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# A Benefit-Risk Assessment of Dapoxetine in the Treatment of Premature Ejaculation

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## Abstract

Premature ejaculation (PE) is considered to be the most common sexual problem affecting men, despite the likelihood that it is under-diagnosed. It is a complex condition with many physical and psychological components, making management complicated. It is important to develop treatments for PE as it adversely affects quality of life for individuals and partners.

Dapoxetine is a short-acting selective serotonin reuptake inhibitor (SSRI) that has been developed principally for the treatment of PE. It is considered more suitable for the treatment of PE than other SSRIs as it can be used as an 'on demand' treatment to be taken a few hours before an expected sexual encounter, reducing the possibility of adverse effects.

Dapoxetine may represent a breakthrough in the treatment of PE as it is the first drug to be licensed for this indication. This review attempts to present a balanced benefit-risk assessment of dapoxetine by examining the evidence from phase III clinical trials, focusing on its efficacy in prolonging intravaginal ejaculatory latency time (IELT), patient sexual satisfaction and safety in patients with PE. The benefits and risks of other therapies that are

used to treat PE off-licence are also reviewed. There has only been one study to date that directly compares dapoxetine to another therapy, paroxetine, for this indication.

It was found that dapoxetine is most effective at a dose of 60 mg in increasing IELT compared with placebo. All studies have also found that dapoxetine is well tolerated as an 'on-demand' therapy and with continual dosing; however, there are little data regarding possible long-term adverse effects. Findings of the dapoxetine development programme demonstrated that dapoxetine is associated with vasovagal-mediated (neurocardiogenic) syncope. No other associated significant cardiovascular adverse events were identified.

Further research is needed to directly compare dapoxetine with other therapies and to investigate the outcomes of dapoxetine used in conjunction with behavioural therapies, and other non-pharmaceutical therapies.

Dapoxetine is currently approved for the treatment of premature ejaculation (PE) in several countries, including Sweden, Austria, Germany and New Zealand, and is being considered for approval in the US and UK.[1,2] It is currently the only pharmaceutical agent approved for the treatment of PE, and is not currently approved for indications other than treatment of PE, although some studies have found that it has both antidepressant and analgesic effects.[3]

## 1. Epidemiology and Natural History of Premature Ejaculation (PE)

This benefit-risk assessment aims to review the use of dapoxetine, a fast-acting selective serotonin reuptake inhibitor (SSRI) in the treatment of men with PE, also referred to as rapid ejaculation. The International Society for Sexual Medicine has developed guidelines for the diagnosis and treatment of PE,[4] which follow previous reviews and guidance on the management of problems in the UK.[5] In the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), PE is defined as *''persistent or recurrent ejaculation with minimal stimulation before, upon, or shortly after penetration and before the person wishes it, and is associated with marked distress or interpersonal difficulty.''*[6] The studies reviewed here used this definition or defined PE as ejaculation before 2 minutes of sexual intercourse in more than 50% of sexual encounters, which causes the patient or their sexual partner distress. PE is estimated to be the most common sexual problem affecting men[1,7] and is also likely to be underdiagnosed as many men do not seek treatment for PE due to its sensitive nature.[3,8] There is currently no pharmacological treatment licensed in the UK for the treatment of PE.[1]

PE is a multifactorial condition, and ideally its treatment should reflect that by addressing both the physiological and psychological components.[9] Short ejaculatory latency is the most specific symptom of PE. In the literature, the threshold for what is considered a short ejaculatory time differs. This leads to the argument of whether PE is in fact truly a medical problem and whether latent ejaculatory time should simply be considered a spectrum of what is 'normal' for an individual.[10,11] It is argued that 'medicalization' of the problem by offering pharmacological treatment could possibly cause more harm than good[11] by increasing patients' anxiety regarding intercourse by giving a formal diagnosis.

In addition to short ejaculatory latency, other symptoms of PE commonly include low perceived control over ejaculation, low satisfaction with sexual intercourse, interpersonal difficulty relating to ejaculation, and low self-esteem.[1,3,7,9] Therefore it is argued that treatment for PE should include a psychosexual element as well as a pharmacological agent.[10] In many of the studies assessing dapoxetine in the treatment of PE, a change in intravaginal ejaculatory latency time (IELT) is the biggest determinant for evaluating the efficacy of the drug. Treatment benefit should consider change in

 

other PE-related components, particularly as IELT varies greatly between men with PE.[9]

## 2. Use of Selective Serotonin Reuptake Inhibitors (SSRIs) in PE

The neurophysiology of ejaculation is complex. The central neural ejaculatory centre is a system of interconnected spinal and cerebral areas.[8] Sensory and cerebral stimuli processed at spinal cord level act with sympathetic, parasympathetic and somatic spinal centres to control the physiological events during ejaculation.[8] Serotonin (5-HT) is identified as having an inhibitory affect on ejaculation.[1,8] Pharmacological intervention manipulating the serotinergic system, e.g. prescription of SSRI antidepressants, causes increased serotonin activity by inhibiting the serotonin reuptake transporter. This has been found to cause a delay in ejaculation,[1,8,12] and delayed ejaculation is a common adverse effect across SSRI antidepressants.

