav 2000; 66: 337-42
126. de Jong TR, Veening JG, Olivier B, et al. Oxytocin involvement in SSRI-induced delayed ejaculation: a review of animal studies. J Sex Med 2007; 4: 14-28
127. de Wied D, Diamant M, Fodor M. Central nervous system effects of the neurohypophyseal hormones and related peptides. Front Neuroendocrinol 1993; 14: 251-302
128. Hallbeck M, Larhammar D, Blomqvist A. Neuropeptide expression in rat paraventricular hypothalamic neurons that project to the spinal cord. J Comp Neurol 2001; 433: 222-38
129. Carter CS. Oxytocin and sexual behavior. Neurosci Biobehav Rev 1992; 16: 131-44
130. Benoussaidh A, Maurin Y, Rampin O. Possible neural mediation of the central effects of oxytocin on uterine motility. Am J Physiol Regul Integr Comp Physiol 2005; 289: R798-804
131. Carmichael MS, Humbert R, Dixen J, et al. Plasma oxytocin increases in the human sexual response. J Clin Endocrinol Metab 1987; 64: 27-31
132. Kruger TH, Haake P, Chereath D, et al. Specificity of the neuroendocrine response to orgasm during sexual arousal in men. J Endocrinol 2003; 177: 57-64
133. Murphy MR, Seckl JR, Burton S, et al. Changes in oxytocin and vasopressin secretion during sexual activity in men. J Clin Endocrinol Metab 1987; 65: 738-41
134. Uckert S, Becker AJ, Ness BO, et al. Oxytocin plasma levels in the systemic and cavernous blood of healthy males during different penile conditions. World J Urol 2003; 20: 323-6
135. Stoneham MD, Everitt BJ, Hansen S, et al. Oxytocin and sexual behaviour in the male rat and rabbit. J Endocrinol 1985; 107: 97-106
136. Hughes AM, Everitt BJ, Lightman SL, et al. Oxytocin in the central nervous system and sexual behaviour in male rats. Brain Res 1987; 414: 133-7
137. Honda K, Yanagimoto M, Negoro H, et al. Excitation of oxytocin cells in the hypothalamic supraoptic nucleus by electrical stimulation of the dorsal penile nerve and tactile stimulation of the penis in the rat. Brain Res Bull 1999; 48: 309-13
138. Yanagimoto M, Honda K, Goto Y, et al. Afferents originating from the dorsal penile nerve excite oxytocin cells in the hypothalamic paraventricular nucleus of the rat. Brain Res 1996; 733: 292-6
139. Arletti R, Benelli A, Bertolini A. Sexual behavior of aging male rats is stimulated by oxytocin. Eur J Pharmacol 1990; 179: 377-81

140. Filippi S, Vannelli GB, Granchi S, et al. Identification, localization and functional activity of oxytocin receptors in epididymis. Mol Cell Endocrinol 2002; 193: 89-100

141. Vignozzi L, Filippi S, Luconi M, et al. Oxytocin receptor is expressed in the penis and mediates an estrogen-dependent smooth muscle contractility. Endocrinology 2004; 145: 1823-34

142. Mens WB, Witter A, an Wimersma Greidanus TB. Penetration of neurohypophyseal hormones from plasma into cerebrospinal fluid (CSF): half-times of disappearance of these neuropeptides from CSF. Brain Res 1983; 262: 143-9

143. Waldinger MD, Rietschel M, Nothen MM, et al. Familial occurrence of primary premature ejaculation. Psychiatr Genet 1998; 8: 37-40

144. Waldinger MD. Lifelong premature ejaculation: definition, serotonergic neuro- transmission and drug treatment. World J Urol 2005; 23: 102-8

145. Waldinger MD, Quinn P, Dilleen M, et al. A multi-national population survey of intravaginal ejaculation latency time. J Sex Med 2005; 2: 492-7

146. Waldinger MD, Zwinderman AH, Olivier B, et al. Proposal for a definition of lifelong premature ejaculation based on epidemiological stopwatch data. J Sex Med 2005; 2: 498-507

147. Williamson IJR, Turner L, Woods K, et al. The 5-HT_{1A} receptor antagonist robalzotan enhances SSRI-induced ejaculation delay in the rat [abstract]. Br J Pharmacol 2003; 138 Suppl. 1: PO32

148. de Jong TR, Pattij T, Veening JG, et al. Citalopram combined with WAY 100635 inhibits ejaculation and ejaculation-related Fos immunoreactivity. Eur J Pharmacol 2005; 509: 49-59

149. Cremers TIFH, de Boer P, Liao Y, et al. Augmentation with a 5-HT_{1A}, but not a 5-HT_{1B} receptor antagonist, critically depends on the dose of citalopram. Eur J Pharmacol 2000; 397: 63-74

150. Johansson L, Sohn D, Thorberg SO, et al. The pharmacological characterization of a novel selective 5-hydroxytryptamine 1A receptor antagonist, NAD-299. J Pharmacol Exp Ther 1997; 283: 216-25

151. de Jong TR, Pattij T, Veening JG, et al. Effects of chronic selective serotonin reuptake inhibitors on 8-OH-DPAT-induced facilitation of ejaculation in rats: comparison of fluvoxamine and paroxetine. Psychopharmacology (Berl) 2005; 179: 509-15

152. Olivier B, Chan JS, Pattij T, et al. Psychopharmacology of male rat sexual behavior: modeling human sexual dysfunctions? Int J Impot Res. Epub 2005 Apr 21

153. Waldinger MD, Olivier B. Animal models of premature and retarded ejaculation. World J Urol 2005; 23: 115-8

154. Pattij T, de Jong T, Uitterdijk A, et al. Individual differences in male rat ejaculatory behavior: searching for models to study ejaculation disorders. Eur J Neurosci 2005; 22: 724-34

155. Pattij T, Olivier B, Waldinger MD. Animal models of ejaculatory behaviour. Curr Pharm Des 2005; 11: 4069-77

Correspondence: Dr *Marcel D. Waldinger*, Department of Psychiatry and Neurosexology, HagaHospital Leyenburg, Leyweg 275, 2545 CH The Hague, The Netherlands.
E-mail: md@waldinger.demon.nl