New Medicine Assessment

Daily selective serotonin re-uptake inhibitors (SSRIs) in the treatment of premature ejaculation (PE)

Recommendation:

RAG Status: **Green/Amber** (depending on local commissioning arrangements)

Daily SSRIs are recommended as an option to treat lifelong PE when pharmacotherapy is indicated and where the patient meets all of the criteria below.

Daily SSRIs are recommended as an option to treat acquired PE only after psychotherapy **and** management of the causative problem have failed to resolve the issue and where the patient meets all of the criteria below.

- An intravaginal ejaculatory latency time of less than 2 minutes **and**
- Persistent or recurrent ejaculation with minimal stimulation or shortly after penetration or before the man wishes **and**
- Marked personal distress or interpersonal difficulty as a consequence **and**
- Poor control over ejaculation **and**
- History of PE in the majority of intercourse attempts over the prior 6 months

Summary of supporting evidence:

- A 1 month active comparator study of daily paroxetine 20 mg versus on demand dapoxetine showed a similar increase in intravaginal ejaculation latency time (IELT) as dapoxetine 30 mg of 117% (53.2 and 54.1 seconds respectively). A significantly greater increase in IELT was demonstrated for dapoxetine 60 mg on demand of 170% (74.7 seconds).
- A 12 week active comparator study demonstrated an increase in IELT of 371% (141 seconds) for dapoxetine 60 mg daily in contrast to a 1094% (339 second) increase for paroxetine 20mg daily and a 62% (21 second) increase for placebo.
- The difference in results from the two active comparator studies could be explained by the difference in duration of the studies and the different dosing schedule for dapoxetine (daily versus on demand).
- A meta-analysis of 8 prospective, double-blind, real time stopwatch studies (n = 263) demonstrated a significant increase in the IELT for clomipramine, fluoxetine, sertraline and paroxetine versus placebo (360%, 295%, 313%, 783% and 47% respectively).
- Two further studies published following the meta-analysis compared the efficacy of citalopram and fluoxetine (n = 106) for 4 – 12 weeks. Fluoxetine and citalopram demonstrated an increase in the mean IELT of 637%-703% and 638%-737% respectively.
- In the few studies which included quality of life measurements as a comparator, the statistically significant increase in IELT demonstrated by SSRIs was also accompanied by increases quality of life.
- Safety data in support of SSRIs in PE is limited to a small number of active comparator and placebo controlled trials, however, appears in line with their safety profile when used in the treatment of depressive illness.

- The two treatment options, dapoxetine vs. daily SSRIs or clomipramine primarily differ in terms of patient experience, with dapoxetine taken on-demand 1-3 hours prior to anticipated intercourse and the SSRIs taken on a daily basis. Whilst the daily use allows for greater spontaneity, it also means patients are more likely to suffer withdrawal effects in the event of sudden cessation of treatment.
- One study demonstrated that when treating PE the majority of patients prefer a medication for daily use in preference to on-demand treatment.

Details of Review

Name of medicine (generic & brand name)**:** Citalopram, fluoxetine, paroxetine, sertraline.
Strength(s) and form(s): Citalopram 20 mg tablets, fluoxetine 20 mg or 40 mg capsules, paroxetine 20 mg tablets, sertraline 50 mg tablets.
Dose and administration: All are taken orally on a once daily basis. A variety of strengths have been trialled dependent on the study. In general, studies have started with lower doses and then adjusted this dose upwards if required.
BNF therapeutic class / mode of action: BNF section 4.3.3 Selective serotonin re-uptake inhibitors
Licensed indication(s): **Citalopram**: depressive illness, panic disorder. **Fluoxetine**: major depression, bulimia nervosa, obsessive-compulsive disorder. **Paroxetine**: major depression, obsessive-compulsive disorder, panic disorder, social anxiety disorder, post-traumatic stress disorder, generalised anxiety disorder. **Sertraline**: depressive illness, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, social anxiety disorder.
Proposed use (if different from, or in addition to, licensed indication above): unlicensed indication – once daily use for the treatment of diagnosed PE.
Course and cost: Long term use **-** citalopram 20 mg x 28 = £1.10, fluoxetine 20 mg x 30 = £1.09, paroxetine 20 mg x 30 = £1.89, sertraline 50 mg x 28 = £1.75.[10]
Current standard of care/comparator therapies: Dapoxetine on-demand has recently been licensed for treatment of PE. It is available as the branded Priligy®. Dapoxetine 30 mg tablets x 3 = £14.71, x 6 = £26.48, Dapoxetine 60 mg tablets x 3 = £19.12, x 6 = £34.42.[10]
Relevant NICE guidance: NICE Evidence Summary: New medicine Premature ejaculation: Dapoxetine.[12] Dapoxetine for PE was not considered appropriate for a NICE technology appraisal and is not currently planned into any other work programme. There is no NICE guidance on PE[12]
Other relevant guidance: European Association of Urology Guidelines on Male Sexual Dysfunction Erectile dysfunction and PE produced annually include recommendations for the management of PE.[1]