Currently fluoxetine, paroxetine, sertraline, citalopram and fluvoxamine are used on an off-licence basis in the UK for the treatment of PE.[1] Studies have identified that paroxetine is the most effective in increasing IELT by several minutes,[13] with sertraline and fluoxetine thereafter.[1] Unfortunately, SSRIs have several adverse effects and continual dosing is required to have an ongoing effect on delaying ejaculation. The SSRI group have a relatively long onset of action as they take around 2–3 weeks to achieve efficacy. There is also a risk of discontinuation syndrome if stopped suddenly so are more suited to a longer-term treatment when being used for treatment of PE[1] in men having regular sexual activity.

SSRIs have some sexual adverse effects such as reduced libido, anorgasmia and erectile dysfunction (ED), which could potentially perpetuate the problem of PE.[1] It is on this basis that dapoxetine, an SSRI with a short half-life, was developed as an alternative to long-acting SSRIs – not as an antidepressant but as an 'on-demand' treatment for PE.[1]

## 3. Pharmacokinetics of Dapoxetine

Dapoxetine hydrochloride is a potent inhibitor of serotonin reuptake transporters. It is a water-soluble powder with a molecular weight of 341.88, pKa of 8.6 and is positively charged at physiological pH. Unlike other SSRIs it is not a halogenated molecule and it includes a naphthyl moiety; these differences may explain some of the differences in its pharmacokinetics in comparison with the other SSRIs.[14] Dapoxetine is suited for 'on-demand' treatment of PE as it is rapidly absorbed[7] and has a short initial half-life. It achieves peak plasma concentrations at approximately 1.5 hours after dosing, which compares to 6 hours for fluoxetine and 5 hours for paroxetine.[15] Following oral administration of dapoxetine there is rapid absorption, followed by a rapid decrease in plasma concentration with plasma levels of only 4% at 24 hours post-dosing. This rapid elimination means there is minimal accumulation after repeated dosing.[15,16] Several recent, phase III, randomized, placebo-controlled trials assessing dapoxetine have had promising results in increasing IELT[1-3,9,17] compared with baseline and placebo, and have found that the drug is generally well tolerated.

## 4. Literature Search Methodology

To search for relevant literature, search terms were firstly identified after reading around the subjects of PE and dapoxetine. The search terms described below were used to search MEDLINE via Ovid in November and December 2010. All searches were set to include related terms. Further literature searches using the same terms were made between November 2010 and March 2011 to review alternative therapies for PE. Titles and abstracts of relevant articles were read and critiqued. If the paper was relevant, the full text of the article was accessed and saved.

The only exclusion criteria for articles deemed relevant were those not available in English. All articles were considered relevant if they discussed dapoxetine as a therapy for PE. The reference lists of the articles were used to find further articles of importance that had not been found in the original searches. Randomized controlled trials were considered the strongest form of evidence, but all other articles were also considered.

Search terms used in the searches were 'benefit risk', 'benefit-risks', 'assessment', 'diagnosis', 'diagnoses', 'diagnose', 'diagnosing', 'diagnostic', 'recognise', 'recognising', 'recognition', 'detect', 'detecting', 'detection', 'screening', 'screen', 'symptoms', 'signs', 'work up', 'workup', 'assessing', 'evaluation', 'evaluating', 'investigations', 'clinical investigation', 'patient evaluation', 'procedure', 'dapoxetine', 'treatment', 'therapeutic aspects', 'disease management', 'therapy', 'therapeutic procedure', 'therapeutic interventions', 'therapies', 'treatments', 'remedy', 'relief', 'amelioration', 'remedies', 'therapeutic', 'relieve', 'ameliorate', 'alleviate', 'relieving', 'alleviating', 'alleviated', 'ameliorated', 'relieved', 'management', 'premature ejaculation', 'ejaculation premature', 'ejaculatio praecox', 'ejaculates too soon'.

## 5. Benefit Evaluation of Dapoxetine

There have been many studies evaluating the benefit of dapoxetine in the treatment of PE but for the purposes of this review only phase III trials have been included.[2,4,18-20] The reasons for discontinuation of the studies can be found in table I.

Two identical, 12-week, double-blind, placebo-controlled, randomized studies involving 2614 men with moderate to severe PE, who were taking either placebo, 30 mg dapoxetine or 60 mg dapoxetine

**Table I.** Reasons for withdrawal from dapoxetine studies

| Study, y | Placebo | 30 mg dapoxetine | 60 mg dapoxetine | 20 mg paroxetine |
|---|---|---|---|---|
| **Pryor et al., 2006**[18] | | | | |
| Lost to follow-up | 61 | 55 | 63 | NA |
| Withdrawal of consent | 49 | 40 | 47 | NA |
| Personal | 45 | 42 | 37 | NA |
| Adverse effects | 8 | 35 | 87 | NA |
| Non-compliance | 13 | 11 | 6 | NA |
| Lack of efficacy | 11 | 10 | 7 | NA |
| Protocol violation | 3 | 0 | 3 | NA |
| Other | 8 | 5 | 10 | NA |
| **Safarinejad, 2006**[20] | | | | |
| Adverse effects | 0 | NA | 4 | 5 |
| Lack of efficacy | 6 | NA | 3 | 2 |
| Lost to follow-up | 4 | NA | 3 | 4 |
| **Safarinejad, 2006**[20] | | | | |
| Adverse effects | 0 | NA | 6 | NA |
| Lack of efficacy | 5 | NA | 2 | NA |
| Lost to follow-up | 5 | NA | 5 | NA |
| **McMahon et al., 2010**[17] | | | | |
| Subject choice | 42 | 70 | 77 | NA |
| Lost to follow-up | 3 | 3 | 0 | NA |
| Adverse effects | 1 | 6 | 18 | NA |
| Death | 0 | 1 | 0 | NA |
| Other | 16 | 21 | 16 | NA |
| **Buvat et al., 2009**[2] | | | | |
| Subject choice | 118 | 81 | 82 | NA |
| Lost to follow-up | 20 | 22 | 20 | NA |
| Adverse effects | 5 | 15 | 32 | NA |
| Other | 53 | 48 | 48 | NA |

**NA** = not applicable.

were carried out.[18] The measurement outcomes for this study were mean IELT and mean sexual satisfaction. Mean IELT was assessed by the subject's partner using a stopwatch. Sexual satisfaction was measured by asking both the subject and his partner to give a rating on a 5-point scale (1 = very poor, 2 = poor, 3 = fair, 4 = good and 5 = very good). At commencement of the study, the baseline mean IELT for the groups was: placebo 0.90 minutes, 30 mg dapoxetine 0.92 minutes and 60 mg dapoxetine 0.91 minutes. Mean baseline scores for sexual satisfaction were: placebo – subject 1.66, partner 1.59; 30 mg dapoxetine – subject 1.65, partner 1.62; 60 mg dapoxetine – subject 1.72, partner 1.74. There was no statistical difference in baseline measurements between the three groups. During the studies, participants were asked to attempt sexual intercourse six times or more per month, taking their medication 1–3 hours prior to commencing sexual activity. Of the 2614 men who started the study, 1958 completed it. At the end of the study, the mean IELT had increased to 1.75 minutes, 2.78 minutes and 3.32 minutes for the placebo, 30 mg dapoxetine and 60 mg dapoxetine groups, respectively. Statistical analysis of the results gave a p-value <0.0001. In addition, sexual satisfaction scores increased to: placebo – subject 1.7, partner 1.69; 30 mg dapoxetine – subject 2.21, partner 2.11; 60 mg dapoxetine – subject 2.31, partner 2.32.

There have been two further studies examining the role of daily dosing of dapoxetine in the treatment of PE.[19,20] The first, a double-blind, placebo-controlled, randomized study, included 340 men with PE who were given either placebo, 60 mg dapoxetine or 20 mg paroxetine; all were taken orally on a daily basis for the duration of the 12-week study. Measured outcomes were mean IELT (measured by the subject's partner) and intercourse satisfaction (measured using the International Index of Erectile Function, a questionnaire used to detect treatment related changes in several domains of male sexual function, rather than just focusing on IELT. The maximum score is 75).[21] At commencement of the study, the baseline mean IELT for the groups were 34 seconds, 38 seconds and 31 seconds for the placebo, 60 mg dapoxetine and 20 mg paroxetine groups, respectively. The mean intercourse satisfaction scores at baseline were: placebo, 10; 60 mg dapoxetine, 10; and paroxetine, 11. There were no statistical differences in baseline measurements between the three groups. Of the 340 men who started the study, 309 completed the full study. At the end of the study, the mean IELT had increased to 55 seconds, 179 seconds and 370 seconds for the placebo, 60 mg dapoxetine and 20 mg paroxetine groups, respectively. Statistical analysis of the difference in increase in IELT gave a p-value of 0.01 for dapoxetine and 0.001 for paroxetine. The intercourse satisfaction scores also increased to: placebo, 12; 60 mg dapoxetine, 14; and 20 mg paroxetine, 17. The second study[20] looked only at dapoxetine in comparison with placebo. This was a double-blind, placebo-controlled, fixed-dose, randomized study that contained 212 potent men with PE. The measured outcomes of this study were mean IELT and sexual satisfaction (however, baseline sexual satisfaction is not reported). Baseline mean IELT was assessed during a 4-week period. IELT, both at the start and the end of the study, followed a skewed distribution; thus the author measured the geometric mean IELT. Participants were also asked to rate their sexual satisfaction from 0 to 5, with 0 being extremely dissatisfied and 5 being extremely satisfied. During the study, participants took either 30 mg dapoxetine or placebo twice daily for 12 weeks, and were given a stopwatch to time IELT during intercourse. Of the 212 men who started the study, 189 completed it. At study end, the dapoxetine group had a 2.9-fold increase in IELT in comparison with a 1.4-fold increase in the placebo group. Comparing the IELT increase between the groups gave a p-value of 0.001. When comparing sexual satisfaction scores, the dapoxetine group reported substantially higher scores than the placebo group (p = 0.04).

It should be noted that unlike the other trials comparing dapoxetine with placebo, both these studies were daily dosing, not on-demand dosing.

The most recently published phase III trial[4] is a 12–week, double-blind, placebo-controlled, randomized study carried out in 52 centres in the Asia-Pacific region. The study comprised 1067 men who were randomized into three groups:

 

placebo, 30 mg dapoxetine and 60 mg dapoxetine to be taken on demand. The measured outcome for this study was IELT, which was measured by the subject's partner during baseline and treatment phases. Mean baseline IELT measurements were 1.0 minute for the placebo group and 1.1 minutes for both dapoxetine groups. Of the 1067 men who started the study, 858 completed it. At study end, the mean IELT had increased to 2.4 minutes, 3.9 minutes and 4.2 minutes for placebo, 30 mg dapoxetine and 60 mg dapoxetine, respectively. Analysis of the increase in IELT when dapoxetine is compared with placebo gives $p \leq 0.001$.[17] There was, however, no statistical difference between the dapoxetine groups.