Background and context

PE is the most common male sexual dysfunction, with prevalence rates of 20-30%. Limited data suggest that the prevalence of lifelong PE is about 2 to 5%.[1] The diagnosis and management of PE is a developing field and it is only relatively recently that Waldinger et al gave the evidence-based definition of lifelong PE as;

'an IELT that takes place within 1 min after vaginal penetration in more than 90% of intercourses, independent of age and duration of relationship.'[13]

The studies carried out assessing preparations in the management of PE have used various definitions to diagnose the condition. The "cut off point" ranged from less than 1 minute in some studies to less than 5 minutes in one study.

The International Society for Sexual Medicines first evidence-based definition, included in the European Association of Urology Guidelines, defines PE as;

'a male sexual dysfunction characterised by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration; and inability to delay ejaculation on all or nearly all vaginal penetrations; and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy'[1]

This definition is limited to men with lifelong PE who engage in vaginal intercourse, there are insufficient objective data to propose an evidence-based definition for acquired PE.[1] Whereas lifelong PE is seen from the first sexual experience and remains throughout life, acquired PE sees a gradual or sudden onset following previous normal ejaculation experiences.[1]

The lack of one specific definition has meant historically, studies conducted into the treatment of PE have had huge variances.[13] This is due to some extent, to the differing definitions used to diagnose PE. But it is also due to different measures used to assess any improvement, whether they are subjective questionnaires completed retrospectively or the more recent measurement of IELT with a stopwatch at the time of intercourse.[13]

The updated European Association of Urology Guidelines, in their section on PE, recommend pharmacotherapy as the first-line treatment option for men with lifelong PE.[1] The guideline includes licensed on-demand dapoxetine and off-label treatments, which include daily use of anti-depressants such as the SSRIs, as treatment options. They do not recommend one treatment option over another.[1] For men with acquired PE, the same pharmacological options are recommended as treatment options. The guideline does not specify whether pharmacological or other treatment options such as patient counselling/education and behavioural therapy should be considered first line.[1]

SSRIs, although primarily used for mood disorders, were found to delay ejaculation and therefore have been widely used 'off-label' as a treatment for PE for many years. They are usually prescribed daily, trials have been carried out for on-demand but this dosing regime has proved less successful. The regular daily dosing has the advantage of allowing a man a greater level of spontaneity, rather than having to plan some hours in advance of intended sexual activity to take an on-demand treatment.

The daily use of SSRIs in the treatment of PE is currently unlicensed; however, various studies to support their use have been conducted.

Summary of evidence

Summary of efficacy data in proposed use:

Evidence in support of the use of SSRIs in the treatment of PE is limited to two direct comparator studies versus dapoxetine and a range of small trials of differing design, interventions, comparators and methods of assessment.

The first direct comparator study compared the use of daily paroxetine (determined by the meta-analysis[2] to give the largest increase in IELT) with the use of dapoxetine.[8] This one month study divided patients into three groups of 50 men; group 1 received on-demand dapoxetine 30 mg, group 2 on-demand dapoxetine 60 mg and group 3 were treated with daily paroxetine 20 mg. Patients were included if they were in a stable relationship for at least 6 months and had an IELT of less than 1 minute.

All three groups saw a significant increase in IELT from baseline, with paroxetine 20 mg and dapoxetine 30 mg giving similar increases of 117% or 53.2 ($p<0.01$) and 54.1 ($p<0.01$) seconds respectively: dapoxetine 60 mg saw a 170% increase in IELT or 74.7 ($p<0.01$) second improvement.

This result is in contrast to the second comparator study, published in 2006 and available as an abstract only,[7] this 12 week study compared dapoxetine 60 mg (n=115), paroxetine 20 mg (n=113) and placebo (n=112) all taken on a daily rather than on-demand basis. IELT increased from a baseline of 38, 31 and 34 seconds to 179, 370 and 55 seconds respectively; showing a far greater increase for paroxetine over the dapoxetine. This study also measured mean intercourse satisfaction domain values of International Index of Erectile Function (IIEF) these increased from a baseline of 10, 11 and 11 for dapoxetine, paroxetine and placebo to 14, 17 and 12 at the end of the 12 weeks for the three groups' respectively[7]: this again favours the paroxetine.

The difference in results for the two active comparator studies could be partially explained by the daily rather than on-demand use of dapoxetine in the 12 week study and the short duration of the 1 month study. Dapoxetine has maximum plasma concentration 1-2 hours post dose, a terminal half-life of 19 hours and plasma levels 5% of peak 24 hours post dose. SSRIs need be given for 1 to 2 weeks to be effective in PE[1] so the SSRI may not have been exhibiting its full therapeutic effect at the end of the 1 month study.