The studies mentioned above only ran for a relatively short time. What are the longer-term effects of dapoxetine?

In 2008, a 24-week, randomized, double-blind, placebo-controlled study was carried out.[2] This study was a phase III trial carried out in 22 countries comparing placebo with 30 mg dapoxetine and 60 mg dapoxetine. The study comprised 1162 men with at least moderate PE. Patients were assessed at baseline and at 4-weekly intervals throughout the trial. The mean baseline IELT was 0.9 minutes across all groups. During the study, participants were asked to take their medication 1–3 hours prior to commencement of sexual activity. Of the 1162 men who started the trial, 618 completed the full 24 weeks. At study end, the mean IELT had increased to 1.9 minutes, 3.1 minutes and 3.5 minutes for placebo, 30 mg dapoxetine and 60 mg dapoxetine, respectively. Statistically comparing the increase of placebo compared with both dapoxetine groups gave a p-value of <0.0001.

## 6. Risk Evaluation of Dapoxetine

The most common adverse effects reported amongst those taking dapoxetine were nausea, dry mouth, headache, dizziness, diarrhoea, vomiting, insomnia and loss of libido.[2,4,18-20] One study[18] reported minor adverse effects in 24.7% of participants taking 30 mg dapoxetine and 43.6% of participants taking 60 mg dapoxetine. Rates of serious adverse effects were low, with a rate of 2.3% amongst those taking 30 mg dapoxetine and 4.3% in those taking 60 mg dapoxetine. Serious adverse effects were reported in 0.3% of those taking 30 mg dapoxetine and 0.6% of those taking 60 mg dapoxetine. In comparison with those taking placebo, 8.3% reported minor adverse effects, 2.9% reported severe adverse effects and 0.9% reported serious adverse effects. In this study, 5% of all participants withdrew due to adverse effects. In the first study carried out by Safarinejad,[19] adverse effects were reported by 18.3% of those taking 30 mg dapoxetine, compared with only 8% of those taking placebo. Overall, 2.4% of those enrolled in the study withdrew due to adverse effects. In the second study by Safarinejad,[20] 25.8% of those taking 30 mg dapoxetine reported adverse effects, with 2.83% of those who started the study withdrawing for this reason. McMahon et al.[17] reported adverse effects in 33.3% of those taking 30 mg dapoxetine and 49.7% of those taking 60 mg dapoxetine. This is in comparison with just 17.9% of those taking placebo. Overall, 8% of those enrolled withdrew from the study due to adverse effects. In the long-term study by Buvat et al.,[2] adverse effects were reported by 56.2% of those taking 30 mg dapoxetine and 61.8% of those taking 60 mg dapoxetine. Comparatively, adverse effects were reported by 38.4% of those taking placebo. Of those who withdrew from this study, 13% did so due to adverse effects.

There are currently no reported drug interactions of dapoxetine in the literature. The cardiovascular safety profile of dapoxetine was investigated during premarketing evaluation of the medication. Dapoxetine is an SSRI and, as a new compound in this class, it merited special attention, given that other SSRI medications approved for the treatment of depression, anxiety and other psychiatric conditions have infrequently been associated with reports of cardiovascular adverse events.[16,17,22] It was also important to assess the cardiovascular safety profile of dapoxetine because the proposed indication (i.e. PE) is not a life-threatening condition, and therefore syncope, albeit rare, might offset the clinical benefits. The highest incidence of syncopal events was reported in the phase I studies, and this was considered likely to be due to study-related precipitating factors (e.g. venipuncture, vital sign measurements, orthostatic

 

**Table II.** Relative risk of adverse effects for placebo and all treatment options

| Treatment | Number of participants | Number of adverse effects | Relative risk |
|---|---|---|---|
| Placebo | 2041 | 382 | 18.7 |
| 30 mg dapoxetine | 1836 | 763 | 41.6 |
| 60 mg dapoxetine | 1615 | 1002 | 62.0 |
| Other SSRIs | 331 | 71 | 21.4 |
| Clomipramine | 72 | 32 | 44.4 |
| Tramadol | 92 | 17 | 18.5 |
| PDE-5 inhibitors | 102 | 21 | 20.1 |
| Local anaesthetic | 115 | 46 | 29.7 |

**PDE-5** = phosphodiesterase type 5; **SSRIs** = selective serotonin reuptake inhibitors.

manoeuvres and ECG/Holter recordings) as the majority of incidences occurred on day 1 of the study (after first dosing but on the same day these precipitating factors occurred). The percentage of subjects with syncope resulting in loss of consciousness in the phase III placebo-controlled studies was low and dose related, but was similar for the placebo (1 of 1857 [0.05%]) and dapoxetine 30 mg (1 of 1616 [0.06%]) groups, although higher in the dapoxetine 60 mg group (6 of 2608 [0.23%]). Simple modifiable risk factors, such as adequate hydration and implementation of prevention manoeuvres, can effectively minimize syncope occurrence.[23]

Serotonin mediates blood pressure control through both afferent and efferent serotonergic pathways, and alteration of serotonergic pathways can provoke or prevent a vasovagal response.[17,18,24] The principal action that leads to hypotension and bradycardia in neurocardiogenic syncope appears to be sudden and profound sympathetic withdrawal.[25]

Table II shows the relative risk of adverse effects for placebo and all treatment options. As the two studies carried out by Waldinger et al.[26,27] do not give full details of adverse effects, these have been excluded when calculating relative risk.

As can be seen, dapoxetine has a higher relative risk of adverse effects than any other treatment option, and this is a dose-dependent risk. This must be taken into account when assessing whether or not dapoxetine should be recommended instead of other existing treatments for PE.

## 7. Alternative Therapies for PE

Available therapies for the treatment of PE include both pharmaceutical and behavioural treatments.

### 7.1 Pharmaceutical

#### *7.1.1 Topical Therapies*

##### Benefits of Local Anaesthetic

The use of topical anaesthetics is well established in the treatment of PE, with the first use dating back to Schapiro in 1943.[28,29]

Choi et al.[30] performed a double-blind, randomized, placebo-controlled trial comparing Severance Secret (SS) cream (comprising nine natural products: Ginseng Radix Alba, Angelicae Gigantis Radix, Cistanchis Herba, Zanthoxylli Fructis, Cinnamoni Cortex, Torlidis Semen, Asiasari radix, Caryophylli Flos and Bufonis Veneum) and placebo in the treatment of PE. 125 men with lifelong PE enrolled in the study, with 106 completing the study. Of those who did not complete the trial, 14 were lost to follow-up, 3 were lost during the screening stage and 2 had insufficient clinical data. All participants were given six identical packets of cream, five with SS cream and one with placebo, and were asked to apply the cream to only the glans of the penis 1 hour prior to intercourse. Outcomes of the study were an increase in mean ejaculatory latency (MEL), which equates to IELT used in other studies, and sexual satisfaction. Pre-treatment MEL, as measured by the participant's partner using a

 

stopwatch, was 1.37 minutes, and mean sexual satisfaction was 11.9%. At study end, the SS cream was found to have increased MEL to 10.92 minutes. Comparatively, the placebo cream was found to have only increased MEL to 2.45 minutes ($p < 0.001$). In respect of sexual satisfaction, the SS cream had increased satisfaction to 82.19%, whereas placebo had only increased satisfaction to 19.81% ($p < 0.001$)

Dinsmore et al.[31] carried out a 10–week, randomized, double-blind, placebo-controlled phase II study comparing the efficacy of TEMPE (topical eutectic mixture for PE), an aerosol spray containing a mixture of lidocaine and prilocaine. Sixty-two men were assessed for eligibility over a 1-month period, with 54 eventually being randomized into either the TEMPE or placebo group. Of the 54 men enrolled, 43 completed the study, 7 were lost to follow-up (TEMPE 3, placebo 4), 3 withdrew consent (TEMPE 2, placebo 1) and 1 man in the TEMPE group withdrew before using the treatment. The measured outcome for the study was IELT, as measured by the participant's partner using a stopwatch. Baseline IELT for the placebo group was 0.9 minutes, and 1.0 minutes for the TEMPE group (no statistical difference). At study end, both groups had an increase in IELT: placebo IELT 1.6 minutes, TEMPE 4.9 minutes, but the TEMPE group was statistically better than placebo in delaying ejaculation ($p < 0.01$).

#### Adverse Effects of Local Anaesthetic

The use of topical therapies avoids systemic adverse effects; however, some studies have reported local adverse effects. As would be expected, the adverse reports for local anaesthetic included mild burning and mild pain, Choi et al.[30] reported these effects in 14.72% and 3.77% of participants, respectively. Dinsmore et al.[31] reported adverse effects in 26% of participants using TEMPE compared with 28% of those using placebo.

### *7.1.2 Systemic Therapies*

Systemic therapies used off-label for treatment of PE include other SSRIs, tramadol, clomipramine and phosphodiesterase type-5 (PDE-5) inhibitors.

#### Other SSRIs

Delayed ejaculation is a well documented adverse effect of SSRIs and, as such, using them as an off-licence treatment option for PE has happened for many years;[4,19] thus, there have been several studies evaluating their efficacy.[19,26,27,32]

*Benefits of other SSRIs*: An early study carried out by Kim and Seo[32] compared the efficacy and safety of fluoxetine, sertraline and clomipramine with placebo in a double-blind control study. The measured outcome of this study was IELT. The original number of study participants was 53, however only 37 completed the full study; five were lost to follow-up, five withdrew due to no efficacy (fluoxetine three, placebo one, sertraline one), five withdrew due to adverse effects (clomipramine three, sertraline one, placebo one) and one withdrew due to no efficacy and adverse effects (clomipramine). All 37 men took each of the three drugs and the placebo daily for 4 weeks per agent, with at least 1 week washout between treatments. Doses were fluoxetine 40 mg, sertraline 100 mg and clomipramine 50 mg. At baseline, pretreatment mean IELT was 46 seconds; during baseline assessments participants were also asked to rate sexual satisfaction. The mean IELT for each treatment as the end of the study was 2.27 minutes for placebo, 2.30 minutes for fluoxetine, 4.27 minutes for sertraline and 5.75 minutes for clomipramine. Statistical analysis of the IELT for the treatment groups, compared with placebo, gave a p-value of $<0.01$. Comparison of the IELT for fluoxetine and sertraline showed sertraline was more effective than fluoxetine in the delay of ejaculation ($p < 0.01$), and comparison of clomipramine with fluoxetine and sertraline showed clomipramine to be more effective than both fluoxetine and sertraline in delaying ejaculation ($p < 0.01$). Additionally, patients taking clomipramine were more likely to report they were satisfied with the results than those taking placebo, fluoxetine or sertraline (52.8%, 41.7%, 19.4% and 25%, respectively).