In 2004, a systematic review was performed of all drug treatment studies for PE published from 1943 to 2003. 79 studies (3034 males) were included and assessed whether the design and methodology of drug treatment studies of PE affect the efficacy outcome (as there is currently no evidence-based consensus on methodology in research and treatment).[2] A meta-analysis was performed on the 35 of the studies which assessed the use of daily SSRIs and clomipramine hydrochloride in the management of PE (which included 1181 males).[2] Only studies reporting quantitative data on the change in ejaculation time were included in the meta-analysis. Due to the variation in scales used to assess efficacy in the different studies the meta-analysis brought the different quantifications on to the same scale and calculated the percentage change from baseline. Most papers did not report the percentage change and so this was calculated using the average baseline IELT and average follow-up IELT. With the exception of 6 papers all reported that delay in ejaculation time was an outcome measure when defining PE. The duration of the studies varied from 1 to 68 weeks, with the average duration between 4 to 8 weeks.[2] The analysis found that paroxetine, sertraline, fluoxetine and clomipramine hydrochloride significantly delayed ejaculation compared with placebo ($p<0.001$).

Eight of the SSRI and clomipramine hydrochloride studies which had been subject to the initial meta-analysis, were considered as being of a high enough quality to be appropriate for a further final analysis.[2] They were all prospective, double-blind, real time stopwatch studies including a total of 263 men. The daily doses used in the studies were; clomipramine 25 or 50 mg, fluoxetine 20 mg or

40 mg, paroxetine 20 mg, sertraline, 50 mg, citalopram 20mg, fluvoxamine 100 mg, mirtazapine 30 mg and nefazodone 400 mg.

The IELT was measured using a stopwatch and the mean increases in values across the 8 studies were as follows: Placebo 47% [95% CI 29-76%], clomipramine hydrochloride 360% [95% CI 201-644%], fluoxetine 295% [95% CI 200-435%], sertraline 313% [95% CI 161-608%] and paroxetine 783% [95% CI 499-1228%].[2] Specific times in seconds are not provided, however the average baseline IELT of all the daily SSRI and clomipramine studies is stated in the meta-analysis as having a mean of 41 seconds ±23 seconds [range of 13-81 seconds].[2] Using the lowest baseline value of 13 seconds, with the lowest percentage increase of fluoxetine, the IELT would increase to over 51 seconds. Using this same lowest baseline with the highest percentage increase of paroxetine would give an IELT increased to almost 115 seconds. Using the same percentage increases with the highest baseline value of 81 seconds gives an IELT increased to 320-715 seconds.

Two studies published following the meta-analysis[3,4] compared the efficacy of citalopram (20mg and 40mg) and fluoxetine (40mg) in a total of 106 patients (aged 18-60 years) with and without anxiety for 4 - 12 weeks. Fluoxetine increased the mean IELT from a baseline of 49–58 seconds to 379–466 seconds (mean % change from baseline 637%-703%) and citalopram increased the mean IELT from a baseline of 32-65 seconds to 268-480 seconds (mean % change from baseline 638%-737%).

Evidence in support of dapoxetine

Dapoxetine was licensed in October 2013 to treat PE in men aged 18-64 years with either a 30 mg or 60 mg dose (adjusted according to response) approximately 1-3 hours prior to sexual activity.[14] It is currently the only licensed oral treatment for PE.

The pivotal licensing studies for dapoxetine included 4 that measured the IELT[5] including nearly 4850 men, and one study including 1238 men which looked at patient reported outcomes such as perceived control over ejaculation, personal distress & interpersonal distress related to ejaculation and satisfaction with sexual intercourse: dapoxetine performed better than placebo in all of these[6]

Dapoxetine 30mg increased the mean IELT from a baseline of 54-66 seconds to 168-234 seconds (mean % change from baseline 211%-254%) and dapoxetine 60mg increased the mean IELT from a baseline of 54-66 seconds to 198-252 seconds (mean % change from baseline 266%-288%). The increase for placebo ranged from 100%-140% (54-84 second improvement).[5]

In contrast to these dapoxetine results, in the meta-analysis and subsequent papers daily SSRIs gave an increased IELT which ranged from 295% to 783% (baseline range of 13-81 seconds gives minimum 38-102 and maximum 239-634 second increase) dependent upon the specific drug used: the placebo increase in IELT was 36-47%[2,3] (range 6-38 second improvement).