A later 6-week study by Waldinger et al.[26] compared the efficacy of placebo with two different SSRIs (paroxetine 20 mg and sertraline 50 mg), along with a 5-HT receptor antagonist, nefazodone 400 mg. As with the study by Kim and Seo,[32] the measured outcome was IELT. Forty-eight partici-

pants were split into four groups; the mean baseline IELT for placebo was 15 seconds, 17 seconds for paroxetine and 13 seconds for sertraline. There was no statistical difference between the groups for baseline IELT. Participants were asked to attend the clinic midway through the study to report any adverse effects. Of the 48 men who started the study, 40 completed it. Of the eight who withdrew, four withdrew due to adverse effects (paroxetine three, sertraline one), three withdrew due to family circumstances (nefazodone one, sertraline one, placebo one) and one withdrew due to lack of efficacy (nefazodone). At study end, the placebo group had a marginally increased mean IELT of 23 seconds (a 1.4-fold increase from baseline), the paroxetine group had a mean IELT of 146 seconds (a 9.1-fold increase from baseline), and the sertraline group had a mean IELT of 58 seconds (a 3.5-fold increase from baseline). Statistical analysis of the results showed that both paroxetine and sertraline were better than placebo at delaying ejaculation ($p < 0.001$ and $p = 0.024$, respectively) and that paroxetine was better than sertraline ($p = 0.002$).

*Adverse effects of other SSRIs:* The most common adverse effects reported for sertraline, fluoxetine and paroxetine were the same as those reported for dapoxetine.[19,26,27,32,33] Safarinejad[19] reported adverse effects in 20% of those taking 20 mg paroxetine. Kim and Seo[32] reported adverse effects in 36.1% of those taking fluoxetine and in 33.3% of those taking sertraline. Waldinger et al.[26] did not report full adverse effects, but reported that 25% of those in the group taking paroxetine and 8.3% of those in the group taking sertraline withdrew from the study due to adverse effects. In a second study by Waldinger et al.,[27] full details of adverse effects were not given. They reported only the most common adverse effects felt on the day of, or the day after, treatment, and that one participant withdrew due to the adverse effects of paroxetine. Wang et al.[33] reported adverse effects in 28.3% of those taking 20 mg paroxetine, with 16.6% withdrawing due to the adverse effects.

### Tramadol

Tramadol is an oral opioid analgesic. The mechanism of its effect on delaying ejaculation is currently poorly understood. It is thought that tramadol weakly inhibits the reuptake of serotonin and noradrenaline, and also has an anaesthetic effect on peripheral nerves.[34,35] However, it is considered that this weak action may not fully explain its efficacy in delaying ejaculation. Further studies to determine whether tramadol has other systemic actions on serotonin receptors have not been conclusive.[35]

*Benefits of tramadol*: Although only two studies have been carried out into the benefits of tramadol in PE, it is certainly an emerging treatment possibility. The first study to investigate the efficacy of tramadol in PE was carried out in 2006.[34] The study was a randomized control study that compared on-demand dosing of placebo with tramadol 50 mg. Sixty-four men enrolled, with 57 completing the study, four were lost to follow-up (placebo two, tramadol two) and three withdrew because of lack of efficacy (placebo one, tramadol two). The measured outcomes for this study were IELT, which was assessed by the participant's partner using a stopwatch, and sexual satisfaction. All participants were potent and had not received any other PE treatments in the 4 weeks prior to commencing the study. All participants were asked to take their capsule 2 hours prior to commencing intercourse.

Mean baseline IELT was 21 seconds for the placebo group and 19 seconds for the tramadol group. At the end of the study, the IELT for the placebo group had very marginally increased to 34 seconds in comparison with an IELT of 243 seconds in the tramadol group. The increase in IELT using tramadol was a 13-fold increase from the baseline IELT. Statistical analysis showed that tramadol was significantly better in increasing IELT than placebo ($p < 0.001$). When measuring sexual satisfaction at the start of the study, no participants reported themselves as being sexual satisfied, and at the end of the study, 69% of those in the tramadol group reported themselves as being sexual satisfied compared with only 14% in the placebo group ($p < 0.001$).

The second study carried out was a single-blind, placebo-controlled, crossover study to investigate the efficacy of tramadol in the treatment of PE.[35] Sixty men, all with lifelong PE, partici-

pated in the study, with everyone completing the study. The outcomes of the study were an increase in IELT (measured by the participant's partner using a stopwatch) and patient-reported satisfaction of control of ejaculation and satisfaction of the sexual act. Participants were split into two groups; group 1 took tramadol 25 mg and then placebo for 8 weeks each, with 1 week washout between treatments, and group 2 did the reverse. The mean baseline IELT was 1.17 minutes, which compares to study-end IELTs of 2.01 minutes for placebo (a 1.7-fold increase from baseline) and 7.37 minutes for tramadol (a 6.3-fold increase from baseline). Statistical analysis of the results proved that tramadol was significantly better at increasing IELT than placebo ($p < 0.0001$).

When looking at satisfaction scores for tramadol, 59 of the 60 participants reported significant increases in their satisfaction in controlling ejaculation and satisfaction of the sexual act.

Tramadol may be better tolerated than long-lasting SSRIs as a treatment for PE as, like dapoxetine, it can be used as required, minimizing potential adverse effects.