Evidence for patient satisfaction

The eight high quality studies included in the meta-analysis[2] mostly either didn't use a quality of life measure in addition to IELT or this wasn't clear from available abstracts. One of the studies did however assess a quality of life element.[15] It consisted of 26 married men with diagnosed PE. 13 received citalopram 20 mg (which could be titrated up to 60 mg if required and tolerated) and 13 received placebo for 8 weeks. In addition to IELT measurements all patients were screened by using the Clinical Global Impression-Improvement scale (CGI-I) and Yonsei Sexual Function Inventory-II (YSFI-II).

According to the CGI-I, after 8 weeks of treatment 5 (38.5%) of the patients receiving citalopram were considered very much improved and a further 4 (30.8%) much improved, compared with 1 patient (7.7%) in the placebo group being considered much improved. In looking at the YSFI-II, mean changes from baseline to last assessment in the citalopram group were significantly higher

compared to placebo in all subscales. These subscales included: sexual desire, quality of erection, anxiety for rapid ejaculation, satisfaction with ejaculation, partners satisfaction with ejaculation, overall sexual satisfaction and the partners overall satisfaction.[15]

The dapoxetine studies also included a quality of life measure.[5] The pooled data for the Clinical Global Impression of Change (CGIC) measure gave 39% of patients in the dapoxetine 60 mg group, and 30.7% in the 30 mg group giving ratings of 'better' or 'much better' at week 12, compared to 14.8% in the placebo group. When also including 'slightly better' i.e. all patients who reported an improvement in their condition, these percentages increased to 71.7% for 60 mg, 62.1% for 30 mg and 36% for placebo.[5]

A 2007 study by Waldinger et al looking at men's treatment preferences in relation to PE, assessed 88 men and found that 81% of them preferred a drug for daily use, 16% preferred an on-demand treatment with a further 3% preferring a topical anaesthetic cream.[11]

Summary of safety data:

SSRIs have a well-established safety profile for their use in depressive illness. Common side-effects to SSRIs include fatigue, drowsiness, yawning, nausea, vomiting, dry mouth, diarrhoea and perspiration.[1] They are usually mild and improve gradually after 2-3 weeks.

The meta-analysis of the use of SSRIs in PE did not specifically provide any information on the safety of SSRIs in the treatment of PE.[2] Nor did it provide information on the numbers of men who did not complete the studies due to side effects.[2]

Safety data relating to the use of SSRIs in PE is limited to a small number of active comparator and placebo controlled trials. In the comparison of paroxetine and dapoxetine[8] 14% (n=7) of patients in the paroxetine treatment arm withdrew from the study due to mood related changes and somnolence compared with 6% (n=3) in the dapoxetine group, in the second direct comparator study[7] the incidence of adverse events with paroxetine and dapoxetine was significantly higher than that of placebo, however, no further detail is provided.

In the study assessing the safety and efficacy of citalopram, three (10%), six (20%) and three (10%) developed dry mouth, nausea and loss of appetite respectively, while 1 patient withdrew due to gastrointestinal upset.[3] The study comparing fluoxetine and citalopram[4] did not provide information on adverse events during the study, however, 5 patients were excluded due to drug side effects like headache, dizziness, insomnia and diarrhoea.[4]

Other side effects reported relevant to PE treatment include decreased libido, anorgasmia, anejaculation and erectile dysfunction.[1]

Because of the risk of suicidal ideation or suicide attempts seen with SSRIs they should not be used to treat PE in men less than 18 years of age and caution should be used when treating men who also suffer from a depressive disorder especially if this is associated with existing suicidal ideation.[1]

Sudden cessation or rapid dose reduction of daily SSRIs should be avoided as it could be associated with SSRI withdrawal syndrome.[1,9]

For the safety profile of individual SSRIs the specific SPCs and the current edition of the BNF should be consulted.

Strengths and limitations of the evidence:

- The two active comparator studies comparing the treatment effect of paroxetine against dapoxetine had significant methodological and outcome differences, for this reason differences in treatment effect need to be interpreted with caution.
- Evidence in support of SSRIs in PE is limited to small studies (<115 patients) with different blinding, comparators, efficacy measures and duration of treatment.
- The systematic review which provides the majority of evidence in support of SSRIs was primarily set up to compare the relevance of methodological design for the interpretation of efficacy of drug treatment of premature ejaculation.
- Where subjective feelings of control, satisfaction and improvement have been used, often these have not included clear operational definitions.
- Only 29% of studies within the systematic review included the use of a stopwatch, watch or clock and of these 35% were single-blind or had an open design.
- A meta-analysis of eight prospective, double-blind, real time stopwatch studies including 263 men, performed as part of the systematic review, demonstrated a statistically significant increase in IELT for paroxetine, fluoxetine, sertraline and clomipramine over placebo.
- The majority of evidence in support of daily SSRIs relates to the change in IELT which is a disease orientated outcome, rather than a patient orientated outcome such as the more subjective patients views on how their PE has been improved, feelings of control, levels of satisfaction etc.

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