*Adverse effects of tramadol*: Adverse effects of tramadol are slightly different to other opioid analgesics, possibly due to its dual serotinergic and adrenergic mechanism as well as having an opioid effect.[36] Safarinejad and Hosseini[34] reported adverse effects in 28.1% of those taking 50 mg tramadol; only 15.6% of those taking placebo reported adverse effects. The adverse effects experienced were nausea, vomiting, dizziness and constipation. The adverse effects reported by Salem et al.[35] were mild dyspepsia and mild somnolence. These were reported in 13.3% of those taking 25 mg tramadol but there were no adverse effects reported by those taking placebo. Tramadol has several potentially dangerous interactions with other pharmaceuticals, which need to be considered when prescribing the agent. There is also a small but relevant risk of developing dependence to tramadol, particularly if using continuous dosing.

### Clomipramine

Clomipramine is a tricyclic antidepressant that is commonly used for the treatment of depression and obsessive compulsive disorder. Similar to tramadol and SSRIs, it is thought that its effect on delaying ejaculation is due to inhibiting the reuptake of noradrenaline and serotonin.[27,32]

*Benefits of clomipramine*: Continuous and on-demand dosing were both found to successfully increase IELT in patients with PE in a double-blind, randomized, placebo-controlled study in 2006.[1,13] Continuous dosing has been found to be most efficacious, with results comparable to those of SSRIs.[1,13]

A 4-week study in 2004 by Waldinger et al.[27] compared clomipramine and paroxetine with placebo in a randomized, double-blind, fixed-dose study. Thirty men were split into three groups; placebo, clomipramine 25 mg and paroxetine 20 mg. The measured outcome was IELT. Each group was monitored for 1 month prior to commencing the study to gain baseline measurements. IELT at baseline, and throughout the study, was measured by the participant's partner using a stopwatch. The median IELT at baseline was 24 seconds, with no statistical difference between the groups. All men were asked to take their capsules 3–7 hours prior to intercourse, but preferably 5 hours prior. Of the 30 men who started the study, 24 completed it, with three men withdrawing for non-medical reasons and three withdrawing due to adverse effects (paroxetine one, clomipramine two). As the IELT results were skewed in distribution, the results were logarithmically transformed before statistical analysis was carried out. At the end of the study, clomipramine was found to have achieved a 4.05-fold increase in IELT from baseline. Comparatively paroxetine has only achieved a 1.4-fold increase, which the authors deemed not to be a clinically relevant delay in ejaculation.

An Iraqi study[37] compared the efficacy of clomipramine in comparison with placebo. This was 6 week, randomized control study, designed to be a prospective study for future work; the measured outcome was IELT at 3 and 6 weeks. Thirty-eight men were split into two groups – placebo and clomipramine (10 mg for first 3 weeks titrated to 25 mg by end of study) – and were asked to take their agent daily. Mean IELT at baseline, and at week 3 and 6 of the study, was measured as

an average of three consecutive episodes of intercourse. Prior to commencing treatment, the mean baseline IELT for the placebo group was 45.4 seconds, and 47.7 seconds for the clomipramine group. Twenty-seven of the 38 men completed the study; nine were lost to follow up and two did not follow the study guidelines and as such were asked to leave the study. At 3 weeks, the mean IELT had increased to 51.2 seconds in the placebo group and 76 seconds in the clomipramine group. At the end of the study, the placebo group had a mean IELT of 55.4 seconds, which compared to a mean IELT of 143.1 seconds for the clomipramine group ($p < 0.05$).

*Adverse effects of clomipramine*: As with dapoxetine and the other SSRIs, the most common adverse effects reported for clomipramine were dry mouth, nausea, headache, drowsiness, insomnia and vomiting.[27,32,37] Cardiovascular and CNS adverse effects are relatively common.[1] These include ECG changes, arrhythmias, heart block, dizziness, agitation, confusion, paraesthesia, convulsions and hallucinations. Kim and Seo[32] reported adverse effects in 63.9% of those taking clomipramine. Waldinger et al.[27] reported that two participants withdrew from the study due to adverse effects (but did not fully detail all adverse effects). Mohammed[37] reported adverse effects in 38% of those taking clomipramine, which compared to 14% of those taking placebo.

Clomipramine is contraindicated in patients with arrhythmias, in a manic stage of bipolar disorder, during the recovery period following myocardial infarction, and those with liver disease.

### Phosphodiesterase Type-5 (PDE-5) Inhibitors

PDE-5 inhibitors are commonly used in treatment of ED. Often ED and PE are concomitant. It is thought that the causation of the two conditions is a 'chicken and egg' situation regarding which condition appears to be the primary condition.[38] ED may result in PE due to wanting to ejaculate early through fear of losing an erection before ejaculation, and PE may cause ED as individuals may have great anxiety regarding their PE.[1] There are many psychological components to both conditions and performance anxiety is likely to play a part in both. Because of the efficacy of sildenafil in the treatment of ED, and the concomitant nature of the conditions, it is likely that it may play a part in the treatment of PE also.[1,38]

*Benefits of PDE-5 inhibitors*: The 2006 study by Atan et al.[39] looked at the efficacy of sildenafil alone and sildenafil with local anaesthetic when compared with placebo and local anaesthetic alone. Eighty-four men were enrolled in the 8-week study, with all men completing the study. The measured outcome of the study was patient-reported improvement of PE (participants were asked to rate how effective the treatment was based on their symptoms being cured, improved or unchanged). The men were split into four groups; group 1 took placebo 45 minutes prior to intercourse, group 2 took 50 mg sildenafil 45 minutes prior to intercourse, group 3 also took 50 mg sildenafil but also applied a topical anaesthetic 15 minutes before intercourse, and group 4 applied a topical anaesthetic only. At study end, after completing at least eight attempts at intercourse, those receiving placebo reported 40% effectiveness, those receiving sildenafil alone reported 55% effectiveness, those receiving sildenafil and topical anaesthetic reported 86.4% effectiveness, and those receiving topical anaesthetic alone reported 77.3% effectiveness.

A randomized trial by Wang et al.[33] compared the efficacy of sildenafil, paroxetine and the squeeze technique in treating PE. This was a 6-month study that included 180 men. The men were split into three groups; group A took 50 mg sildenafil on demand, group B took 20 mg paroxetine daily and group C used the squeeze technique. Of the 180 men enrolled, 144 completed the study and all of those who left the study did so because of lack of efficacy or adverse effects (group A had 1 withdrawal, group B had 11 withdrawals, group C had 22 withdrawals). The measured outcome for the study was IELT, measured with a stopwatch by the participant's partner. The mean baseline IELT for the groups was 1.09 minutes for group A, 1.11 minutes for group B and 1.06 minutes for group C; there was no statistical difference in baseline IELT between the groups. At study end, group A had a mean IELT of 6.29 minutes, group B had an end IELT

 

of 4.93 minutes and group C had an end IELT of 2.62 minutes. All three end IELT results were found to be statistically improved when compared with baseline IELT ($p = 0.00$), with those in group A reporting the biggest increase in IELT.

A systematic review by McMahon et al.[24] found that generally the evidence for benefit was weak but there is some good evidence that the benefit of PDE-5 inhibitors is best when combined with other treatments.

*Adverse effects of PDE-5 inhibitors*: Atan et al.[39] reported adverse effects of flushing and headache, which were reported by 16.7% of those subjects taking sildenafil. Wang et al.[33] also reported headache and flushing as adverse effects. Additionally, participants reported congestion and nausea. Overall, adverse effects were reported by 31.7% of participants taking sildenafil,

### 7.2 Non-Pharmaceutical Treatments

The trend towards pharmacological treatment of PE is relatively recent; traditionally, behavioural therapy was considered the treatment of choice for PE.[11] Throughout the 1990s, and previously, PE was considered entirely a psychological problem with no physiological component.[11]

Behavioural interventions for the treatment of PE include the 'start-stop' and the 'squeeze' techniques.[1] The start-stop technique was first described in 1956 by Semans, a urologist.[11,40] The technique involves the partner stimulating the penis until the feeling of almost reaching climax occurs. Stimulation is then stopped until the feeling is lost. This cycle is repeated until the man feels he has more control over ejaculation.[1,11]

The squeeze technique was introduced by sex therapists in the 1970s.[11] This is similar to the stop-start technique except after stimulation is stopped the partner squeezes the frenulum of the penis, resulting in partial loss of erection.[1]

Sex therapy is used to teach these techniques to couples by showing men how to recognize pre-ejaculatory signs to create a 'choice point'.[1] It also has a greater role in the treatment of PE. Other aims of sex therapy are to increase self-esteem and regain confidence in sexual performance, reduce performance anxiety and improve communication within a couple, among others. Evidence suggests that behavioural therapies for PE are effective initially but often are not long-lasting, with a high proportion of patients representing at a later date with the same problem.[11]

There is a strong argument for 'combination therapy' for the treatment of PE by utilizing both behavioural and pharmacological treatments.[10,41]

### 7.3 Comparison of Dapoxetine with Other Therapies

To date, there has only been one study comparing dapoxetine with any other treatment – in 2006, Safarinejad[19] compared dapoxetine with paroxetine. In terms of benefit, paroxetine was found to be significantly better than dapoxetine in delaying ejaculation ($p < 0.01$). Paroxetine increased mean IELT from 31 to 370 seconds. Comparatively, dapoxetine increased mean IELT from 38 to 179 seconds. In terms of risk of the participants taking dapoxetine, four withdrew from the study due to adverse effects and a further 19 reported minor adverse effects. Of the participants taking paroxetine, five withdrew from the study due to adverse effects and a further 21 reported minor adverse effects (see table I for reported adverse effects). No significant difference was found in the number of adverse effects.

In general terms, the studies looked at for this review showed similar results for all SSRIs in both their efficacy in increasing IELT and reported adverse effects.[2,18,19,25-27,32,42-44]

## 8. Benefit-Risk Evaluation of Dapoxetine

PE is a common sexual problem affecting men of all ages and has a massive impact on quality of life for individuals and partners. Therefore, treating PE is very important. Several double-blind, placebo-controlled trials and literature reviews have shown that dapoxetine delays ejaculation and improves sexual satisfaction, with a 60 mg dose showing the greatest effect.[2,18,19,25,34,42]

Dapoxetine has been generally well tolerated throughout all studies. The most common adverse effects reported were considered minor and

the occurrence of serious adverse effects has been less than 1% across all studies.[2,18,19,32,34,43]

## 9. Conclusions

PE is an important clinical condition to treat given its considerable impact on quality of life for many. Several pharmacological and behavioural therapies have been tested for treating PE. Results from trials assessing dapoxetine for the treatment of PE have been very promising so far and its benefits appear to outweigh the risks, although long-term risks are not yet known given that all trials have been recent and have been relatively short in length. Further research is needed to assess the efficacy of a combination of several therapies.[1]

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